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Silver-catalysed double decarboxylative addition–cyclisation–elimination cascade sequence for the synthesis of quinolin-2-ones†

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An atom-efficient silver-catalysed double carboxylative strategy for the one-step synthesis of quinolin-2-ones *via* an addition–cyclisation–elimination cascade sequence of oxamic acids to acrylic acids, mediated either thermally or photochemically, is reported. The reaction was applicable to the synthesis of a broad range of quinolin-2-ones and featured a double-disconnection approach that constructed the quinolin-2-one core *via* the formal and direct addition of a C(sp^2)–H/C(sp^2)–H olefin moiety to a phenylformamide precursor.

Introduction

Quinolin-2-ones represent an important class of privileged nitrogen-containing heterocycles as they feature impressive biological profiles and utility in chemical biology (Fig. 1, **1**–**4**).[1–4] For example, tipifarnib (**1**)[2] is used as an experimental agent in the treatment of cancer (FPT: IC_{50} = 0.86 nm [lamin B] and 7.9 nm [K-RasB]), while NI-42 (**2**) is a high affinity BRPF inhibitor (BRPF1: IC_{50} = 7.9 nm).[3] Trifluoromethylated analogues (**4**) are known androgen receptor antagonists and are particularly useful fluorescence tracers in chemical biology.[4] Furthermore, quinoline-2-ones serve as important synthetic building blocks for accessing their bioactive 3,4-dihydroquinolin-2-one relatives (such as **5** and **6**)[1]—particularly toward their enantioselective synthesis.[5]

In broad terms, the construction of quinolin-2-ones are largely envisaged *via* two main disconnections; either between the aryl group and the double bond (Fig. 2A-left)—*via* arylation processes (of the type **I**)[6] or between the carbonyl group and the double bond (Fig. 2A-right)—*via* insertion into double/triple bonds (of the type **II**).[7] Other approaches include oxidation of quinoline salts,[8a] ring expansion of isatins,[8b,c] and aldol-type ring closures.[8d] By contrast, we were intrigued by the notion of simultaneously disconnecting at both ends of the double bond for a more modular synthesis—formally enabling the direct installation of a C(sp^2)–H/C(sp^2)–H olefin moiety into a phenylformamide precursor (Fig. 2B; of the type **III**).[9]

To the best of our knowledge, only two reports of this type of approach toward the synthesis of quinolin-2-ones have been described in the literature (Fig. 2B).[10] Donald and co-workers reported a photoredox catalysed addition–cyclisation sequence to produce 3,4-dihydroquinolin-2-ones, that spontaneously eliminated HCl to afford quinolin-2-ones when using chloroacrylate derived Michael acceptors.[10a] This however featured only 3 examples (with modest yields), and the use of the *N*-phthalimido esters is somewhat of a disadvantage in terms of the overall atom efficiency. Additionally, substituted chloroacrylates and chloroacrylonitriles are not easily obtained. The second report is by Feng and co-workers who instead described the use of oxamic acids and vinyl sulfones in a related transformation.[10b] While the use of oxamic acids is more atom efficient, the method was limited to producing only

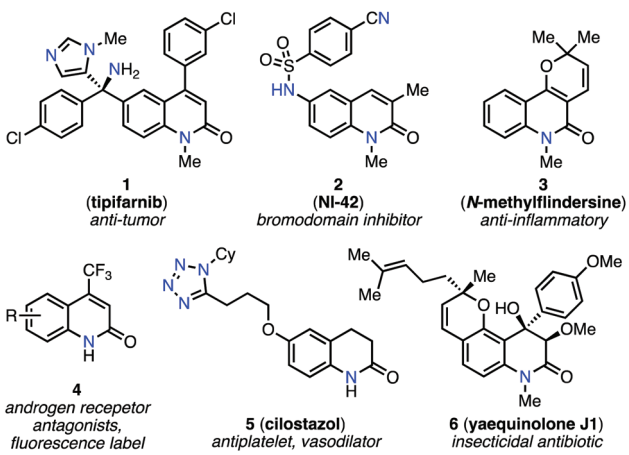

Fig. 1 Representative set of quinolin-2-ones and 3,4-dihydroquinolin-2-ones.

