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Anticancer Activity of 4-Aryl-1,4-Dihydropyridines

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Abstract: We have synthesized 22 symmetric and asymmetric 4-aryl-1,4-dihydropyridines (1,4-DHPs) by a "green" microwave-assisted one-pot multicomponent Hantzsch reaction and evaluated their cytotoxicity to three human cancer cell lines regarding U-251MG (human glioblastoma), HeLa 229 (human cervical adenocarcinoma), and MCF-7 (human breast carcinoma). None of the 1,4-DHPs were cytotoxic to U-251MG cells. Most of the 1,4-DHPs did not affect HeLa 229 or MCF-7 cell viability. On the other hand, symmetric 1,4-DHPs **18** (diethyl 4-(4-benzyloxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate), **19** (diethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate), and **20** (diethyl 4-(3-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) reduced the HeLa (IC_{50} = 3.6, 2.3, and 4.1 μM, respectively) and MCF-7 (IC_{50} = 5.2, 5.7, and 11.9 μM, respectively) cell viability. These 1,4-DHPs were more cytotoxic to the HeLa and MCF-7 cells than to the GM07492 (normal human fibroblast) cells, as evidenced by their selectivity indexes. Therefore,1,4-DHPs **18**, **19**, and **20** may serve as novel lead compounds to discover other 1,4-DHP derivatives with improved anticancer potency and selectivity.

Keywords: Hantzsch esters; HeLa 229; human breast carcinoma; polyhydroquinolines

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1. Introduction

1,4-Dihydropyridines, specifically 4-aryl-1,4-dihydropyridines (1,4-DHPs), can block calcium channels [1]. However, 1,4-DHPs display diverse biological (e.g., antimicrobial [2]) and pharmacological (e.g., antihypertensive [3], anticonvulsant [4], and analgesic [5]) activities. Over the last two decades, the interest in the anticancer activity of 1,4-DHPs has increased because they can reverse multi-resistance in cancer [6] and potentiate the anticancer and antimetastatic activities of some cytotoxic drugs [7].

The one-pot multicomponent Hantzsch reaction is the preferred method for synthesizing 1,4-DHPs [8]. The reaction affords different 1,4-DHPs depending on the reactants and their stoichiometry. For instance, reacting a 1,3-cyclohexadione (e.g., dimedone), ethyl acetoacetate, and an aldehyde in the presence of an adequate nitrogen source yields asymmetric 1,4-DHPs known as "polyhydroquinolines" (I, Figure 1). On the other hand, using two molar equivalents of ethyl acetoacetate under these same conditions produces symmetric 1,4-DHPs known as "Hantzsch esters" (II, Figure 1). Some improved methodologies employ microwave irradiation to reduce the reaction times [9] and consumption of non-toxic solvents, such as ethanol [10].

As part of our interest in the biological and pharmacological potential of synthetic [11–13] and natural products [14,15], and on the basis of previous reports on the anticancer activity of 1,4-DHPs [6,9,16–26], we have synthesized 22 1,4-DHPs by a microwave-assisted one-pot multicomponent Hantzsch reaction and evaluated how they affect human cervical adenocarcinoma (HeLa), human breast carcinoma (MCF-7), and human glioblastoma (U-251MG) cell viability.

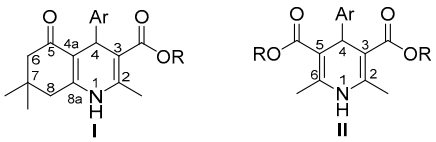


Figure 1. Basic structures of polyhydroquinolines (**I**) and Hantzsch esters (**II**).

