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Synthesis of Symmetrical Monocarbonyl Analogs of Curcumin (MACs) Containing 2-Bromobenzylidene Moiety and Spectrophotometric Assessment of Their Reactivity with 2-(Dimethylamino)ethanthiol †

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Abstract: The cross-conjugated dienones containing the 1,5-diaryl-3-oxo-1,4-pentadienyl pharmacophore have diverse biological activities. These sometimes called monocarbonyl analogs of curcumin (MACs) have especially pronounced biological activity when containing electron-withdrawing group at the ortho position of the benzene ring. Their biological activity most likely stems from selective Michael reaction with thiols. It has been reported in the literature that in vitro certain MACs (in particular, **EF24**) react as electrophiles with glutathione and form bis adducts. Five MACs were prepared ((*2E*,*5E*)-2,5-bis(2-bromobenzylidene)cyclopentanone, (**2BrCP**), (*2E*,*6E*)-2,6-bis(2-bromobenzylidene)cyclohexanone (**2BrCX, B2BrBC**), 4-*tert*-butyl-(*2E*,*6E*)-2,6-bis(2-bromobenzylidene)-cyclohexanone (**4tB2BrCX**), (*3E*,*5E*)-3,5-bis(2-bromobenzylidene)-4-piperidone, (**2Br4PIP**), and (*3E*,*5E*)-3,5-bis(2-fluorobenzylidene)-4-piperidone, **EF24**), purified and characterized by spectroscopic means. The relative reactivity of these MACs towards 2-(dimethylamino)ethanethiol was assessed via previously developed UV-Vis spectroscopic method and compared to **EF24**, which reacts readily in solution with thiols such as glutathione and cysteamine. All of the bis(2-bromobenzylidene) MACs, react slower with 2-(dimethylamino)ethanethiol in 80:20 (v/v) acetonitrile/water compared to **EF24**. The relative reactivity of the analogs with 2-(dimethylamino)ethanethiol was **EF24** > **2Br4PIP** > **2BrCX** > **2BrCP**> **4tB2BrCX**.

Keywords: monocarbonyl analogs of curcumin; symmetrical 2-bromobenzylidene MACs; synthesis; 2-(dimethylamino)ethanethiol; Michael reaction with thiols; UV-Vis spectroscopy

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1. Introduction

It is well established that compounds containing the 1,5-diaryl-3-oxo-1,4-pentadienyl pharmacophore have pronounced biological activity(ies) [1–5]. These cross-conjugated dienones are cytotoxic/antiproliferative to tumor cells and they also exhibit anti-inflammatory, antimicrobial and antiparasitic activity [3]. They target the ubiquitin-proteasome system (UPS), which is known to be crucial for the viability of tumor cells, and are involved in the inhibition of deubiquitinases (DUBs). The Ar-CH=CH-CO-CH=CH-Ar moiety usually contains molecular scaffolds such as cycloalkanes, tetrahydropyrans, tetrahydrothiopyrans, piperidines, *N*-alkylpiperidines and *N*-acylpiperidines (Figure 1). One of the common features of the biologically active dienones

is the presence of electron-withdrawing substituent in the benzene ring, especially in the ortho position. In the literature these dienones are referred to C5-curcuminoids [6] or monocarbonyl analogs of curcumin (MACs) and they have been extensively studied from different aspects [7–13].

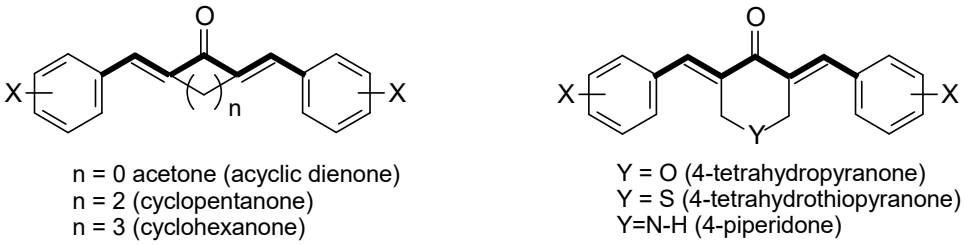

Figure 1. General structure of biologically active compounds containing the 1,5-diaryl-3-oxo-1,4-pentadienyl pharmacophore.