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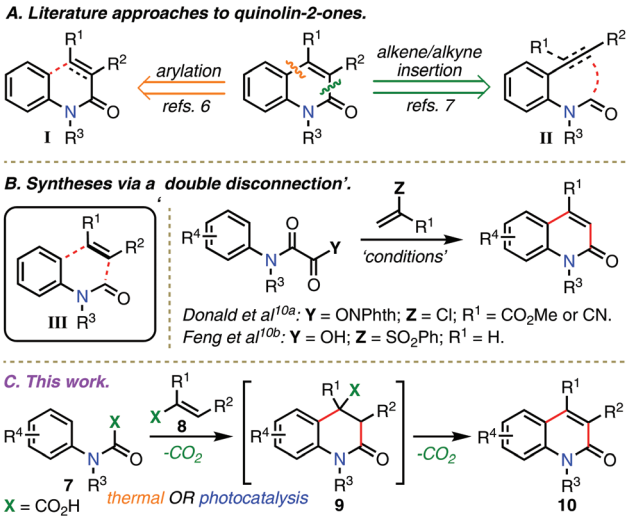


Fig. 2 (A and B) Previous reports on the synthesis of quinolin-2-ones. (C) Our approach.

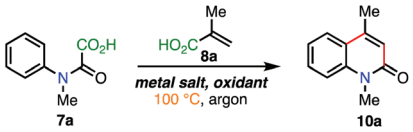
unsubstituted quinolin-2-ones at C3 and C4. In context, the work by Jiao must be highlighted.[7a] Here, they reported an impressive rhodium catalysed three-component reaction involving an aniline, carbon monoxide, and an internal alkyne, that could additionally assemble the amide moiety of the quinolin-2-one. Some drawbacks however involved the use of toxic CO gas, a stoichiometric amount of a transition-metal oxidant, and the need for high reaction temperatures—with minor limitations on the internal alkyne used. Inspired by these reports, we herein describe a silver-catalysed addition–cyclisation–elimination cascade sequence for the synthesis of quinolin-2-ones utilising readily available oxamic and acrylic acids *via* a double radical decarboxylation mediated either thermally or photochemically (Fig. 2C).

Results and discussion

In our work toward to the synthesis of bisoxindoles, we recently reported that oxindole-derived quaternary acids of the type **9** could generate their corresponding methine radical under oxidative conditions,[11] and hypothesised that when applied to 6-membered systems (**9**), a relatively fast H-abstraction would produce the desired quinolin-2-ones **10**—rather than a 3,4-dihydroquinolin-2-one dimer as per our previous work[11]—due to the stability of the extended π-system of **10**. This led us to identify readily available and/or easily synthesised acrylic acids (**8**) and oxamic acids (**7**) as key starting materials to facilitate a more atom efficient oxidative cascade sequence through the loss of CO_2 (Fig. 2C). Indeed, radical decarboxylation strategies[12] and related deoxygenations[13] have emerged as powerful tools toward enabling sustainable and atom efficient transformations.

In search of a suitable set of oxidative conditions for our envisaged cascade, our optimisation studies began using

Table 1 Selected optimisation results for the thermal reaction



Entry	Metal salt (mol%)	Oxidant (equiv.)	Solvent	Yield[a] (%)
1	—	$Mn(OAc)_3$[b] (3)	PhMe	52
2	$Mn(OAc)_3$[b] (50)	$K_2S_2O_8$ (3)	ACN/H_2O	16
3	$AgNO_3$ (20)	$K_2S_2O_8$ (3)	ACN/H_2O	34
4	**$AgNO_3$ (50)**	**$K_2S_2O_8$ (3)**	**ACN/H_2O**	**58**
5[c,d]	$AgNO_3$ (50)	$K_2S_2O_8$ (3)	ACN/H_2O	Trace
6	None	$K_2S_2O_8$ (3)	ACN/H_2O	35

[a] Determined by ^{1}H NMR (1,3,5-trimethoxybenzene standard). [b] As the dihydrate. [c] Reaction carried out at room temperature. [d] Starting material recovered.

