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A (2-(Pyrrolidin-1-yl)ethan-1-olate)(1-oxo-3-phenyl-1,4-dihydronaphthalen-2-olate) μ-Oxo-Bridged Dicopper(II) Dimeric Complex

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Abstract: The reaction of 2-(1H-pyrrol-1-yl)ethanol with 3-hydroxyflavone in the presence of copper(II) bromide yielded a dimeric copper(II) complex, [μ-O-(κ²-*O*,*O*-flav)(κ²-*N*,*O*-2PEO)Cu]$_2$ (**1**) (flav = 3-hydroxyflavonolate; 2PEO = 2-(1H-pyrrol-1-yl)ethanolate) with both the flav and 2PEO ligands bound to the copper(II) atom in a κ²-bonding mode. The dimer is held electrostatically by bridging oxygen atoms between two copper atoms. Complex **1** was characterized by single-crystal X-ray diffraction, infrared, and UV-Vis spectroscopy, elemental analysis, and melting point determination. The complex crystallizes in the monoclinic space group $P2_1/n$ (14) with cell values of a = 11.85340(10) Å, b = 8.51480(10) Å, c = 23.8453(2) Å; β = 99.3920(10)°.

Keywords: amino alcoholate complexes; copper coordination compounds; dimeric complexes; 3-hydroxyflavone; 2-(1H-pyrrol-1-yl)ethanol

Citation: Artis, R.; Padgett, C.W.; Musso, K.; Shank, N.; Marks, A.; Quillian, B. A (2-(Pyrrolidin-1-yl)ethan-1-olate)(1-oxo-3-phenyl-1,4-dihydronaphthalen-2-olate) μ-Oxo-Bridged Dicopper(II) Dimeric Complex. *Molbank* **2024**, *2024*, M1846. https://doi.org/10.3390/M1846

Academic Editors: Nicholas Leadbeater and Kristof Van Hecke

Received: 17 May 2024
Revised: 24 June 2024
Accepted: 28 June 2024
Published: 5 July 2024

1. Introduction

Copper is an endogenous metal found in a plethora of enzymes [1]. One of the major functions of copper metalloenzymes is the binding and activation of molecular oxygen for biological functions such as oxidations of aryl groups, O_2 transport, generation of hydrogen peroxide, methane oxidations, and others [2]. A specialized field of chemistry has been established with the aim of preparing copper coordination compounds that serve as functional enzyme models to better understand relevant biological reactions and to harness these properties for practical oxidations of organic compounds [3–5]. For example, much interest has been garnered in the preparation of model copper coordination compounds of flavanol and/or quercetin 2,3-dioxygenase to understand the flavonoid oxidation mechanism [4,6–9], wherein depside and carbon monoxide are produced. In an effort to create a new genre of potential photonically driven carbon monoxide-releasing molecules (PhotoCORMS) [10,11], our group prepared flavonolate–copper complexes supported by tridentate ligands to examine the influence of the ligand on carbon monoxide release [4]. During this study, it was discovered that reactions of 3-hydroxyflavone with copper(II) bromide in the presence of alcohols (methanol, ethanol, and isopropanol) form chromane hemiacetals or geminal diols (hydrates) depending on reaction conditions (Figure 1A) [12]. The chromane hemiacetals were found to convert to chromane geminal diols with heating. To probe for a suspected 3,4-dione intermediate in this conversion [13,14], the hemiacetals were reacted with phenylenediamine derivatives to produce cyclic quinoxaline motifs that have been generically termed chromenoquinoxalines [15]. These molecules can be best described as fused chromane and quinoxaline systems (Figure 1B) [15]. The similarity of these molecules to steroids made them interesting molecular platforms to investigate and develop a new class of selective estrogen receptor modulators (SERMs)