The biological activity according to Dimmock and co-workers [1,14] stems from the electrophilicity of their selectivity towards thiols. The reactivity of these Michael acceptors should, to a first approximation, depend on the electrophilicity, which in turn can be tuned by the substituents on the benzene ring. Indeed, it has been shown in vitro that certain compounds EF24, EF31, EF25 and GO-Y030 react with glutathione and form bis adducts. MACs have especially pronounced biological activity when containing electron-withdrawing group at the ortho position of the benzene ring. Several derivatives, namely EF24 [15,16], C66 ((2*E*,6*E*)-2,6-bis[2-(trifluoromethyl)benzylidene]cyclohexanone) [17–20], Y20 ((2*E*,6*E*)-2-(2-bromobenzylidene)-6-(2-(trifluoromethyl)benzylidene)cyclohexanone) [21], B2BrBC ((2*E*,6*E*)-2,6-bis(2-bromobenzylidene)cyclohexanone) [22–25] have been extensively studied. Care needs to be taken when evaluating the properties and activities of these analogs because similarly to curcumin [26], many of these cross-conjugated derivatives are pan-assay interference compounds (PAINS) [3,27].

In the past several years our research efforts have been focused on synthesis, experimental and theoretical studies of these *ortho*-substituted analogs [20,24,25,28,29]. We have established that symmetricial bis 2-fluorobenzylidene, 2-(trifluoromethyl)benzylidene and bis 2-bromobenzylidene derivatives are quite potent. Additionally, we were inspired by the study of Fioravanti et al. where they have discovered that cyclic bis-(2-bromobenzylidene) compounds behaved as dual p300/CARM1 inhibitors and induced apoptosis in cancer cells [23]. Recently, we have developed a spectrophotometric assay for comparison of the reactivity of MACs towards thiol and instead of commonly used cysteamine we employed 2-(dimethylamono)ethanethiol (2DMAESH) [25].

Herein we present the preparation of symmetrical MACs containing 2-bromobenzylidene moiety (Figure 2) and spectrophotometric assessment of their reactivity towards 2DMAESH. Emphasis will be placed on the synthesis and characterization of 4-*tert*-butyl-(2*E*,6*E*)-2,6-bis(2-bromobenzylidene)-cyclohexanone (**4tB2BrCX**), since the 4-*tert*-butylcyclohexanone analogs of curcumin are scarce in the literature.

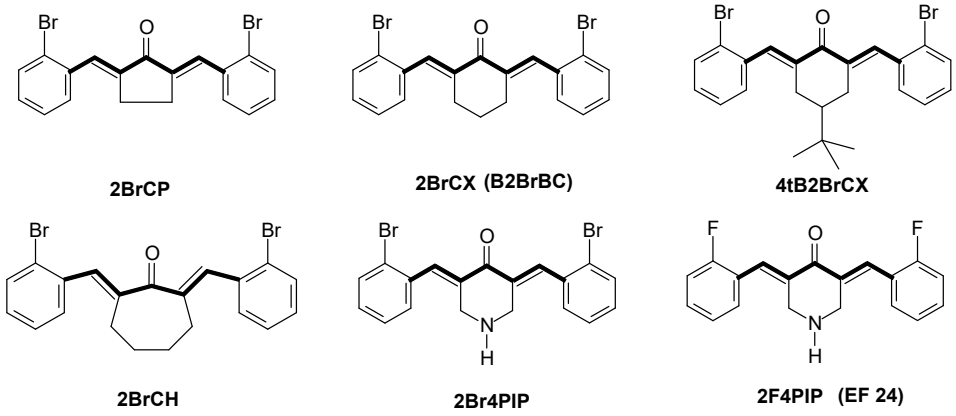

Figure 2. Structures of symmetrical MACs containing 2-bromobenzylidene moiety and EF24.