2. Materials and Methods

2.1. Synthesis of 1,4-DHPs **1–22**

The 1,4-DHPs were synthesized according to the one-pot multicomponent methodology described in the literature, with some modifications [27]. In the general procedure, 2.0 mmol of dimedone (Sigma-Aldrich, St. Louis, MO, USA), 2.0 mmol of ethyl acetoacetate (Sigma-Aldrich), and 0.06 g (5.0 mol%) of ytterbium triflate (Sigma-Aldrich), as reaction catalyst, were diluted in ethanol (5.0 mL). Subsequently, 2.0 mmol of benzaldehyde (Sigma-Aldrich) and 2.0 mmol of ammonium acetate (Scientific Exodus, Hortolândia, Brazil) were added. All the reagents were added at room temperature. The reaction mixture was taken to the microwave reactor CEM FocusedMicrowaveTM Synthesis System, model Discover (CEM Corp, Matthews, NC, USA), set in the Power Time, where it was maintained for 20 min at a fixed power of 100 W. 1,4-DHPs **1–22** have previously been reported in the literature, and their structures were identified on the basis of their NMR (^{1}H, ^{13}C, and DEPT 135) and mass spectra (see Supplementary Materials) and by comparison with literature data [27–40].

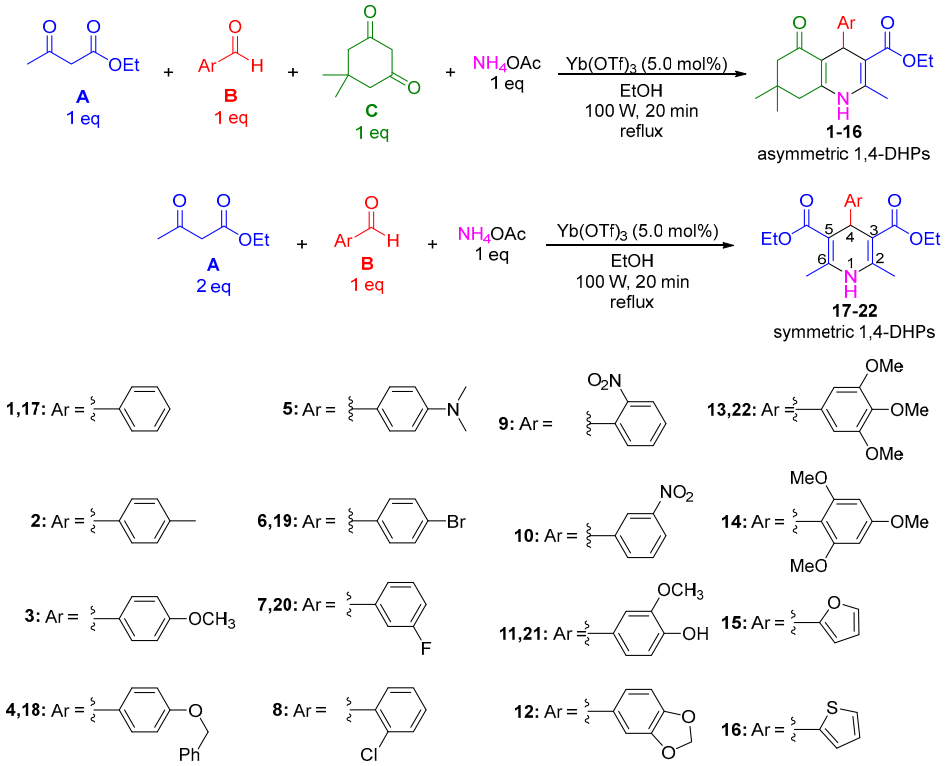
2.2. Cell Viability Analysis

Cell viability was assessed by using the Resazurin colorimetric method (ACS Científica, São Paulo, SP, Brazil); the protocol described by Riss and co-workers [41] was followed. The GM07492A (human lung fibroblast), HeLa (human cervical adenocarcinoma), MCF-7 (human breast adenocarcinoma), and U-251MG (human glioblastoma) cell lines were seeded in 96-well plates. Each well contained 1×10^4 cells in 100 µL of culture medium as indicated for each strain (HAM-F10 + DMEM (Dulbecco's Modified Eagle Medium) or DMEM) supplemented with 10% fetal bovine serum. Twenty-five hours after sowing, the 1,4-DHPs were tested up to 100 µM. Negative (no treatment), solvent (1% DMSO-dimethylsulfoxide), and positive (25% DMSO) control cultures were included. After 24 h at 37 °C, the culture medium was removed, and the cells were washed with 100 µL of PBS (phosphate-buffered saline). Subsequently, the cells in each well were exposed to 80 µL of HAM-F10 culture medium without phenol red (Sigma-Aldrich, St. Louis, MO, USA) and 20 µL of resazurin salt (dissolved in PBS). The 96-well plates were incubated at 37 °C for 4 h. Absorbance was measured at 570 nm on a multi-plate reader (ELISA-Asys-UVM 340/Microwin 2000 (Biochrom, Cambridge, England)) at a reference length of 600 nm. All the absorbance results, obtained in the form of cell viability, were calculated and subsequently demonstrated as IC_{50} (half-maximal inhibitory concentration—the concentration that can inhibit cell viability by 50%). Experiments were carried out in triplicate. SI was calculated as the ratio between the IC_{50} obtained for the non-tumor lineage (GM07492A) and the IC_{50} of each cancer cell line (MCF-7, U-251MG, and HeLa).