and downregulators (SERDs) [16–18]. It was envisioned that preparing chromenoquinoxaline species with flanking substituted alkoxy groups at the acetal carbon could serve as a synthetic handle for further modification. We were particularly interested in flanking amines as they have been commonly incorporated into the structures of effective SERMs and SERDs [19]. Our attempts to replace the alkoxy group of the chromenoquinoxaline with amino alcohols (2-(1H-pyrrol-1-yl)ethanol and 2-(dimethylamino)ethan-1-ol) failed with available methods. An alternative route was envisaged, wherein the amino alcohols were introduced at the chromane hydrates or hemiacetals followed by subsequent reaction with phenylenediamine derivatives to form the desired chromenoquinoxaline. However, the reaction of 2-(1H-pyrrol-1-yl)ethanol with 3-hydroxyflavone in the presence of copper(II) bromide led to the isolation of an unusual copper(II) dimeric complex with both flavonolate and 2-(pyrrolidin-1-yl)ethan-1-olate attached in a κ^2 -bonding mode. To our knowledge, this is the first report of a dimeric amino alcoholate copper(II) complex bearing a flavonolate ligand [20,21].

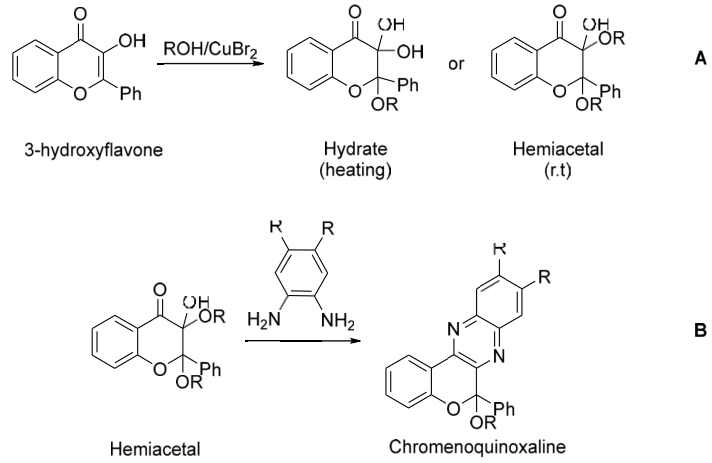

Figure 1. The reaction of 3-hydroxyflavone with alcohols in the presence of copper(II) bromide to produce chromane hydrates and hemiacetals (**A**). The reaction of chromane hemiacetals with *o*-phenylenediamine derivatives to produce chromenoquinoxalines (**B**).

2. Results and Discussion

To better understand the scope of 3-hydroxyflavone with substituted alcohols possessing electron-donating groups under oxidative conditions, 3-hydroxyflavone was reacted with 2-(1H-pyrrol-1-yl)ethanol in the presence of an equivalent of copper(II) bromide under neat conditions (Figure 2). The reaction was stirred for 10 days at room temperature to yield a viscous pale-green slurry. It had been previously discovered that long reaction times are required to oxidize 3-hydroxyflavone to the hemiacetal or geminal diol chromanes [12]. Notably, the reaction appeared significantly different in color from those previously performed in methanol, ethanol, and isopropanol, which produced dark, brownish-colored solutions. After filtering the solution from suspected copper coordination compounds and salts, a viscous clear mass was isolated in low yield. ^{1}H NMR analysis of the viscous residue revealed only starting materials. The insoluble solids trapped during the filtration process were extracted into chloroform. Slow evaporation of the solvent produced copious amounts of emerald-green plates and dark-bluish, block-like crystals with a metallic luster. The emerald-green crystals were ultimately determined to be a copper(II) dimeric complex with both 3-hydroxyflavonolate (flav) and 2-(pyrrolidin-1-yl)ethanoxide (2PEO = -O$(CH_2)_2$N$(CH_2CH_2)_2$) ligands attached in a κ^2-boding arrangement, [μ-O-(κ^2-*O*,*O*-flav)(κ^2-*N*,*O*-2PEO)Cu]$_2$ (**1**) (Figure 2). The dark-bluish crystals were determined to be the previously reported *bis*(flavonolate) copper(II) complex, (flav)$_2$Cu (**2**) [7,22].

