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A Versatile and Fast Photocatalyzed Deoxygenation of Organic *N*-oxides with a Rhenium Complex in the Presence of H₂O

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ABSTRACT: The oxidation of *N*-heterocycles is key to their functionalization since it enhances their reactivity in the ortho position. However, an efficient post-reduction is often required to access the targeted compound. Here, a rhenium-based photocatalyst enables the versatile and fast deoxygenation of *N*-heterocyclic and alkyl *N*-oxides, avoiding sacrificial oxophilic reagents. The strong influence of the reaction conditions (solvent, H₂O as additive, irradiation set-up) is demonstrated. The system shows a high functional group tolerance towards other reducible functions (free alcohol, carboxylic acid, ester, nitrile, halogen,...) and light-sensitive *N*-heterocycles.

Found in DNA, vitamin B6, or the co-factor NADP, *N*-heterocycles are essential to life and ubiquitous in natural products, agrochemicals, and pharmaceutical compounds.¹⁻³ Their selective functionalization is thus critical to accessing useful and reactive compounds. A popular synthetic strategy to functionalize selectively *N*-heterocycles in the ortho position relies on their *N*-oxidation that strongly activates the ortho C–H bonds.⁴⁻¹⁰ However, subsequent deoxygenation is often required to access the targeted *N*-heterocycle.¹¹ Accordingly, thermal, electrochemical, and photochemical methods for reducing *N*-oxide compounds have been developed.¹² Most rely on using an excess of low-valent transition metals or strongly oxophilic reagents such as phosphine,¹³ borane,¹⁴ and silicon¹⁵⁻¹⁶ derivatives in the presence or absence of an organometallic catalyst.

Triggered by the photoactivity of *N*-heterocyclic *N*-oxides, UV irradiations were used for their deoxygenation in the 60s.¹⁷ However, highly energetic UV light irradiation also led to skeletal rearrangements and loss of selectivity. More recently, photocatalyzed *N*-oxide deoxygenations have been reported under visible light irradiation. They rely on photocatalysts that are supposed to perform single electron transfer to the *N*-oxides. Lee *et al.* described the deoxygenation of π -extended *N*-oxide derivatives using [Ru(bpy)₃]Cl₂ ($E_{1/2}^{III/I} = -1.09$ V vs. SHE)¹⁸⁻²⁰ and Na₂Eosin Y²¹ as photocatalysts in the presence of sacrificial electron and proton donors such as hydrazines¹⁸ or Hantzsch esters.¹⁹ Under these conditions, pyridine *N*-oxides with a stronger N–O bond could hardly be reduced, and the more reductive photocatalyst [Ir(ppy)₂(dtbbpy)](PF₆) ($E_{1/2}^{III/II} = -1.27$ V vs. SHE)²⁰ was employed.¹⁸⁻¹⁹ The same group recently disclosed a visible-light-induced Meerwein-Ponndorf-Verley reduction of quinoline *N*-oxides using a strongly oxidizing acridinium photocatalyst. Pyridine *N*-oxides were also reduced, albeit after prolonged reaction times.¹² Interestingly, Konev, Wangelin, *et al.* demonstrated that the photocatalyst was not required for deoxygenation when a Hantzsch ester was used as the electron donor, although the kinetics were slower. The authors suggested that an electron donor-acceptor complex formed in dichloromethane between the *N*-heterocyclic *N*-oxide and the Hantzsch ester was responsible for the observed reactivity.²²

In our search for a versatile photocatalytic system able to deoxygenate a wide range of nitrogen oxides, we recently discovered that photocatalysts of type [(bpy)Re(CO)₃Cl] (bpy=2,2'-bipyridine ligand) were efficiently reducing both N₂O ($E^0(\text{N}_2\text{O}/\text{N}_2) = +1.77$ V vs. SHE) and pyridine *N*-oxide (**2a**) ($E_{1/2}(\text{2a}/\text{pyridine}) = -1.04$ V vs. SHE) without the use for an oxophilic reagent.²³ In this proof-of-concept, the reaction occurred in the presence of Hünig's base (diisopropyl ethyl amine, DIPEA) as the electron and proton donor under white cool LEDs (8 W) irradiation, and the 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbbpy) complex **1** was the most efficient photocatalyst. However, our system suffered from several limitations, hampering its synthetic applicability. The reduction of electron-rich pyridine *N*-oxides required extended reaction times, e.g., 126 h for 4-(dimethylamino)pyridine 1-oxide (**2b**), with a high catalyst loading (5 mol%). Moreover, sensitive functional groups were not tolerated. The cleavage of the cyano group of *p*-cyanopyridine *N*-oxide (**2c**) was observed along with its deoxygenation, and light-sensitive products such as quinoline degraded.