3. Results

3.1. Synthesis of 4-Aryl-1,4-Dihydropyridines (1,4-DHPs) **1–22**

We synthesized 1,4-DHPs **1–22** (Scheme 1) by microwave-assisted one-pot multicomponent Hantzsch reaction. We used ammonium acetate, ytterbium triflate, and ethanol as the nitrogen source [42], catalyst [27], and reaction solvent, respectively. The reaction lasted 30 min. We isolated the 1,4-DHPs by vacuum filtration, purified them by recrystallization in ethanol, and obtained them as solids in yields ranging from 15 to 40% with purities varying from 93 to 98%. We obtained asymmetric 1,4-DHPs **1–16** as racemates.



Scheme 1. Synthesis of compounds **1**–**22** by using a microwave-assisted one-pot multicomponent Hantzsch reaction.

3.2. Anticancer Activity of 1,4-DHPs **1–22**

We assessed the effects of 1,4-DHPs **1**–**22** at concentrations between 0.8 and 100 μM on the HeLa, MCF-7, and U-251MG cell viability in terms of their half-maximum inhibitory concentration (IC_{50}). We also assessed the effects of these 1,4-DHPs on GM07492 (normal human fibroblast) cell viability, as shown in Table 1.

Table 1. IC_{50} and selectivity indexes (SIs) of 1,4-DHPs **1**–**22** (0.80–100 μM) after 24 h against different cell lines.

1,4-DHP	Cell Lines					
	GM07492A	HeLa	SI	MCF-7	SI	U-251MG
1	>100	>100	NC	>100	NC	>100
2	>100	>100	NC	>100	NC	>100
3	>100	>100	NC	>100	NC	>100
4	>100	>100	NC	>100	NC	>100
5	>100	>100	NC	>100	NC	>100
6	>100	>100	NC	62.10 ± 2.41 *	NC	>100
7	>100	>100	NC	>100	NC	>100
8	6.48 ± 2.44	>100	NC	>100	NC	>100
9	>100	>100	NC	>100	NC	>100
10	>100	>100	NC	>100	NC	>100
11	>100	>100	NC	>100	NC	>100
12	>100	>100	NC	>100	NC	>100
13	>100	>100	NC	>100	NC	>100
14	>100	>100	NC	>100	NC	>100
15	>100	>100	NC	>100	NC	>100
16	84.42 ± 12.17	51.83 ± 0.03 *	1.62	>100	NC	>100
17	>100	59.00 ± 10.23 *	>1.69	>100	NC	>100
18	9.69 ± 0.25	3.60 ± 0.96 *	2.69	5.19 ± 1.60 *	1.86	>100
19	3.88 ± 0.37	2.31 ± 0.28 *	1.67	5.74 ± 0.88	0.67	>100
20	11.00 ± 0.22	4.10 ± 1.24 *	2.68	11.95 ± 0.91	0.92	>100
21	>100	39.67 ± 2.60 *	2.54	>100	NC	>100
22	>100	>100	NC	>100	NC	>100

GM07492A—human lung fibroblast; HeLa—cervical adenocarcinoma; MCF-7—human breast adenocarcinoma; U-251MG—human glioblastoma. Values are mean ± SD. * Significantly different from the non-tumor cell line GM07492A ($p < 0.05$). NC—not calculated.