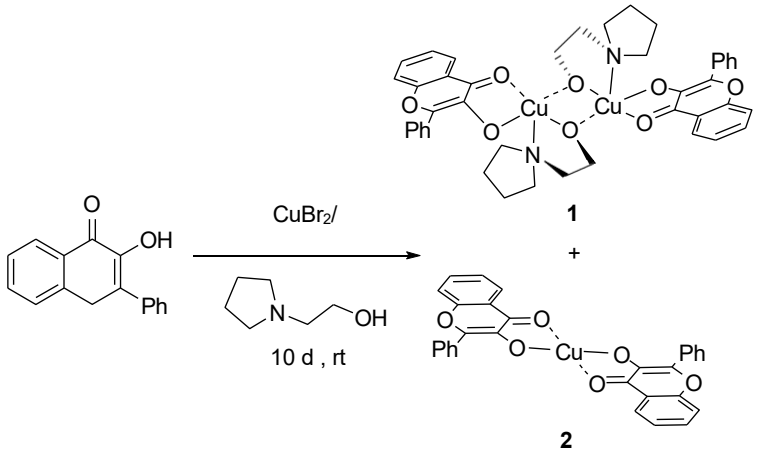

Figure 2. The reaction of 3-hydroxyflavone with 2-(1H-pyrrol-1-yl)ethanol in the presence of copper(II) bromide to produce compounds **1** and **2**.

2.1. X-ray Diffraction Studies of **1**

Compounds **1** and **2** were examined by single-crystal X-ray diffraction. Only the structural details of **1** are presented as **2** has been previously reported [22]. The structure of **1** is shown in Figure 3 along with structural data in Table 1. Of note, the 2POE ligand is highly disordered, caused by rocking of the pyrrole and ethyl groups of the 2POE ligand resulting in the exchange of spatial position. Only the major component of the disordered 2POE ligand is shown for clarity. The complex crystallizes in the monoclinic space group. Crystal data for $C_{44}H_{44}Cl_6Cu_2N_2O_8$ (MW: 1068.59): monoclinic, space group $P2_1/n$ (14) with cell values of a = 11.85340(10) Å, b = 8.51480(10), c = 23.8453(2) Å; β = 9.3920(10)°, V = 2374.43(4) Å^3, Z = 2, T = 297.1(3) K, μ(CuKα) = (λ = 1.54184 Å), Dcalc = 1.495 g/cm^3, 24710 reflections measured (7.516 ≤ 2Θ ≤ 136.498°), to 4351 unique (Rint = 0.0233, Rsigma = 0.0154) which were used in all calculations. The final R1 was 0.0382 (I > 2σ(I)) and wR2 was 0.1128 (all data). The structure of **1** reveals a dimeric Cu(II) complex mediated by bridging oxygen atoms of the 2PEO ligand to form a diamond-shaped $(Cu–O)_2$ four-membered core; a common feature observed with previously reported dimeric copper(II) amino alcoholate complexes [20], which are largely an electrostatic artifact [23]. To our knowledge, this is the first dimeric amino alcoholate copper complex bearing tandem flavonolate and 2PEO ligands. The environment around each copper atom in **1** is five-coordinate. Due to the highly distorted bonding geometry of the copper atoms in **1**, their geometric description was determined by calculating their τ_5 values using the method developed by Addison, which describes the "index of the degree of trigonality" [24]. A τ_5 value of 0.59 was calculated for compound **1**, placing its geometry slightly more relevant to highly distorted trigonal bipyramidal than square pyramidal. Five-coordinate copper dimeric complexes with distorted trigonal bipyramidal geometry supported by μ-oxo interactions are somewhat scarce, as they commonly lead to coordination polymers [20,25,26]. Previous reports of discrete dimeric copper(II) amino alcoholate complexes have been primarily four-coordinate square planar [23,27], five-coordinate square pyramidal [23], or six-coordinate octahedral geometries [23]. Notably, the geometry of the active site of quercetin 2,3-dioxygenase has been reported to have a distorted trigonal bipyramidal geometry [9]. The bridging oxygen atoms bring the copper atoms in **1** very close (2.971Å), but are well out of the range of a Cu–Cu bond distance since the interatomic distance of metallic copper atoms at 293 K is 2.556 Å. For comparison, the well-known hydrated copper(II) acetate species with a suspected Cu–Cu bond has a distance of 2.617 Å [28,29]. The Cu Cu separation distance in **1** is a bit shorter than that of the *oxo*-bridged copper complex supported by a multidentate Schiff base (3.0291 Å) [30] but similar to the five-coordinate distorted bipyramidal complex, $[Cu(deae)Cl_2]_2$, deae = 2-(diethyl-amino)ethanolato (2.931 Å) [26]. Liu and Song reported a coordination polymer with copper supported by 5-nitro-benzene-1,2,3-tricarboxylic acid