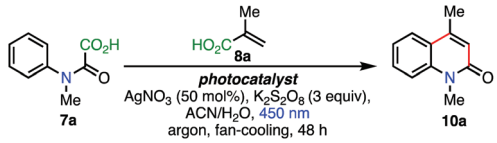
oxamic **7a** and acrylic acid **8a** as model substrates (Table 1, see the ESI† for full data). In accordance with our prior work,[11] we first investigated the use of stoichiometric of $Mn(OAc)_3$ as the oxidant for the reaction—the use of 3 equiv. accounting for each of the 3 independent oxidation steps (Table 1, entry 1). Gratifyingly, the desired quinolin-2-one **10a** was produced in 52% yield. Although pleasing, we were acutely aware of the significant drawbacks associated with the use of super stoichiometric transition-metal metals in the context of sustainability. To this end, we opted for 50 mol% $Mn(OAc)_3{\cdot}2H_2O$ (~17 mol% effective loading over the 3 steps) in the presence of $K_2S_2O_8$—a low-cost and readily available oxidant[14]—which produced **10a** in a poor 16% yield (Table 1, entry 2). The use of $AgNO_3$/$K_2S_2O_8$ is a well-known system for net oxidative transformations, particularly in the context of decarboxylation chemistry.[6a,14] Pleasingly, an improved 34% yield was obtained in the presence of 20 mol% $AgNO_3$ (Table 1, entry 3), while 50 mol% $AgNO_3$ produced the best set of conditions; affording **10a** in 58% yield (Table 1, entry 4). It is worth noting that 50 mol% $AgNO_3$ (17 mol% effective loading per oxidation step) was found to be optimum as higher loadings (such as 80 and 100 mol%) did not affect the yield and 30 mol% afforded **10a** in 40% yield (see ESI†). Carrying out the reaction at room temperature was ineffective for the reaction (Table 1, entry 5, while performing the reaction in the absence of a metal salt afforded **10a** in 35% yield (Table 1, entry 6). Various other metal salts, solvent systems, and persulfates where also investigated, but these were all found to produce inferior results (see the ESI†).

Reactions that require significant heating are very energy intensive and therefore raises sustainability concerns in the context of global energy security. Furthermore, accessing these chemistries are particularly challenging in regions with fragile or severely constrained national energy grids—especially when extended heating periods are required.[15] Indeed, high temperatures preclude thermally sensitive starting materials and products. For this reason, there is notable value in developing room temperature alternatives for these

processes. In this light, and with the chemistry of the cascade sequence established, we set out to develop a comparable photoredox-mediated room temperature alternative. As mentioned, the room temperature reaction as per Table 1, entry 5 was found to be ineffective and this is due to the high activation barrier associated with disproportionation of $K_2S_2O_8$ to afford its highly oxidising $SO_4^{\bullet-}$ radical anion.[16] On the other hand, photoexcited ruthenium complexes are known to efficiently reduce persulfate anions ($S_2O_8^{2-}$) to their corresponding sulfate radical anions ($SO_4^{\bullet-}$) at room temperature,[14c,17] and we therefore envisaged that employing this strategy would enable our cascade sequence to proceed efficiently at room temperature. In the event, modifying our reaction conditions accordingly produced **10a** in a comparable 54% yield when using $[Ru(Bpz)_3](PF_6)_2$ in the presence of visible-light (Table 2, entry 1). Switching to the organic photocatalyst **4-CzIPN**[18] provided the optimum photoredox conditions; affording **10a** in 58% yield (Table 2, entry 2), while acridium and iridium photocatalysts produced **10a**, in 43% and 38% yields, respectively (Table 2, entries 3 and 4). In the absence of a photocatalyst, **10a** was obtained in 22% yield, indicating that light activated homolysis of $S_2O_8^{2-}$ is facilitated to some extent. (Table 2, entry 5). Full data is available in the ESI.† With the optimised conditions at hand, the substrate scope of the addition–cyclisation–elimination cascade sequence was investigated, paying attention to any differences between the thermal and photochemical strategies in a randomised sample set (Scheme 1). Indeed, reaction time is an obvious advantage for the thermal reaction (18 h *vs.* 48 h).