2. Materials and Methods

2.1. General

All of the reagents and solvents were of analytical and HPLC grade, obtained from Sigma Aldrich (2-bromobenzaldehyde, cyclopentanone, cyclohexanone, 2-(dimethylamino)-ethanethiol hydrochloride), Merck (ethyl acetate, hexane, methanol, acetonitrile (HPLC grade)), Alfa Aesar (4-piperidone hydrochloride monohydrate) and from Alkaloid AD Skopje (96% ethanol, methylene chloride, sodium hydroxide). All the chemicals were used without further purification. The melting-point measurements were performed by a Mel-Temp II capillary apparatus (Us Lab. devices) and were uncorrected. Infrared spectra were recorded with the ATR (attenuated total reflection) technique using Cary 630 FTIR spectrometer with diamond system. UV spectra were recorded in acetonitrile along with UV kinetic measurements performed on a Varian Cary 50 Scan UV–Vis spectrophotometer. TLC analysis was carried out using silica plates with 10:1 dichloromethane/ethyl acetate (for the 4-piperidone analogues) and 8:1 hexane/ethyl acetate (for the rest MACs) as mobile phases and subsequently R_f values were calculated. The synthesis of analogs **2BrCP**, **2BrCX**, **2Br4PIP**, **EF24**, have been previously reported in the literature [22,24,28]. A sample of (2E,7E)-2,7-bis(2-bromobenzylidene)cycloheptanone **2BrCH(ep),** was obtained from a collaborator's lab and its purity was checked by TLC and GC-MS.

2.2. Preparation of 4tB2BrCX

The analog was prepared using a previously reported procedure [24,28] with minor modifications. A total of 7.5 mmol of 4-tert-butylcyclohexanone (7.5 mmol) was mixed with 2 equivalents of 2-bromobenzaldehyde (15 mmol), in a round-bottom flask. After adding 10 mL of methanol, the reaction mixture was stirred for 5 min at room temperature, with an electromagnetic stirrer, followed by the dropwise addition of 20% (*w*/*v*) aqueous NaOH solution (2.5 mL) over 10 min period. While adding the base, the mixture acquired a yellow color and after a few minutes, a yellow precipitate was obtained. The reaction mixture was then vigorously stirred well at ambient temperature, for 5 h. Then, the reaction mixture was cooled in an ice-bath for about 10 min, followed by the vacuum filtration on a Büchner funnel. The yellow precipitates were washed with distilled H_2O and ice-cold methanol. After drying, the obtained solid was purified by recrystallization from 7:3 methanol/dichloromethane.

(2*E*,6*E*)-4-*tert*-butyl-2,6-bis(2-bromobenzylidene)cyclohexanone (4tB2BrCX): rec. from 7:3 CH_3OH/CH_2Cl_2. Yield (2.708 g, 74%). Mp 159–161 °C. R_f (8:1 hexane/ethyl acetate) = 0.28. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 2.7 Hz, 2H), 7.65 (dd, *J* = 8.0, 0.9 Hz, 2H), 7.37–7.29 (m, 4H), 7.23–7.17 (m, 2H), 2.94 (dd, *J* = 14.9, 2.7 Hz, 2H), 2.38–2.19 (m, 2H), 1.52 (tt, *J* = 12.5, 3.2 Hz, 1H), 0.85 (s, 9H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.05 (C=O), 137.60 (C),

136.56 (CH), 136.49 (C), 133.22 (CH), 130.47 (CH), 129.87 (CH), 127.14 (CH), 125.26 (C), 44.59 (CH), 32.84 (C), 29.47 (CH_2), 27.33 (CH_3). **FT-IR** (KBr): 1661 cm^{-1} (C=O); **UV-Vis**: λ_{max} (CH_3CN) = 312 nm (ε = 23,577 $L \cdot mol^{-1} \cdot cm^{-1}$), 235 nm (ε = 14,274 $L \cdot mol^{-1} \cdot cm^{-1}$); **GC-MS**, t_R = 23.176 min; **EI-MS** (*m*/*z*, rel. intensity): M^+ + 4 (490, 0.23%), M^+ + 2 (488, 0.48%), M^+ (486, 0.23%), 410 (28%), 409 (100%), 408 (28%), M^+-Br (407, 100%), 271 (20%), 269(8.8%), 165 (7.8%), 128 (10.1%), 115(22.8%), 57 (10.7%)

2.3. UV/Vis Kinetic Thiol Assay

The thiol assay was performed by slight modification of the original literature [25]. Quartz cuvettes were used with path length of 1 cm, supplied with caps used to cover the reaction mixture during the measurements. As a solvent system 80:20 *v*/*v* acetonitrile/water mixture was used. All measurements were done at ambient temperature (25 °C).