Realizing that the limits of the catalytic system are primarily due to the slow reaction rate, we aimed to improve the catalytic efficiency. We thus focused on stabilizing the catalyst and optimizing key parameters in photocatalysis – photon and proton flux. Herein, we demonstrate that changing the photocatalytic set-up and adding H₂O dramatically affect the reaction rate and enable the fast deoxygenation of functionalized *N*-oxides with high tolerance towards coordinating or other reducible functional groups.

We first evaluated the addition of chloride ions (NEt₄Cl, 1 equiv.) in the reaction mixture since we had observed an increased photocatalytic activity in the reduction of N₂O.²³ The catalyst stability increased, but no significant reaction acceleration was observed in the case of pyridine *N*-oxide deoxygenation (TOF₀ = 6.2 h⁻¹ vs. 5.5 h⁻¹, see ESI section 2.1 for details).²⁴

We thus implemented a setup change.²⁵ A more powerful Kessil lamp (40 W, 440 nm) was used to increase the photon flux, instead of cool white LEDs (8 W). Using the previously optimized conditions ([*(dtbpy)Re(CO)₃Cl*] (**1**, 5 mol%) as a catalyst and DIPEA (5.7 equiv.) in acetonitrile), a significant increase in the catalytic activity was observed. Pyridine *N*-oxide (**2a**) was deoxygenated in 45 % yield after 30 minutes of irradiation (Figure 1, orange curve) *versus* 26 % with the original setup (Figure 1, purple curve).

We also envisaged that improving the proton transfers should favor the N–O bond cleavage. Inspired by previous work on CO₂ reduction,^{26–28} H₂O (3 M) was added to the reaction mixture. In that case, we observed that the reaction speed doubled to reach 85 % yield in pyridine (**2a**) after 30 min (Figure 1, green and orange curves).

With such a catalytic performance, we considered lowering the catalyst loading. Both 1 and 2 mol% catalyst loadings led to comparable initial rates (Figure 1, red and blue curves). However, with 1 mol% of photocatalyst **1**, the conversion reached a plateau of 79 % after 2.5 h. In contrast, full conversion and 87 % yield of pyridine (**2a**) were observed after 2.5 h when 2 mol% of [*(dtbpy)Re(CO)₃Cl*] (**1**) were used.