(O_2N-H_3btb) with bridging oxo groups (O_2N-H_3btb)$_2$Cu [31]. Unlike **1**, the coordination environment around each copper atom in (O_2N-H_3btb)$_2$Cu is closer to a distorted square pyramidal geometry instead of trigonal bipyramidal with a phenoxide group sitting at the apical position of the basal (Cu–O)$_2$ diamond plane. This geometry is likely preferred due to the inflexibility of the benzene core. The four-membered (Cu–O)$_2$ core of **1** has an O3–Cu1–O3 bond angle of 81.56(7)° and a Cu1–O3–Cu1 bond angle of 98.44(8)°. The C1–O3 bond distances of the (Cu-O)$_2$ core are slightly different (1.918(2) Å and 2.004(2) Å), which highlights the differing nature of the Cu-O bonds (dative- and σ-bonding). The C–O bonds in the (C–O)$_2$ ring in **1** compare well with complexes of similar structure [20,21,31]. The Cu–O bond distances of the flavonolate ligand are substantially different (Cu1–O1 = 1.918(2) Å and Cu1–O2 = 2.248(3) Å), relaying an aryloxide σ-bond and a dative carbonyl interaction. This is contrary to those for **2**, wherein the carbonyl interaction with the copper atom is substantially shorter (1.939(1) Å, reported 1.944(3) Å) [22].

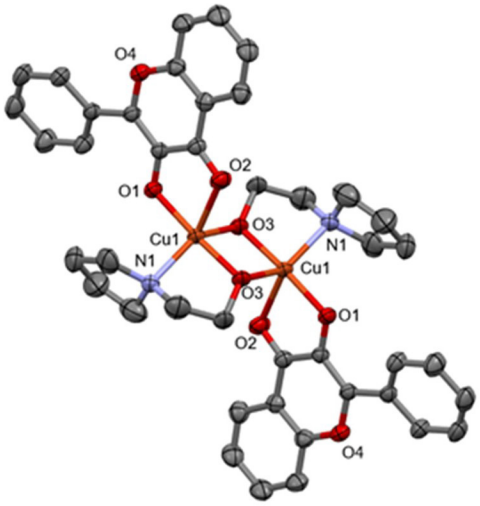

Figure 3. Single crystal X-ray structure of [μ-O-(κ²-*O*,*O*-flav)(κ²-*N*,*O*-2PEO)Cu]$_2$ (**1**). Thermal ellipsoids are drawn at 30% probability. Hydrogen atoms on the carbon atoms have been deleted and only the major component of the disordered 2POE ligand is shown for clarity.

Table 1. Geometrical parameters (Å, °) for **1** at the copper center for major conformer.

Bonds	Distances	Atoms	Angles
Cu1⋯ Cu1	2.971	Cu–O3–Cu1	98.44(8)
Cu1–O1	1.918(2)	O1–Cu1–O2	79.91(7)
Cu1–O2	2.247(2)	O1–Cu1–O3	175.51(8)
Cu1–O3	1.918(2)	O1–Cu1–O3	98.73(7)
Cu1–O3	2.004(2)	O1–Cu1–N1	96.8(2)
Cu1–N1	2.073(7)	O2–Cu1–O3	98.00(7)
O1–C2	1.313(3)	O2–Cu1–N1	117.6(1)
O2–C3	1.249(3)	O3–Cu1–N1	85.5(2)
		O3–Cu1–O3	81.56(7)
		N1–Cu1–O3	143.1(2)

2.2. Spectroscopy of **1**

The infrared spectrum of compound **1** shows strong stretches at 2841 and 2960 cm^{-1} that represent sp^3 hybridized C-H bonds of the 2PEO ligand and a strong ν(C=O) stretch for the carbonyl group (1556 cm^{-1}) of the flav ligand that is shifted to lower energy as compared to the free ligand (1602 cm^{-1}), suggesting the carbonyl in **1** has significantly reduced C=O