To perform the assay, 0.4 mg/mL stock solutions of MACs in acetonitrile were prepared. Just prior to measurements 2.5 mg/mL thiol (2-(dimethylamino)ethanethiol hydrochloride—2DMAESH) solution was prepared in the 80:20 *v*/*v* acetonitrile/water mixture. Then, 3 mL of the thiol solution were added in the cuvette, combined with 100–200 μL of MACs stock solutions and the reaction mixture was thoroughly mixed. The kinetic measurement started immediately afterwards. Absorption spectra were recorded from 200 to 600 nm using an UV−Vis spectrophotometer for a span of 120 min at different 2, 5, 15 and 30 min intervals (12 data points were collected in the 2 h time interval) and the absorbance drop at maximum absorption wavelength was monitored for each of the MACs. The raw maximum absorbance data were corrected vs. blank (80:20 *v*/*v* acetonitrile/water mixture) to correct for the absorbance of the thiol alone.

3. Results and Discussion

3.1. Chemistry

The MACs presented herein were prepared using literature procedures via Claisen-Schmidt reaction (crossed-aldol reaction). We have taken special precaution about the purity of the compounds and have developed gas-chromatographic mass spectrometric (GC-MS) method for assessment of their purity. Care needs to be taken to protect the samples from light during storage and especially in solution because these compounds are prone to *E*/*Z* isomerization. **4tB2BrCX** was prepared in 74% yield and its structure was established by spectroscopic means. From IR spectrum the peak bellow 1670 cm^{-1} indicate conjugated carbonyl group, which is also supported by the UV-vis spectral data (λ_{max} = 312 nm). The presence of two bromine atoms can be deduced from the isotope pattern in the MS spectrum. The key data comes from the ^{1}H NMR where the *tert*-butyl group corresponds to the singlet at 0.85 ppm and in ^{13}C NMR it is the intense peak at 27.33 ppm. The rest of the peaks in the NMR spectra are in agreement with the proposed structure.

3.2. Spectrophotometric Study

All analogs show an intense long-wavelength absorption band (LAB) (λ_{max} from 282 nm for **2BrCH** to 341 nm for the cyclopentanone derivative, **2BrCP**) and one more band at shorter wavelengths. The LABs can be assigned to n − π* type transitions while the shorter-wavelength bands correspond to π − π* type transition (from λ_{max} from 235 nm to 242 nm). The key data is provided in Table 1 and the UV-Vis spectra of all pertinent analogs are depicted in Figure 3.

Table 1. Melting points and key spectroscopic/chromatographic data of the synthesized symmetrical monocarbonyl analogs of curcumin (MACs).

Comp.	mp (°C)	FT-IR (cm^{-1})	UV-VIS λ_{max1} (nm)	UV-VIS λ_{max2} (nm)	GC-MS t_R (min)	EI-MS (*m*/*z*)

2BrCP	165–166	1693 (C=O)	341	242 nm	22.702	$M^+ + 4$ (420), $M^+ + 2$ (418), M^+ (416)
2BrCX	131–133	1662 (C=O)	312 nm	237 nm	21.206	$M^+ + 4$ (434), $M^+ + 2$ (432), M^+ (430)
4tB2BrCX	159–161	1670 (C=O)	312 nm	236 nm	23.176	$M^+ + 4$ (490), $M^+ + 2$ (488), M^+ (486)
2BrCH	109–112	1664 (C=O)	282 nm	235 nm	21.437	$M^+ + 4$ (448), $M^+ + 2$ (446), M^+ (444)
2Br4PIP	162–163	1669 (C=O)	313 nm	240 nm	24.775	$M^+ + 4$ (435), $M^+ + 2$ (433), M^+ (431)+
EF 24	134–136	1660 (C=O)	317 nm	229 nm	24.316	M^+ (311)

