

Synthesis and Evaluation of Cytotoxic Activity of 2-Aryl-2-(3-Indolyl)Propionic Acid Derivatives

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Abstract

2-Aryl-2-(3-indolyl)acetohydroxamic acids have emerged as promising antitumor agents; however, their poor pharmacokinetic profile remains a significant drawback. To address this limitation, we have synthesized a homolog of such acids—specifically 2-aryl-2-(3-indolyl)propionic acid ($IC_{50} > 100$ mM (U87)), along with several other derivatives: ethyl ester ($IC_{50} > 100$ mM (U87)), hydroxamate ($IC_{50} 21.2 \pm 1.0$ mM (U87)) and hydrazide ($IC_{50} > 100$ mM (U87)). The cytotoxicity of these compounds against glioblastoma cell lines was evaluated and compared to that of the parent acetohydroxamic acid derivatives.

Keywords: indoles; hydroxamic acids; propionic acids; anti-cancer; activity

1. Introduction

With the continuous development of medical technologies leading to a substantial reduction in cardiovascular disease mortality, the treatment of oncological diseases is progressively acquiring heightened significance. Given the high mortality from these diseases, the identification of novel pharmacophores and the structural modification of existing agents constitute primary objectives in organic and medicinal chemistry [1,2]. In particular, indole derivatives have established themselves as potent drug candidates. These moieties are ubiquitous in nature, appearing in a broad spectrum of alkaloids exhibiting diverse biological activities [3–7].

Among the biologically active derivatives of indole, those previously synthesized by our group, 2-aryl-2-(3-indolyl)acetohydroxamic acids, which demonstrated potent anticancer activity against apoptosis-resistant and multidrug-resistant cancer cells in vitro, deserve particular attention. The most attractive among the found effects is the ability of such hydroxamic acids to induce reverse differentiation of U87 glioblastoma cells into a low-oncogenic state resembling astrocytes, similar to retinoic acid (Scheme 1) [8]. However, despite promising preliminary data, in vivo mice studies revealed significantly reduced efficacy, attributed to rapid systemic clearance [9]. To improve the pharmacokinetic profile, we initially attempted to protect the hydroxyl group, which is susceptible to glucuronidation. However, this strategy proved unsuccessful, as the *O*-protected derivatives exhibited significantly lower activity compared to the parent compounds [10]. To address this limitation, it is necessary to explore new possibilities for modifying the pharmacophore fragment by conducting extended SAR studies which not only opens the possibility for introducing



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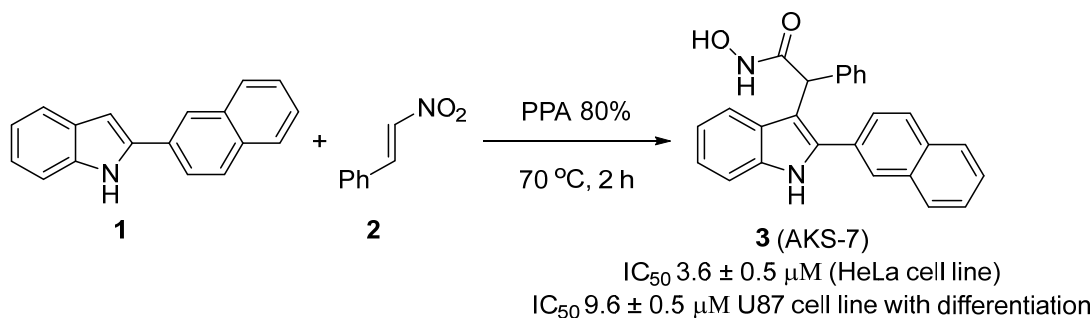
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alternative glucuronidation-inert fragments but also highlights a significant alternative: high activity rates can effectively compensate a suboptimal pharmacokinetic profile. One of the standard approaches in medicinal chemistry is the homologation of the key fragment, which allows for an increase in the mobility of the carbon chain and, in some cases, an increase in the binding constant to the target [11]. Within the framework of the above-mentioned studies, we synthesized a homolog of the most potent lead compound, AKS-7 (2-naphthyl-2-(3-indolyl)acetohydroxamic acid), along with some derivatives to evaluate their biological activity, including the corresponding ester and hydrazide.



Scheme 1. Preparation of 2-aryl-2-(3-indolyl)acetohydroxamic acid (AKS-7).