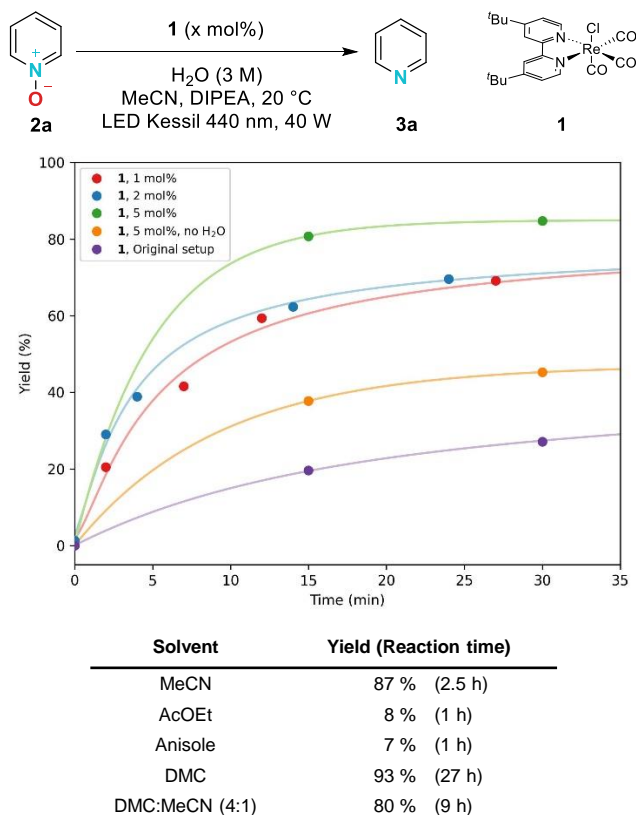
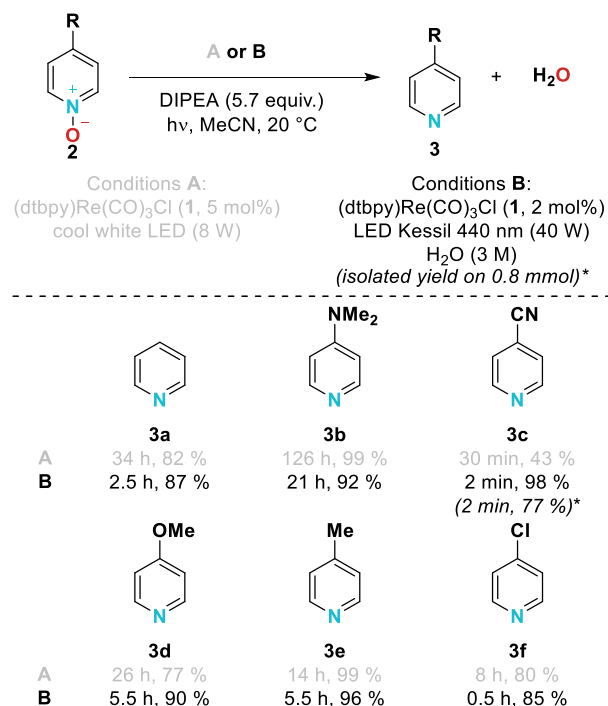


Figure 1. Optimization of the reaction parameters: addition of H₂O, catalyst loading, and influence of the solvent.

We probed whether more sustainable solvents than acetonitrile could also be used (Figure 1, bottom).²⁹ In ethyl acetate and anisole, only 8 and 7 % yield of pyridine were measured by ¹H NMR, after 1 h, respectively. In dimethylcarbonate, the reaction was also slow (18 % after 45 min) but proceeded to completion after 27 h (93 % yield). Interestingly, when a 4:1 DMC:MeCN mixture was used, catalytic activity was recovered and after 1 h of irradiation, 42 % of pyridine was formed (80 % after 9 h), hinting at the importance of the presence of a coordinating solvent for a high activity of the catalytic system. Acetonitrile was thus kept as the solvent of the reaction.

In MeCN, the newly optimized conditions –[*(dtbpy)Re(CO)₃Cl*] (**1**, 2 mol%), DIPEA (5.7 equiv.), H₂O (3 M) in MeCN upon irradiation at 440 nm – were tested on the scope previously described on a 0.1 mmol scale.²³ All *p*-substituted pyridine *N*-oxides **3a–f** were reduced in 85–98 % yields with shorter reaction times compared to the previous reaction conditions, as determined by ¹H NMR monitoring (Scheme 1). Up to a 16-fold reduction of the reaction time was possible depending on the substrate. Again, the more electron-rich the pyridine, the slower the reaction was. The complete conversion of 4-(dimethylamino)pyridine 1-oxide (**2b**) was observed in only 21 h, compared to the 126 h previously required. The deoxygenation of *p*-cyanopyridine *N*-oxide (**2c**) required 2 min, and the corresponding pyridine **3c** was obtained in 98 % yield. No significant degradation of the cyano substituent was observed, even on a preparative scale of 100 mg (0.8 mmol), and pyridine **3c** was isolated in 77 % yield.

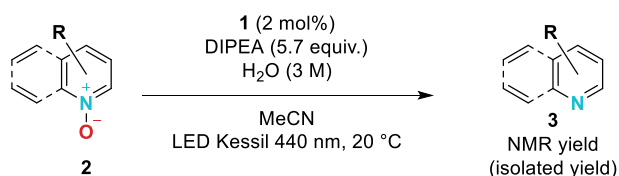


Scheme 1. Comparison of the previously described conditions (A)²³ and the new conditions (B) on the reaction outcome. Reactions were performed on a 0.1 mmol scale in *J. Young* NMR tubes. Yields determined by ¹H NMR (reference: mesitylene).