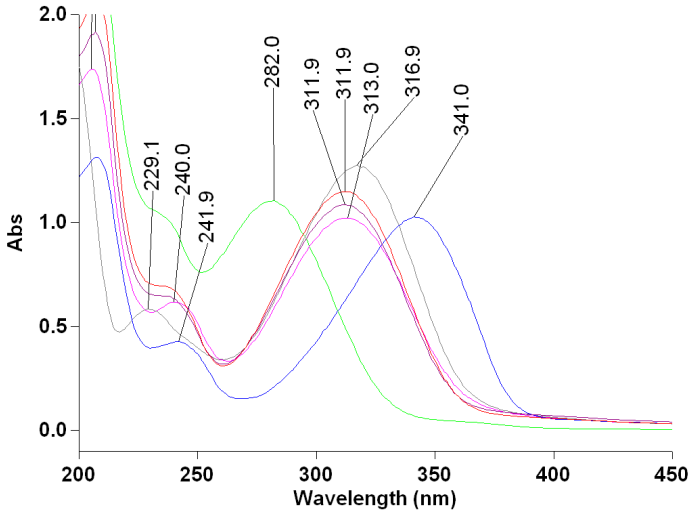

Figure 3. UV-Vis spectra in acetonitrile of symmetrical 2-bromobenzylidene MACs. 2BrCP (blue trace) 2-BrCX (violet trace), 4tB2BrCX (red), 2BrCH(ep) (green trace), 2-Br4PIP (pink trace), 2-F4PIP (EF24, gray trace).

Based on our experience most cysteamine is not ideal for assays investigating electrophilicity of MACs because it has a reactive nucleophilic primary amine that can react in a 1,2-fashion with the ketone to give 1,4-thiazepines [25]. Since MACs have two electrophilic sites, this intermediate can affect the addition of of the second equivalent of thiol. We have decided to eliminate the addition of the EDTA (for prevention of oxidation of thiol) and focus on short assays of 3 h with freshly prepared solution of 2DMAESH. This turned out not to affect the results and one can use relatively concentrated solutions (2.5 mg/mL, 0.0174 M) i.e., 400 fold excess compared to concentration of MAC, and have a spectral window from 290 nm–800 nm. Unfortunatelly, we were not able to carry out this thiol assay with (2*E*,7*E*)-2,7-bis(2-bromobenzylidene)cycloheptanone **2BrCH(ep)**, because its LAB was at 282 nm (Figures 3, S2a and S1b).

The "proven" analog **EF24** reacted the fastest of all of the compounds. It is known that **EF24** reacts reversibly with glutathione in vitro [30] and it is reasonable to use it for comparison purposes (Figure 4a). Based on the time-dependent decrease at the λ_{max}, the next most reactive compound was the other 4-piperidone derivative **2Br4PIP** (Figure 4c). The next compound based on reactivity was **2BrCX**, followed by **2BrCP**; the least reactive was the *tert*-butyl cyclohexanone derivative **4tB2BrCX** which within 3 h window had noticable change (Figure S2b). These processes may have complex kinetics which will be explored in detail by our group in the next period. To a first approximation the *ortho*-

bromo substituents influence the electrophilicity of MACs and this case the 4-piperidone derivative (**2-Br4PIP**) is the most reactive of the the 2-bromobenzylidene analogs.