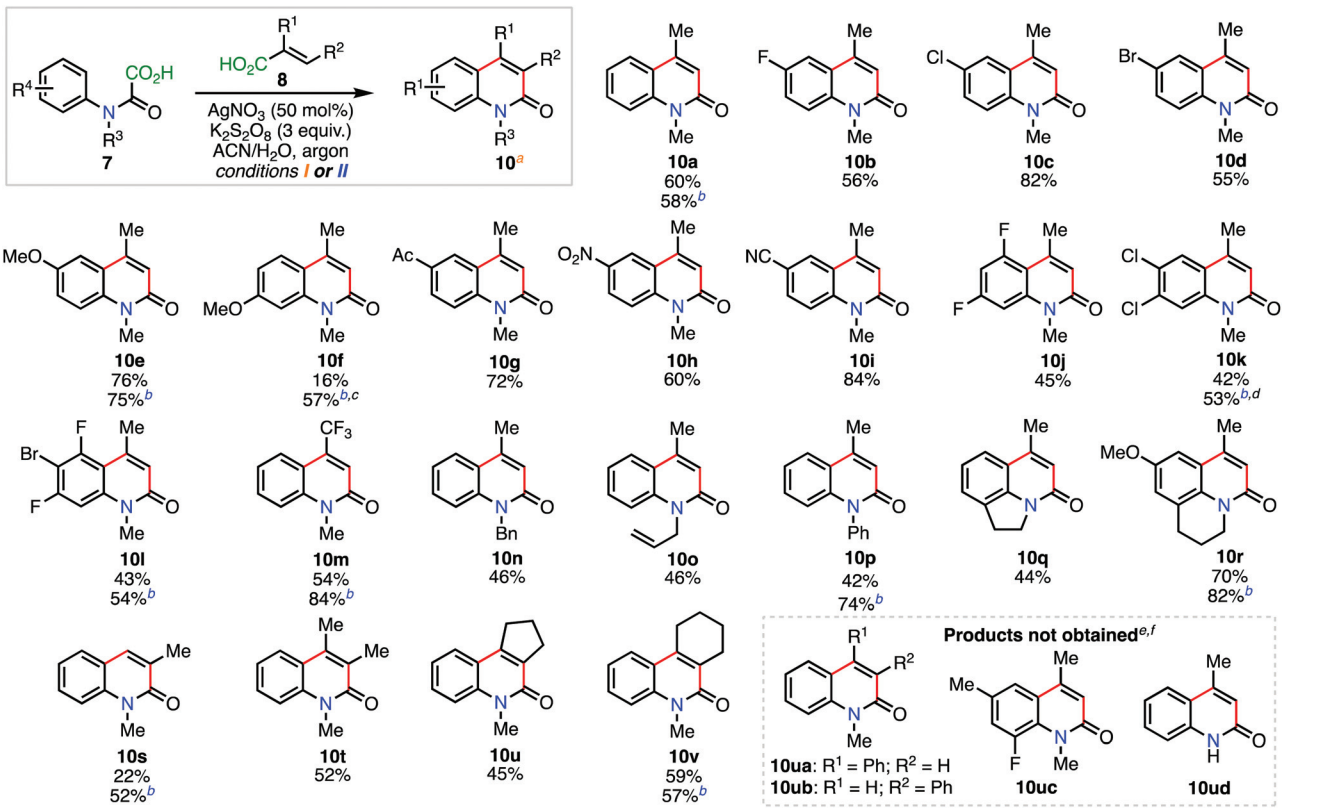
Repeating the reaction with the model system afforded **10a** in 60% and 58% isolated yields for the thermal and photo-

Table 2 Selected optimisation results for the photoredox reaction



Entry	Photocatalyst (mol%)	Yield[a] (%)
1	$[Ru(Bpz)_3](PF_6)_2$ (5)	54
2	**4-CzIPN (2)**	**58**
3	(Mes-Acr-Ph)BF_4 (10)	43
4	$(Ir[df(CF_3)ppy]_2dtbpy)PF_6$ (2)	38
5	None	22