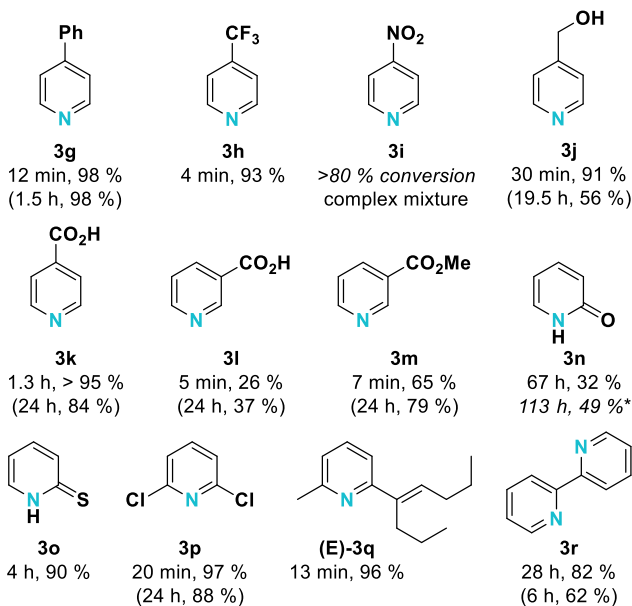
Owing to the higher efficiency of the reaction conditions, the reaction scope was evaluated on a large library of *N*-heterocycle *N*-oxides (Scheme 2). 4-Phenylpyridine (**3g**) was obtained in 98 % yield after 12 min of irradiation, although it is a light-sensitive compound. The electron-poor CF₃-substituted pyridine *N*-oxide **2h** was deoxygenated within 4 min in 93 % yield. The nitro derivative **2i** also reacted but led to a complex mixture, the nitro group being unselectively reduced under the reaction conditions. 4-Pyridyl carbinol *N*-oxide (**2j**) was deoxygenated in 91 % yield within 30 min, the labile primary alcohol remaining untouched. Isonicotinic acid *N*-oxide (**2k**) was completely converted into the corresponding pyridine **3k** in 1.3 h. However, with its *meta*-substituted isomer, the reaction stopped after 5 min, and nicotinic acid (**3l**) was obtained in a maximum yield of 26 %. Full conversion was recovered when using the corresponding methyl ester **2m**, giving methyl nicotinate (**3m**) in 65 % yield after 7 min. A similar behavior was observed with *N*-oxide **2n**, bearing an alcohol substituent in the 2-position (32 % yield after 67 h). Increasing the amount of catalyst to 4 mol % allowed the reaction to reach 49 % yield, after an extended reaction time of 113 h. For these specific substrates (**2m** and **2n**), we suppose that the reduced compounds are chelating the metal photocatalyst **1**, thus inhibiting the reaction. 2-Substituted pyridine *N*-oxides **2o** and **2p** gave the corresponding pyridines in 90 % and 97 % yields, respectively. When the *E/Z* mixture of *N*-oxide **2q** (97:3) was subjected to the reaction conditions, the isomer (*E*)-**2q** was reduced in 96 % yield after 13 min of irradiation, whereas the (*Z*)-isomer was unreactive under the same reaction conditions. This result was also observed with the previous system.²³ The slight difference in reactivity may come from the higher steric hindrance around the *N*-oxide in (*Z*)-**2q**, hinting at a necessary coordination of the substrate on Re-complex **1** during the catalytic cycle. Bipyridine *N,N'*-dioxide (**2r**) underwent deoxygenation in 85 % yield, albeit in an extended reaction time of 28 h, furnishing bipyridine (**3r**). The poor solubility of the oxide **2r** certainly explains the slower deoxygenation of this substrate compared to other pyridine derivatives.