2. Materials and Methods

U87 cell line was purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA) and cultured in DMEM supplemented with 10% fetal bovine serum (FBS). NHDF (code CC-2509) cell line was purchased from Lonza (Basel, Switzerland) and was cultivated in FGM-2 BulletKit culture medium (Lonza) in T25 flasks and maintained and grown at 37 °C, 95% humidity, and 5% CO₂. The antiproliferative properties of the synthesized compounds were evaluated using the MTT assay [12]. All compounds were dissolved in DMSO at a concentration of either 100 or 50 mM prior to cell treatment. The cells were trypsinized and seeded at 4×10^3 cells per well into 96-well plates. The cells were grown for 24 h, treated with compounds at concentrations ranging from 0.001 to 100 µM, and incubated for 48 h in 200 µL of medium. Then, 20 µL of MTT reagent in serum-free medium (5 mg/mL) was added to each well, and the cells were incubated for a further 2 h. The medium was removed, and the resulting formazan crystals were resolubilized in 200 µL of DMSO. A490 was measured using a Molecular Devices THERMOmax plate reader (Thermo Fisher Scientific, Silicon Valley, CA, USA). The experiments were performed in quadruplicate and repeated at least twice for each compound. Cells treated with 0.1% DMSO were used as a negative control; 1 µM phenyl arsine oxide (PAO) was used as a positive control.

Reagents, solvents, and catalysts were purchased from commercial sources (Acros Organics (Thermo Fisher Scientific, Gilles, Belgium) and Sigma-Aldrich (Merck KGaA, St. Louis, MO, USA)) and used without purification. All reactions were performed in oven-dried flasks open to the atmosphere and monitored by thin layer chromatography on TLC precoated (250 µm) silica gel 60 F254 glass-backed plates (EMD Chemicals Inc., Merck KGaA, Darmstadt, Germany). Visualization was accomplished with UV light. Flash chromatography was performed using silica gel (32–63 µm, 60 Å pore size) using mixtures of petroleum ether (40–60 °C)/acetone or petroleum ether (40–60 °C)/ethyl acetate as eluent. ¹H and ¹³C NMR spectra were recorded on Bruker DRX-400 and DRX-500 spectrometers (Bruker, Billerica, MA, USA). Chemical shifts (δ) are reported in ppm relative to the TMS internal standard. Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br. (broad). See Supporting Information for ¹H and ¹³C NMR spectral charts.

3-(2-(Naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanoic acid (6). A 50 mL round-bottomed flask equipped with a magnetic stirring bar and reflux condenser was charged with *N,N*-dimethylformamide (20.0 mL) and titanium(IV) chloride (1.90 g, 10.0 mmol). Next, 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (2.32 g, 10.0 mmol) and 2-naphthylindole (2.43 g, 3.0 mmol) were introduced sequentially, in one portion each. The reaction mixture was heated at reflux for 2 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion, the mixture was quenched with water, and the resulting aqueous solution was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were concentrated under reduced pressure using a rotary evaporator. The crude residue was purified by silica gel column chromatography (30 g of silica gel, eluent: petroleum ether/acetone, 5:1) to afford the target compound. The title compound was obtained as light-brown powder, mp 131–134 °C (benzene/petroleum ether). The yield was 1.57 g (4.0 mmol, 40%). R_f = 0.28 (petroleum ether/acetone 2:1). ^1H NMR (400 MHz, DMSO- d_6) δ 12.15 (s, 1H), 11.41 (s, 1H), 8.14 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 5.8 Hz, 1H), 7.93 (d, J = 6.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.62–7.52 (m, 3H), 7.40 (d, J = 7.9 Hz, 1H), 7.31–7.20 (m, 4H), 7.17–7.06 (m, 2H), 6.96 (t, J = 7.3 Hz, 1H), 5.00 (t, J = 7.2 Hz, 1H), 3.35–3.29 (m, 1H), 3.21 (dd, J = 15.5, 7.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 173.7, 144.9, 137.0, 135.5, 133.4, 132.7, 131.0, 128.8 (2C), 128.6, 128.4, 128.2, 128.0, 127.6 (2C), 127.4, 127.2, 127.1, 126.9, 126.3, 121.8, 120.6, 119.4, 114.2, 112.0, 41.8, 38.2. HRMS (ESI-TOF, m/z): calculated for $\text{C}_{27}\text{H}_{21}\text{NNaO}_2$ $[\text{M} + \text{Na}]^+$ 414.1464; found 414.1469 (1.2 ppm).