At concentrations lower than 100 μM, none of the 1,4-DHPs were cytotoxic to U-251MG cells. Among the polyhydroquinolines (**1**–**16**), only 1,4-DHPs **6** and **16** significantly reduced MCF-7 (IC_{50} = 62.1 μM) and HeLa (IC_{50} = 51.8 μM) cell viability, respectively, compared to GM07492 cells. The selectivity indexes (SIs) (i.e., the ratio between the IC_{50} for a normal cell line, or the GM07492 cells therein, and the IC_{50} for a cancer cell line) calculated for 1,4-DHPs **6** and **16** in the cases of the MCF-7 and HeLa cells were higher than 1, which indicated that these 1,4-DHPs were slightly more selective for these cancer cells compared to GM07492A cells. At concentrations lower than 100 μM, none of the other asymmetric 1,4-DHPs affected HeLa or MCF-7 cell viability

On the other hand, except for 1,4-DHP **22**, all the Hantzsch esters (**17**–**21**) reduced the HeLa cell viability. The lowest IC_{50} values against the HeLa cells were obtained for 1,4-DHPs **18** (IC_{50} = 3.6 μM), **19** (IC_{50} = 2.3 μM), and **20** (IC_{50} = 4.1 μM). Although these compounds also reduced the GM07492A cell viability, their SI values were higher than 1 (2.69, 1.67, and 2.68, respectively), indicating interesting cytotoxicity to the HeLa cells compared to GM07492A cells. In the cases of 1,4-DHPs **17** and **21**, the higher IC_{50} values against the HeLa cells (59.0 and 39.7 μM, respectively) were followed by their lower cytotoxicity to the GM07492 cells as compared to 1,4-DHPs **18**, **19**, and **20**. 1,4-DHPS **18**, **19**, and **20** were also cytotoxicity to the MCF-7 cells, with IC_{50} values of 5.2, 5.7, and 11.9 μM, respectively. However, only 1,4-DHP **18** was slightly selective for the MCF-7 cells (SI = 1.86).

Most of the 1,4-DHPs at concentrations lower than 100 μM were not cytotoxic to the GM07492A cells. Except for 1,4-DHP **8**, the 1,4-DHPs that were cytotoxic to the GM07492A cells were more cytotoxic to cancer cells (HeLa or MCF-7) than to GM07492A cells, as evidenced by their SI higher than 1.

4. Discussion

4.1. Synthesis of Compounds **1–22**

The one-pot multicomponent Hantzsch reaction has been extensively used to synthesize 4-aryl-1,4-dihydropyridines [43–51]. The methodology we used to obtain 1,4-DHPs **1**–**22** combines many aspects that are attractive from the synthetic point of view: (1) it employs ethanol, a "green", non-toxic, and cheap solvent reaction; (2) the reaction uses microwave irradiation, so it is faster compared to conventional heating methods; and (3) the 1,4-DHPs are isolated and purified by simple and cheaper methods that do not require time-demanding chromatographic processes.

4.2. Cytotoxicity of 1,4-DHPs **1–22** *to Cancer Cell Lines*

Although the anticancer properties of 1,4-DHP derivatives have been reported for several cancer cell lines, most studies have focused on HeLa [7,18,21,52,53] and MCF-7 [7,10,16–18,24,25] cells. To the best of our knowledge, studies on the anticancer activity of 1,4-DHPs against U-251MG cells have not been published. Moreover, special attention has been dedicated to the anticancer activity of structurally more complex 1,4-DHPs [10,16,17,26,54], whereas only a few studies have investigated the anticancer action of simple 1,4-DHPs [9,18,55].

According to Hughes et al. (2011), a compound is considered a promising anticancer agent when its IC_{50} is equal to or less than 10 μM [56]. The SI is another very important parameter when developing cytotoxic drugs. A high SI indicates preferential cytotoxic action against a specific cell line. A higher SI indicates greater specificity for cancer cells. According to Suffness and Pezzuto, an SI of 2.0 or higher is interesting because the therapeutic window of a compound in the body is defined by the concentration limits at which it exerts its desirable and toxic actions, and its safe use is proportional to the size of that interval [57].