Other *N*-heterocyclic derivatives were also reduced. Quinolines **3s-v** were obtained in 57–98 % within 4 min–1 h. The time of irradiation required to convert all the quinoline *N*-oxides was again strongly dependent on the electron-richness of the aromatic core. These results exemplify the efficiency of the new catalytic conditions, since the light-sensitive quinolines **3s-v** were degraded under our previous reaction conditions.²³ Quinoxaline *N,N'*-dioxide (**2x**) and *N*-oxide phthalazine (**2y**) were reduced within minutes in 70 % and 86 % yield, respectively, and phenazine (**3z**) was obtained in 80 % yield, albeit with a longer reaction time (3.5 h). Acridine *N*-oxide was however unreactive under the optimized conditions. A Stern-Volmer analysis showed that the rhenium photocatalyst **1** luminescence is quenched in the presence of acridine *N*-oxide, and the rate of excitation decay was measured as being about 10 times faster than with DIPEA (see ESI section 3.4 for more details).

The deoxygenation was successfully scaled up to 2.0 mmol (ca. 400 mg) in vials without any significant reaction conditions change. H₂O (3 M) was added by opening the vial to air, and the reaction mixture was irradiated without further precautions (see ESI section 4.4 for more details). Although contamination by air could occur, 14 deoxygenated *N*-heterocycles (**3c,g,j-m,p,r-s,u-x,z**) were isolated in moderate to excellent yields (30–98 %, Scheme 1 and Scheme 2). Small contaminations by oxygen were thus not deleterious to the reaction. Complete conversion was generally obtained under extended reaction times (2 min–24 h) compared to the 0.1 mmol scale. This phenomenon was ascribed to a decreased photon flux in 1 cm-diameter vials compared to NMR tubes: the light penetration has indeed been estimated at less than 2 mm.³⁰ The poorly-soluble bipyridine *N,N'*-dioxide (**2r**) reached faster full conversion in vial than in NMR tube (6 h vs. 21 h), certainly due to the active stirring which helped to solubilize the starting material. In contrast, the scale-up with phthalazine (**2y**) was ineffective: a gas evolution and complete degradation of the reaction mixture were observed.