Ethyl 3-(2-(naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanoate (7). In a 25 mL round-bottomed flask equipped with a magnetic stirring bar and reflux condenser, 3-phenyl-3-(2-(naphthalen-2-yl)-1H-indol-3-yl)propionic acid (1.173 g, 3 mmol) was dissolved in ethanol (1.5 mL), followed by the addition of a catalytic amount of concentrated sulfuric acid (0.09 mL). The reaction mixture was heated at reflux for 8 h until the completion of the reaction (TLC control). After consumption of starting material, water was added to the mixture, and the solution was neutralized with aqueous ammonia. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic layers were concentrated under reduced pressure using a rotary evaporator, and the crude residue was purified by silica gel column chromatography (20 g of silica gel, eluent: petroleum ether/ethyl acetate, 8:1) to afford the title compound. The title compound was obtained as light-yellow oil. The yield was 0.93 g (2.22 mmol, 74%). R_f = 0.38 (petroleum ether/ethyl acetate 4:1). ^1H NMR (400 MHz, CDCl_3) δ 8.20 (s, 1H), 8.00–7.95 (m, 1H), 7.93–7.86 (m, 2H), 7.85–7.80 (m, 1H), 7.70–7.62 (m, 2H), 7.57–7.50 (m, 2H), 7.39 (t, J = 7.4 Hz, 3H), 7.32–7.24 (m, 3H), 7.24–7.16 (m, 2H), 7.13–7.06 (m, 1H), 5.15 (t, J = 7.8 Hz, 1H), 3.93 (qq, J = 10.8, 7.1 Hz, 2H), 3.42–3.18 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 172.4, 144.2, 136.4, 135.7, 133.4, 132.9, 130.5, 128.60, 128.56 (2C), 128.3, 127.9, 127.9, 127.6 (2C), 126.7, 126.5, 126.5, 126.3, 122.3, 120.9, 119.9, 114.6, 111.2, 60.4, 40.5, 38.4, 29.8, 14.0. HRMS (ESI-TOF, m/z): calculated for $\text{C}_{29}\text{H}_{25}\text{NNaO}_2$ $[\text{M} + \text{Na}]^+$ 442.1777; found 442.1778 (0.2 ppm).

***N*-Hydroxy-3-(2-(naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanamide (8).** A 25 mL round-bottomed flask equipped with a magnetic stirring bar and reflux condenser was charged with ethyl 3-phenyl-3-(2-(naphthalen-2-yl)-1H-indol-3-yl)propanoate (419 mg, 1.0 mmol) and methanol (2 mL). Then, 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) (456 mg, 3 mmol) and hydroxylamine hydrochloride ($\text{NH}_2\text{OH}\cdot\text{HCl}$) (700 mg, 10 mmol) were added in one portion to the above solution at 0 °C. The reaction mixture was heated at reflux temperature upon vigorous stirring for 1 h (TLC control). Upon completion, the mixture was diluted with water and neutralized by the addition of glacial acetic acid. The resulting solution was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were concentrated under reduced pressure, and the crude residue was purified by silica gel column chromatography (10 g of silica gel, eluent: petroleum ether/ethyl acetate, 5:1) to

yield the target hydroxamic acid. The title compound was obtained as dark-gray solid, mp 128–130 °C (benzene/petroleum ether). The yield was 227 mg (0.56 mmol, 56%). R_f = 0.4 (petroleum ether/ethyl acetate 5:1). ^1H NMR (400 MHz, DMSO- d_6) δ 11.38 (s, 1H), 10.48 (s, 1H), 8.74 (s, 1H), 8.20 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 6.6 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.61–7.55 (m, 3H), 7.39 (d, J = 7.5 Hz, 1H), 7.24–7.18 (m, 4H), 7.12–7.07 (m, 2H), 7.00–6.94 (m, 1H), 5.09 (t, J = 7.5 Hz, 1H), 3.17 (dd, J = 14.6, 8.2 Hz, 1H), 2.94 (dd, J = 14.5, 7.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 167.7, 144.7, 136.6, 135.0, 133.0, 132.3, 130.5, 128.2 (2C), 128.1, 128.0, 127.7, 127.6, 127.3 (2C), 127.1, 126.8, 126.7, 126.4, 125.8, 121.3, 120.3, 118.8, 114.2, 111.6, 37.5, 37.4. HRMS (ESI-TOF, m/z): calculated for $\text{C}_{27}\text{H}_{22}\text{N}_2\text{NaO}_2$ [$M + \text{Na}$] $^+$ 429.1573; found 429.1576 (0.7 ppm).