Here, we assessed the cytotoxicity of 16 dimedone-derived asymmetric (**1**–**16**) and 6 ethyl acetoacetate-derived symmetric (**17**–**22**) 1,4-DHPs to HeLa, MCF-7, and U-251MG cells. None of the investigated 1,4-DHPs at concentrations lower than 100 μM were cytotoxic to U-215MG cells. This observation and the lack of literature data on the cytotoxicity of

1,4-DHPs to this cancer cell line suggest that this class of compounds is not cytotoxic to U-251MG cells.

The anticancer activity of some polyhydroquinolines is reported in the literature. For example, Langle and co-workers evaluated the inhibitory effects of a library of *b*-annelated 1,4-DHPs derived from compound **6** in the transforming growing factor-β (TGFβ) whose deregulation is associated with several diseases, including cancer [58]. However, the authors used compound **6** only as a synthetic intermediate, and its inhibition to TGFβ was not assessed. On the other hand, the anticancer activity of compounds **1**–**16** has not been reported to date. Here, we found that these 1,4-DHPs at concentrations lower than 100 μM did not affect HeLa, MCF-7, or U-251MG cell viability. The exception was 1,4-DHP **6**, which reduced the MCF-7 cell viability (IC_{50} = 61.1 μM, SI > 1.6). The presence of a 4-bromophenyl moiety is essential for the anticancer action of coelenteramines against different cancer cell lines, such as lung (A549), gastric (AGS), breast (MCF-7), and prostate (PC-3) cancer cells [19,59]. Perumal and co-workers reported that the 4-bromophenyl moiety plays a crucial role in the antimicrobial activity of 1,4-DHP **6** against fungi (*Candida albicans*) and Gram-positive (*Phaseolus vulgaris)* and Gram-negative (*Bacillus subtilis*) bacteria [38].

Unlike polyhydroquinolines **1**–**16**, the anticancer activity of Hantzsch esters has been extensively investigated. Although these Hantzsch esters are similar to 1,4-DHPs **17**–**22**, their structures are more complex due to the presence of alkyl [60] or aryl [22,23,61] at N-1, a substituent at C4 other than a substituted phenyl (e.g., imidazolyl [62], tiophenyl [25], pyridinyl [63], furanyl [63,64], pyrrolyl [63], and naphtalenyl [63]), different acyl groups at C3 and C5 [22–25,60,61], and oxygenated [17] and nitrogenated [53] or sulphurated [16] substituents at the methyl group at C2 and C6. The acyl groups at C3 and C5 include aromatic ketones [23,61], aliphatic [23,61,63] and aromatic [62] esters, and amides [18,22,23,61,65]. Moreover, Kumar and co-workers addressed the anticancer activity of 1,4-DHP **21** against HepG2 (half-maximum growth inhibition (GI_{50}) = 17.2 μM), MCF-7 (GI_{50} = 18.3 μM), and HeLa (GI_{50} = 18.8 μM) cells and compared it to the anticancer action of doxorubicin (GI_{50} = 0.01, 0.02, and 0.05 μM) [18]. However, these authors did not report data on the selectivity of 1,4-DHP **21** for these cancer cell lines. Herein, we verified that 1,4-DHP 21 reduced HeLa cell viability (IC_{50} = 39.7 μM), with an SI of 2.54. Therefore, 1,4-DHP **21** was about 2.5 times more toxic to the HeLa cells than to GM07492A cells. The difference between our results and the literature results could be related to the exposure time [66] or the method that was used to evaluate the cell viability (resazurin versus MTT) [67]. On the other hand, 1,4-DHP **21** at concentrations lower than 100 μM did not affect MCF-7 cell viability.

1,4-DHPs **18**, **19**, and **20** displayed the lowest IC_{50} values for HeLa cells (3.60, 2.31, and 4.10 μM, respectively). Nevertheless, only 1,4-DHPs **18** and **20** had SI values higher than 2. 1,4-DHPs **18** and **19** also reduced the MCF-7 cell viability, but they were less selective for MCF-7 than for HeLa cells (i.e., SI < 2). 1,4-DHP **18** bears a 4-benzyloxy group, two carbonyl oxygens, and a nitrogen group. Recently, Clara and co-workers demonstrated that these groups act as H-bond acceptors for the active-site residue of anticancer protein 1M17 [68]. Datar and co-workers reported that 1,4-DHP **18** is a potent hypotensive agent that reduces the arterial blood pressure of Wistar rats at 10 mg/kg [69].