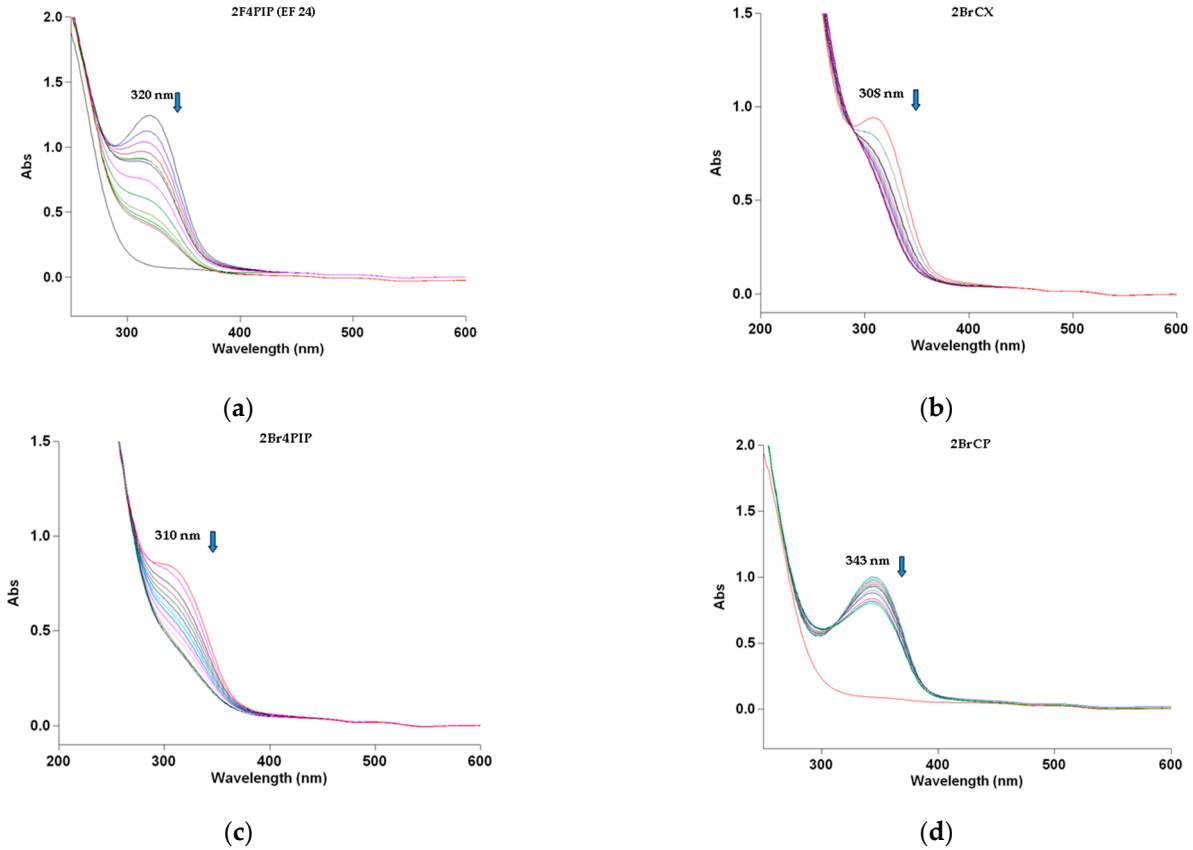

Figure 4. UV-VIS spectra of MACs added to 2-(dimethylamino)ethanethiol (2.5 mg/mL) in 80:20 acetonitrile/H_2O (0 to 150 min: red trace in (**d**) is just from a solution of 2-(dimethylamino) ethanethiol (2.5 mg/mL)).The top trace from corresponds to 0 min. The rest correspond consecutively to reaction times of 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, 45 min, 60 min, 90 min and 120 min: (**a**) Monitoring reaction between EF24 and 2DMAESH; (**b**) Monitoring reaction between 2BrCX and 2DMAESH; (**c**) Monitoring reaction between 2BrPIP and 2DMAESH; (**d**) Monitoring reaction between 2BrCP and 2DMAESH.

4. Conclusions

A series of MACs containing 2-bromobenzylidene moiety and (*3E,5E*)-3,5-bis(2-fluorobenzylidene)-4-piperidone (**EF 24**) were prepared and carefully purified. A previously reported thiol assay method using 2-(dimethylamino)ethanethiol, (2DMAESH), instead of cystamine was further simplified and utilized to establish relative reactivity of the MACs. From the tested compounds, the fastest drop of the LAB changes were observed in the reaction of 2DMAESH with EF 24, followed by **2Br4PIP 2BrCX** and **2BrCP**. The least reactive is the herein presented compound, **4tB2BrCX**, which after 3 h has only minor changes in the UV spectrum. Acetonitrile and water are appropriate solvents, and they can also be suitable for the salts of the 4-piperidone derivatives. This method can be used for other MACs and related systems that have a relatively intense LAB above 300 nm.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: UV-Vis spectra of individual compouds in acetonitrile; Figure S2: UV-VIS spectra of MACs added to 2-(dimethylamino)ethanethiol (2.5 mg/mL) in 80:20 acetonitrile/H_2O a).

Author Contributions: Conceptualization, J.B.; methodology, J.B., Z.L., K.D., I.T.; formal analysis, Z.L., I.T., K.D.; investigation, Z.L., I.T., K.D.; data curation, I.T., K.D.; writing—, J.B., I.T., K.D., Z.L.;

writing—review and editing, J.B., I.T., K.D.; supervision, J.B.; project administration. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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