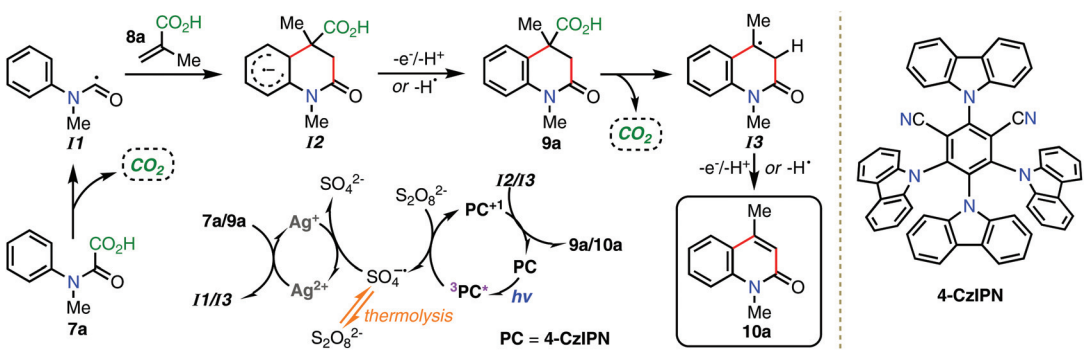
[a] Determined by ^1H NMR (1,3,5-trimethoxybenzene standard).



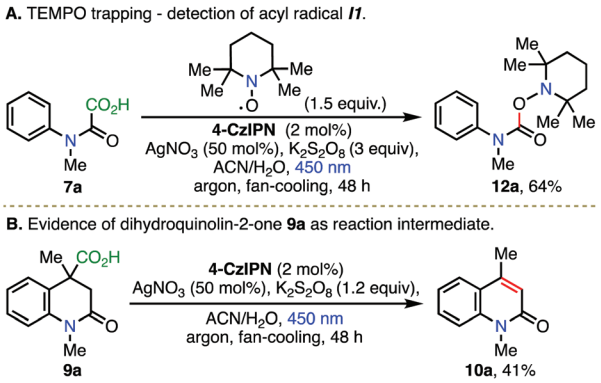
Scheme 1 Substrate scope. Conditions I: 100 °C, 18 h. Conditions II: 4-CzIPN (2 mol%), 450 nm (18 W), fan-cooling, 48 h. [a]Unless otherwise state, isolated yields *via* conditions I. [b]Isolated yield obtain *via* conditions II. [c]Obtained as a 1 : 1.5 mixture of separable regioisomers. [d]Obtained as a 1 : 1.1 mixture of separable regioisomers.[e]Mediated either thermally or photochemically. [f]Complex mixture of products obtained. In some cases, unreacted oxamic acid starting material could be detected (20–60% recovered).