π-bonding due to both conjugation and electron-donation to the copper center [32]. The ν(C=O) stretch is quite similar to other metal-flavonolate complexes [32–34]. There are also weaker shoulder stretches at 1586 cm^{-1} and 1609 cm^{-1} that might suggest the carbonyl group is somewhat labile. For comparison purposes, ν(C=O) stretches for **2** are very weak, appearing as two weak, thin, sharp stretches at 1615 and 1571 cm^{-1} [22], further suggesting the flavonolate ligand in **1** is not bound as strongly as it is in **2**. The carbonyls in **2** likely have significant delocalization with very little π-bonding. The C-N stretch in **1** appears at 1409 cm^{-1}, while the C-O stretch occurs at 1210 cm^{-1}.

The UV-Vis spectroscopy of compound **1** displays a strong intraligand π-π* transition band for the coordinated flav ligand at 428 nm (log ϵ = 4.62) along with a shoulder band at 403 nm (log ϵ = 4.57). The moderate absorption at 332 nm (log ϵ = 4.33) is likely attributed to ligand-to-metal charge transfer [35,36]. Intense absorptions also occur at 260 nm (log ϵ = 4.62) with a shoulder at 274 nm (sh, log ϵ = 4.45). A very weak energy band occurs at 674 nm (log ϵ = 1.79), characteristic of a d-d transition band at the copper center. Performing variable temperature UV-Vis spectroscopy on the complex reveals very little difference in the majority of the absorptions in the spectrum; however, a peak at 240 nm intensifies with ramping of temperature (55 °C max) and weakens when chilled (5 °C lowest). This falls in the range of the cutoff of chloroform (245 nm) [37] and suggests the complex interacts with the solvent at different temperatures (see Supporting Information). Notably, the UV-Vis spectrum of **1** is nearly identical to **2**, indicating the flav ligand is largely responsible for the observed absorptions.

3. Materials and Methods

3.1. General

All chemicals were purchased from commercial sources and used as received unless otherwise noted. Single crystal X-ray diffraction measurements were performed on a Rigaku XtaLab Synergy-i diffractometer equipped with a Cu micro-focused source at 1.5418 Å and a HyPix Bantam detector. Infrared spectra were recorded on a Perkin Elmer Spectrum-100 FTIR using ATR methods. Melting point determinations were recorded on a Reach Device RD-MP digital melting point apparatus. Thermal UV-Vis Analysis: All spectra were taken on a Cary 100 UV-Vis double-beam instrument with a multicell-changer. Stock solutions of the complexes were diluted in chloroform to give an absorbance of ~0.2 at 450 nm at room temperature. During heating, the Teflon tops of the cuvettes were taped closed, and the temperature was monitored in a dedicated, specialty cuvette in the cell changer. At temperatures below 15 °C, the cell changer was flushed with a stream of nitrogen gas to prevent condensation on the cuvettes. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, GA, USA.

3.2. Synthesis of **1** *[μ-O-(κ²-O,O-flav)(κ²-N,O-2PEO)Cu]₂*

3-Hydroxyflavone (2.00 g, 8.48 mmol) and copper(II) bromide (2.01 g, 9.33 mmol) were added to a 100 mL round bottom flask equipped with a magnetic stir bar. 2-(1H-pyrrol-1-yl)ethanol (10 mL, 84.93 mmol) was added to the flask. The reaction was stirred for 10 days at room temperature to yield a pale-green slurry. The slurry was filtered over Celite and washed with diethyl ether. The ether was collected and discarded. The green solid was then washed with THF and the filtrate was discarded. The green filter cake was washed with chloroform to elute a brownish-green filtrate. The filtrate was collected and extracted twice with a solution of 6M potassium carbonate. The chloroform solution was collected and dried with magnesium sulfate. The solution was filtered again to collect a green solution. The solution was left to evaporate in a fume hood overnight to reveal numerous crystals of different colors (green, bluish-yellow, and yellow). The crystals were then dissolved in chloroform and passed through a column of Celite. The green solution was collected. A dark material was trapped on the frit, which was washed through with dichloromethane to provide a brownish-yellow solution. Both the green and brownish-yellow solutions were allowed to evaporate at room temperature. The brownish-yellow solution produced the