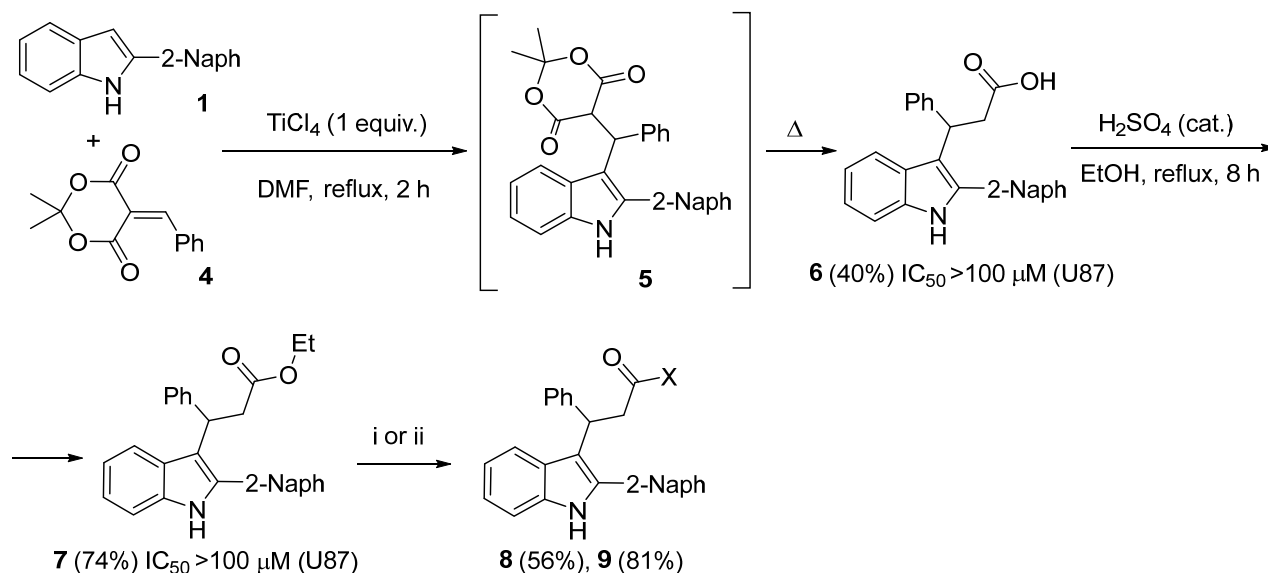
3-(2-(Naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanehydrazide (9). A 25 mL round-bottomed flask equipped with a magnetic stirring bar and reflux condenser was charged with ethyl 3-phenyl-3-(2-naphthyl-1H-indol-3-yl)propionate (419 mg, 1.0 mmol) and MeOH (4 mL). To the above solution, hydrazine hydrate ($\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$) (4 mL, 80 mmol) was added in one portion at room temperature. The resulting mixture was heated at reflux with vigorous stirring for 8 h until the reaction reached completion (TLC control). After consumption of starting material, the mixture was diluted with water and acidified with glacial acetic acid to achieve a neutral pH. The aqueous phase was then extracted with ethyl acetate (3×10 mL). The organic solvent was removed under reduced pressure using a rotary evaporator, and the crude residue was purified by column chromatography (10 g of silica gel, petroleum ether: ethyl acetate, 4:1). The title compound was obtained as light-brown solid, mp 140–142 °C (benzene/petroleum ether). The yield was 328 mg (0.81 mmol, 81%). R_f = 0.2 (petroleum ether/ethyl acetate 2:1). ^1H NMR (400 MHz, DMSO- d_6) δ 11.37 (s, 1H), 9.09 (s, 1H), 8.19 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 8.01–7.97 (m, 1H), 7.96–7.92 (m, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.60–7.55 (m, 3H), 7.39 (d, J = 8.0 Hz, 1H), 7.26–7.19 (m, 4H), 7.12–7.07 (m, 2H), 6.96 (t, J = 7.4 Hz, 1H), 5.10 (t, J = 7.5 Hz, 1H), 4.33 (br.s, 2H), 3.27 (dd, J = 14.8, 8.5 Hz, 1H), 2.96 (dd, J = 14.7, 6.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 170.2, 144.8, 136.6, 134.8, 132.9, 132.2, 130.5, 128.2 (2C), 128.1, 128.0, 127.7, 127.6, 127.3 (2C), 127.1, 126.8, 126.6, 126.4, 125.7, 121.3, 120.3, 118.8, 114.4, 111.5, 79.2, 37.5. HRMS (ESI-TOF, m/z): calculated for $\text{C}_{27}\text{H}_{23}\text{N}_3\text{NaO}$ [$M + \text{Na}$] $^+$ 428.1733; found 428.1729 (−0.9 ppm).