1,4-DHP **20** displays a 3-fluorophenyl moiety. Many compounds bearing the 3-fluorophenyl moiety are cytotoxic to HeLa cells [70,71]. In general, the biological activities of fluorine-containing compounds have been assigned to the highly electronegative and small fluorine and its ability to establish weak hydrogen bonds [72]. However, the presence of this group alone does not ensure anticancer activity, as will be further discussed.

On the basis of a literature survey, Kumar and co-workers identified some key structural motifs for anticancer activity, namely the presence of an aromatic ring preferably substituted with electron-withdrawing groups at the *ortho*- or *meta* position, a heterocyclic ring, and an unsubstituted nitrogen in the dihydropyridine ring [9]. Given that all the 1,4-DHPs tested here have an aromatic ring and an unsubstituted nitrogen in the dihydropyridine ring, their different effects on cancer cell viability should be due to differences in the

nature and position of the aromatic ring substituents. 1,4-DHP **20**, which has an electron-withdrawing fluorine atom at the meta position, meets these criteria and follows the recent findings reported by Faizan and co-workers [73]. Nevertheless, 1,4-DHP **18**, which provided the lowest IC_{50} for HeLa and MCF-7 cells, displays an electron-donating benzyloxy group at the para position. Only a few 1,4-DHPs bearing electron-donating groups (e.g., OCH_3 and OH) at the para position are cytotoxic to HeLa and MCF-7 cells [9,53,74].

Another important feature of the structure–anticancer activity relationship of 1,4-DHPs that can be deduced from our results is the presence of 4-benzyloxyphenyl and 3-fluorophenyl groups, which, alone, do not ensure cytotoxicity to HeLa or MCF-7 cells. This was corroborated by the non-cytotoxicity of polyhydroquinolines **4** and **7**, which also bear these groups but were not cytotoxic to HeLa or MCF-7 cells. In this scenario, the symmetry of the 1,4-dihydropyridine ring in Hantzsch esters may play a relevant role in the anticancer activity of 1,4-DHPs **18**, **19**, and **20**. Recently, Faizan and co-workers compared the anticancer activity of symmetric and asymmetric Hantzsch amides (i.e., they display an amide group at C3 and C5 instead of esters). The authors addressed that the asymmetric derivatives displayed a broader range of steric interactions compared to the symmetric 1,4-DHPs, whereas steric effects may be more prominent in symmetrical derivatives displaying bulky aryl groups at the amide nitrogen [73]. However, in the cases of compounds **18**, **19**, and **20**, which display ethoxy groups, the effect of the symmetry on the anticancer activity needs to be further investigated.

5. Conclusions

None of the tested 1,4-DHPs reduced the U-251MG (human glioblastoma) cell viability. However, two Hantzsch esters (**18** and **20**) affected HeLa (human cervical adenocarcinoma) and MCF-7 (human breast carcinoma) cell viability with interesting selectivity. The higher anticancer activity of the Hantzsch esters compared to the polyhydroquinolines suggested that symmetry in the 1,4-dihydropyridine ring may play a key role in the anticancer activity of 1,4-DHPs against HeLa and MCF-7 cells. However, this should be confirmed by further studies with more structurally diverse Hantzsch esters.

Our study demonstrated that some simple Hantzsch esters may be as effective as other more complex 1,4-DHPs against the Hela and MCF-7 cancer cell lines. Considering that synthesizing these esters has numerous advantages (e.g., environmentally friendly ethanol is used; the reaction involves only one synthetic step; and the whole process, including product isolation, is simple and fast), 1,4-DHPs **18**, **19**, and **20** might serve as novel lead compounds for discovering other 1,4-DHP derivatives with improved anticancer potency and selectivity. Studies aiming to obtain synthetic derivatives of compounds **18**, **19**, and **20** and evaluate their anticancer activity are underway.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/futurepharmacol4030031/s1, Figures S1–S88: ^{1}H and ^{13}C NMR, DEPT 135, and mass spectra of compounds **1**–**22**.

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

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