chemical reactions, respectively, while the mono-halogenated oxamic acids afforded **10b–10d** in 55–82% yields. The 4-methoxy-substituted product **10e** was produced in comparable isolated yields of 76% and 75% for the thermal and photochemical reactions, respectively. On the other hand, **10f**, the 3-substituted variant was obtained in only 16% isolated yield, which improved to 57% yield under photoredox catalysis. Electron-withdrawing substituents were well tolerated, affording **10g–10i** in 60–84% isolated yields. The difluorinated oxamic acid analogue **10j** was obtained in 45% yield, while the dichlorinated variant **10k** was produced in 42% yield, that could be improved to 53% when performed under photochemical conditions. Trisubstituted oxamic acids were also suitable, affording **10l** in 43% yield, and improved to 54% yield using photoredox catalysis. As mentioned, 4-trifluoromethylated quinolin-2-ones have particularly utility in chemical biology. Pleasingly in context, **10m** was produced in 54% yield using 2-(trifluoromethyl)acrylic acid, which was improved to an excellent 84% under the room temperature photochemical conditions. Modification of the nitrogen protecting group was also well tolerated affording **10n–10r** in up to 82% yield, with notable increases in yield when performed under photoredox conditions (*i.e.* **10p** and **10r**). Variation of the acrylic acid was also possible producing the 3-substituted quinolin-2-one **10s** in 22% yield that could be significantly improved to 52% yield photochemically. Disubstituted acyclic and cyclic acrylic acids were also suitable; producing 3,4-disubstituted quinolin-2-ones **10t–10v** in 52–59% isolated yields, with no obvious advantage photochemically (as per **10v**). It is worth noting that compounds **10m** and **10r** were produced using recycled **4-CzIPN** obtained in sequence during the substrate scope explorations. Specifically, **10m** was obtained using the photocatalyst recovered during the synthesis of **10l**, and then **10r** was obtained using the photocatalyst recovered from **10l**. Clear limitations to the cascade sequence, though, were apparent; both thermally and photochemically. For example, aryl substituted products (such as **10ua** and **10ub**) could not be produced, while 2-substituted oxamic acids were also found to be incompatible (producing **10uc**). Unprotected oxamic acids were not suitable (producing **10ud**) however this, in principle, could be overcome by debenzylation of **10n**. Across the sample set, the photoredox-mediated reaction was either found to be comparable to the thermal reaction, or significantly outperform it. All things considered, we would deem the photoredox-mediated cascade sequence a superior strategy, particularly in the context of sustainable and energy efficient synthesis. The proposed mechanism of the reaction, using the model system as a representative example is shown in Scheme 2. Following visible-light excitation, and in accordance with previous literature,[14c,17] the excited state catalyst (^{3}**PC***) reduces the persulfate anion ($S_2O_8^{2-}$) to the sulfate radical anion ($SO_4^{\bullet-}$), generating its **PC**$^{+1}$ state. The highly oxidising $SO_4^{\bullet-}$ [19] then oxidises Ag^+ to the active Ag^{2+} species[16] that subsequently generates carbamoyl radical ***I1*** *via* radical decarboxylation of **7a**, with concomitant return to its Ag^+ state. It should be noted that stoichiometric $AgNO_3$ on its own did not promote the reaction (see the ESI†), supporting Ag^{2+} as the active oxidizing species.[16] Then, an addition–cyclisation sequence produces cyclohexadienyl radical anion ***I2***, which is transformed into dihydroquinolin-2-one **9a** following SET oxidation by **PC**$^{+1}$ and the loss of a proton, while returning the catalyst to its ground state (**PC**). This overall transformation affording **9a** is consistent with related literature reports.[10,20] Elimination toward product **10a** is envisaged to follow a similar pathway. Namely, radical decarboxylation of **9a** by Ag^{2+} to afford methine radical ***I3***, oxidation by **PC**$^{+1}$ to the benzylic tertiary carbocation and finally the loss of a proton. As for the thermal reaction, $SO_4^{\bullet-}$ (×2) is instead generated *via* thermolysis, following which the reaction mechanism proceeds as described. But, rather than SET oxidation by **PC**$^{+1}$ and loss of a proton to afford **9a** and **10a**, H-abstraction by the second $SO_4^{\bullet-}$ generated during thermolysis is proposed. Mechanistic studies supported the existence of carbamoyl radical ***I1*** as well as carboxylic acid **9a** as transient intermediates (Scheme 3).

Carrying out the reaction in the presence of TEMPO but without the acrylic acid (**8a**), produced TEMPO-carbamate **12a** in 64% yield; supporting the formation of carbamoyl radical ***I1*** (Scheme 3A). It should be noted that in the presence of the acrylic acid (**8a**), TEMPO adduct **12a** was obtained as the major product in 83% yield, together with a 16% yield of the quino-



Scheme 2 Proposed mechanism.



Scheme 3 Mechanistic studies.

lin-2-one product **10a**. Committing the independently synthesised quaternary 3,4-dihydroquinolin-2-one **9a** to the reaction conditions using 1.2 equiv. $K_2S_2O_8$ (accounting for only one decarboxylation) successfully afforded **10a** in 41% yield; demonstrating that **9a** is a likely intermediate in the reaction (Scheme 3B), while quaternary TEMPO intermediate—in support of methine radical ***I3***—could not be detected in the corresponding TEMPO trapping experiment. Instead, similar conversion to **10a** was observed.

Conclusions

In summary, we have developed a silver-catalysed addition–cyclisation–elimination cascade sequence for the synthesis of biologically relevant quinolin-2-ones, mediated either thermally or photochemically, and enabled by a double radical decarboxylation strategy. The reaction was applicable to a wide substrate scope and the photochemical conditions were found to be largely superior to the thermal reaction—particularly in the context of sustainability. Mechanistic studies such as TEMPO trapping experiments were used to support the proposed reaction mechanism presented. Inspired by the utility of carboxylic acids to serve as environmentally friendly and sustainable radical precursors, this work has demonstrated a formal and direct installation of an olefin moiety to an organic molecule, and it is hoped that this strategy will pioneer interesting advances in late-stage olefination chemistry.

Author contributions

All synthesis investigation work was carried out by C. M. M. Conceptualisation, supervision, validation, and writing of the manuscript was completed by W. F. P. Final approval was obtained from all authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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