3. Results and Discussion

In search for a synthetic route to substituted indolylpropionic acids, we have selected 5-benzylidene-Meldrum's acid as an alkylating agent, capitalizing on the established versatility of Meldrum's acid derivatives in carbonyl chemistry (Scheme 2). Mechanistically, we postulate that the initial step involves the addition of indole **1** to the Michael acceptor **4** with subsequent thermal decomposition of resulting intermediate **5** accompanied by decarboxylation which gives as a result indolylpropionic acid **6** in a 40% yield. Based on literature precedents, the reaction was performed in refluxing dimethylformamide (DMF) in the presence of 1 equivalent of titanium(IV) chloride (TiCl_4) as a Lewis acid (Scheme 2).

For subsequent transformations, the ester **7** was synthesized by classical Fisher method in ethanol medium in the presence of a catalytic amount of sulfuric acid. The resulting ester was then converted into hydroxamic acid **8** in 56% yield by reaction with hydroxylamine in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base under reflux. Notably, that reaction at room temperature gives a lower yield of 26%. Furthermore, hydrazide **9** was obtained in 81% yield by heating the ester **7** with large excess of hydrazine hydrate in refluxing methanol. The evaluation of the anti-cancer activity of the synthesized compound **6**, **7**, **8** and **9** was performed using a U87 glioblastoma cell line. The results are presented in the scheme below. It should be noted that the homologous hydroxamic acid derivative **8** exhibited lower cytotoxic activity; however, it remained within the same order of magnitude

as the lead compound. Also, it has a poorer selectivity index in comparison to lead compound **3**, which demonstrates that increasing the length of the linker between the acetamide and indole moieties, contrary to our expectations, reduces the biological potential of the molecule. Acid **6**, ester **7**, and hydrazide **9** demonstrated no significant inhibitory effects against the cancer cell lines. Most surprising was the lack of significant effect of hydrazide **9**, which contains the 2-(indol-3-yl)propionamide moiety close to 2-(indol-3-yl)acetamide fragment, which has previously been shown to be sufficient for anticancer activity [8–10] (Scheme 2).



i (**8**): $\text{NH}_2\text{OH}\cdot\text{HCl}$, DBU, MeOH 2 mL, reflux, 2 h, $\text{X} = \text{NHOH}$, $\text{IC}_{50} 21.2 \pm 1.0 \mu\text{M}$ (U87), $46 \pm 5 \mu\text{M}$ (NHDF Fibroblast);
ii (**9**): $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$, MeOH 4 mL, reflux, 2 h, $\text{X} = \text{NHNH}_2$, $\text{IC}_{50} > 100 \mu\text{M}$ (U87)

Scheme 2. Synthesis of 3-(2-(naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanoic acid **6** and its derivatives **7–9**.

4. Conclusions

A convenient synthetic method was developed for 3-(2-(naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanoic acid, employing 5-benzylidene-Meldrum's acid derivatives as alkylating agents. With this novel homolog of 2-aryl-2-(3-indolyl)acetohydroxamic acid in hand, its key derivatives—hydroxamate, ester, and hydrazide—were subsequently synthesized, and the anticancer activity of all synthesized compounds was evaluated on a U87 cell line model. The obtained data significantly complements our understanding of the pharmacophoric fragment and paves the way for future structure–activity relationship (SAR) studies.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/org7010011/s1>, Figure S1. ^1H NMR spectral charts for 3-(2-(Naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanoic acid; Figure S2. ^{13}C $\{^1\text{H}\}$ NMR spectral charts for 3-(2-(Naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanoic acid; Figure S3. ^1H NMR spectral charts for Ethyl 3-(2-(naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanoate; Figure S4. ^{13}C $\{^1\text{H}\}$ NMR spectral charts for Ethyl 3-(2-(naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanoate; Figure S5. ^1H NMR spectral charts for N-Hydroxy-3-(2-(naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanamide; Figure S6. ^{13}C $\{^1\text{H}\}$ NMR spectral charts for N-Hydroxy-3-(2-(naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanamide; Figure S7. ^1H NMR spectral charts for 3-(2-(Naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanehydrazide; Figure S8. ^{13}C NMR spectral charts for 3-(2-(Naphthalen-2-yl)-1H-indol-3-yl)-3-phenylpropanehydrazide.

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Data Availability Statement: The original contributions presented in this study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

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

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