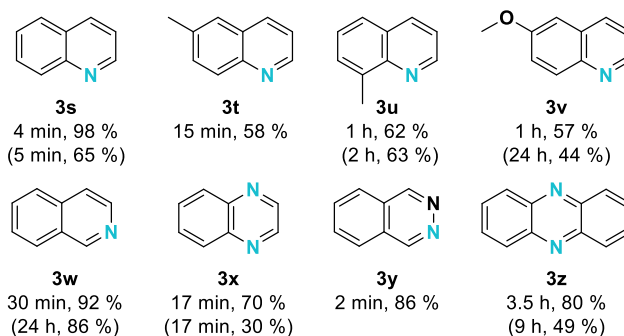


Scope of pyridine derivatives



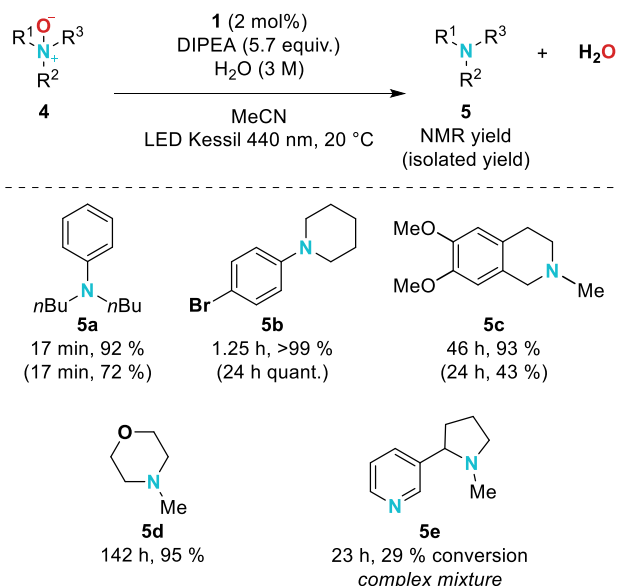
*4 mol% of catalyst **1** were used

Scope of π -extended aza-heterocycles



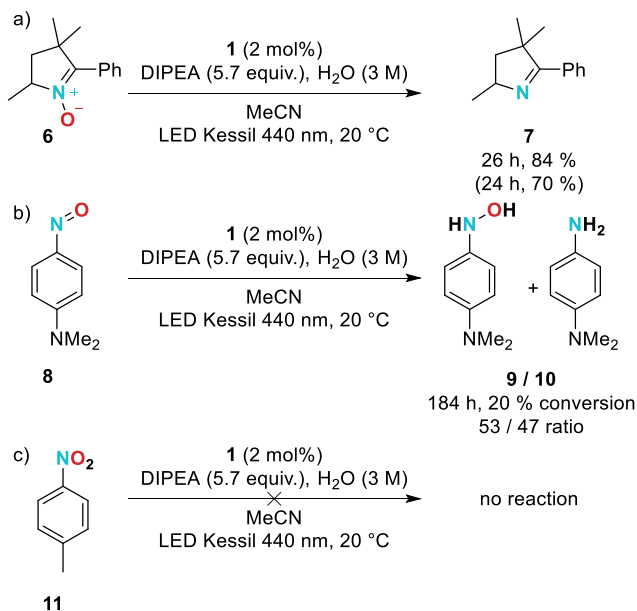
Scheme 2. Scope of the reaction with pyridines and π -extended aza-heterocycles. Reaction conditions for NMR yields: substrate (0.1 mmol), **1** (2 mol%), DIPEA (5.7 equiv.), H₂O (3 M), CD₃CN (0.5 mL). Yields were determined by ¹H NMR analysis of the crude reaction mixture (internal standard: mesitylene). Isolated yields were obtained on 0.2-0.8 mmol scales in vials. Reactive centers are highlighted in blue.

Aniline *N*-oxides were also deoxygenated under the same reaction conditions and products **5a** and **5b** were obtained in 92 % and quantitative yield, respectively. The deoxygenation of aliphatic amines was also effective, albeit required extended reaction times. Isoquinoline **4c** and *N*-methyl morpholine *N*-oxide (**4d**) yielded 93 % and 95 % of their respective reduced products, in 46 h and 142 h, respectively. In the case of nicotine *N,N'*-dioxide (**4e**), the deoxygenation seemed to be occurring preferentially on the pyridine ring first. However, a low conversion and a mixture of products were obtained after 23 h.



Scheme 3. Scope of amine derivatives. Reaction conditions for NMR yields: substrate (0.1 mmol), **1** (2 mol%), DIPEA (5.7 equiv.), H₂O (3 M), CD₃CN (0.5 mL). Yields were determined by ¹H NMR analysis of the crude reaction mixture (internal standard: mesitylene). Isolated yields were obtained on 0.2-2.0 mmol scales in vials.

We finally evaluated the applicability of this photocatalytic deoxygenation method to other *N*-oxide compounds. The nitron **6** achieved full conversion, although the reaction required 26 h to complete, and imine **7** was obtained in 84 % yield (70 % on preparative scale). With nitroso derivative **8**, a low conversion rate was observed, and an equimolar mixture of hydroxylaniline **9** and aniline **10** (53:47) was obtained after 184 hours of irradiation. Finally, the deoxygenation of nitroarene **11** proved ineffective (Scheme 4).



Scheme 4. Deoxygenation of other classes of *N*-oxide compounds. (Isolated yield)

The versatility of the photocatalytic system was thus demonstrated. Interestingly, pyridine *N*-oxides could be very efficiently converted without resorting to using Ir complexes such as in the system described by Lee *et al.*^{19, 21} Furthermore, alkylamines *N*-oxides are also reactive, hinting at a very different mode of activation compared to the systems described by Konev and Wangelin,²² and without resorting to strong reducing agents such as silanes as described by Lakhdar and Grimaud.¹⁵

The mechanism of this catalytic system remains to be determined, and this study raised several questions, as well as provided some observations that may be of interest. Namely, it seems that a coordination of some substrates on Re complex **1** is occurring, and the influence of steric hindrance hints at an inner rather than outer sphere electron transfer. Furthermore, the influence of the reaction medium will need investigating: the role of H₂O, probably in favoring proton transfers, and the importance of the presence of MeCN, possibly through the coordination on a rhenium-containing intermediate and stabilizing it.

In this study, we thus unveiled a robust and simple catalytic system that enables the deoxygenation of a large variety of *N*-oxide containing substrates. In the presence of H₂O as an additive, the reaction occurs rapidly, in less than 5 minutes in some cases, and does not require the use of sacrificial oxophilic reagents. Mechanistic studies are ongoing to shed light on the key transformation features.

ASSOCIATED CONTENT

Supporting Information. Detailed description of experimental methods and characterization of the compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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