previously published *bis*(flavonolate)copper(II) complex (**2**)(0.5684 g, 25%), while the green solution produced large emerald-green crystals of the title compound (**1**) (1.667 g, 47%). mp 162 °C dec. IR (ATR, cm^{-1}) $\tilde{\upsilon}$: 3350 (br, w, residual water), 2960 and 2841 (m, C-H aliphatic), (1556(s), 1586(m), and 1609 (w)) C=O, 1210 (C-O). UV-Vis (CH_2Cl_2), λ_{max}, nm: (log ϵ): 260 (4.62), 274 (sh, 4.45), 332 (4.33), 403 (sh, 4.57), 428 (4.62), 674 (1.79). Anal. Calc'd for **1** ($C_{42}H_{46}Cu_2N_2O_8$) Theo.(Found): C 60.49 (60.58); H 5.56 (5.10), N 3.36 (3.21).

4. Conclusions

We have prepared the first dimeric dicopper(II) complex supported by flavonolate and 2-(pyrrolidin-1-yl)ethanoxide ligands. In addition, this complex represents the first amino alcoholate bearing a pyrrole group. The initial aim of this study was to determine the influence of electron-donating groups on alcohols in the oxidation of 3-hydroxyflavone in the presence of $CuBr_2$ with the ultimate goal of preparing chromane hemiacetals and/or geminal alcohols. In the case of amino alcohols, it appears that the formation of stable copper complexes is more favorable than oxidizing the flavone to the desired species. This is likely due to favorable interactions between the highly basic amine and Lewis acidic copper atoms. To form the desired oxidized chromanes using amino alcohols will likely require a non-metallic oxidative reagent.

Supplementary Materials: The following supporting information can be downloaded, Figure S1: Variable UV-Vis spectrum of compound **1** as a function of temperature in $CHCl_3$, Figure S2. Infrared spectrum of compound **1** (ATR), Figure S3. Variable temperature UV-Vis spectrum of compound **2** as a function of temperature in $CHCl_3$. Figure S4. Infrared spectrum of compound **2** (ATR), Table S1. Crystal data and structure refinement for compound **1**. Table S2. Fractional atomic coordinates (×104) and equivalent isotropic displacement parameters (Å2 × 103) for compound **1**. Ueq is defined as 1/3 of the trace of the orthogonalized UIJ tensor. Table S3. Anisotropic displacement parameters (Å2 × 103) for compound **1**. The anisotropic displacement factor exponent takes the form: 2π2[h2a*2U11 + 2hka*b*U12 + . . .] for compound **1**, Table S4. Bond lengths for compound **1**. Table S5. Bond angles for compound **1**. Table S6. Torsion angles for compound **1**. Table S7. Hydrogen atom coordinates (Å × 104) and isotropic displacement parameters (Å2 × 103) for compound **1**. Table S8. Atomic occupancy for compound **1**.

Author Contributions: Conceptualization, B.Q., R.A.; methodology B.Q., R.A.; formal analysis, B.Q., K.M., C.W.P., N.S. and A.M.; investigation, B.Q.; data curation, B.Q., K.M., C.W.P., N.S. and A.M.; writing—original draft preparation, B.Q.; writing—review and editing, B.Q., R.A., A.M., N.S. and K.M.; visualization, B.Q.; supervision, B.Q.; project administration, B.Q.; funding acquisition, B.Q., R.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Science Foundation Major Research Instrumentation fund, NSF-MRI 2215812 and 2018774. R.A. thanks the H. Gordon Mayfield Summer Research Scholarship, Georgia Southern University Council on Undergraduate Research Council, and Honors program for partial support of this work.

Data Availability Statement: The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author/s. Final atomic coordinates, geometrical parameters, and crystallographic data have been deposited to the Cambridge Crystallographic Data Centre, 11 Union Road, Cambridge, CB2 1EZ, UK (https://www.ccdc.cam.ac.uk/structures/) and are available on request quoting the deposition number CCDC 2355478.

Acknowledgments: B.Q. acknowledges the National Science Foundation; Major Research Instrumentation funds (NSF-MRI 2215812 and 2018774) for SCXRD and HRMS analyses. R.A. thanks the Georgia Southern University Council on Undergraduate Research (COUR) and the Fleming D. Roach, MD Scholarship.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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