

# Synthesis and Antitumor Activity of Hybrid Compounds Based on Aryl-Substituted Isatins and 2-Chloroethynyl (4-(Dimethylamino)phenyl)(2-hydrazinyl-2-oxoethyl)phosphinate

A. V. Bogdanov<sup>a,\*</sup>, A. A. Ivanova<sup>b</sup>, A. D. Voloshina<sup>a</sup>, R. R. Rakhmatullin<sup>b</sup>, A. V. Samorodov<sup>c</sup>,  
Z. A. Valiullina<sup>c</sup>, I. D. Krylova<sup>c</sup>, and S. V. Bukharov<sup>b</sup>

<sup>a</sup> *A.E. Arbuzov Institute of Organic and Physical Chemistry, Federal Research Center  
“Kazan Scientific Center of the Russian Academy of Sciences”, Kazan, 420088 Russia*

<sup>b</sup> *Kazan National Research Technological University, Kazan, 420015 Russia*

<sup>c</sup> *Bashkir State Medical University, Ufa, 450008 Russia*

\*e-mail: abogdanov@inbox.ru

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**Abstract**—New phosphorus-containing isatin-3-hydrazones were synthesized by the condensation reaction of 5-substituted isatins with 2-chloroethyl [4-(dimethylamino)phenyl](2-hydrazinyl-2-oxoethyl)phosphinate (KAPAKh). The resulting compounds were shown to have high antitumor activity against duodenal adenocarcinoma (HuTu80) and cervical epithelioid carcinoma (M-HeLa) cell lines with low toxicity towards erythrocytes and normal human liver cells.

**Keywords:** hydrazones, isatin, phosphorus, phosphine oxides, biological activity

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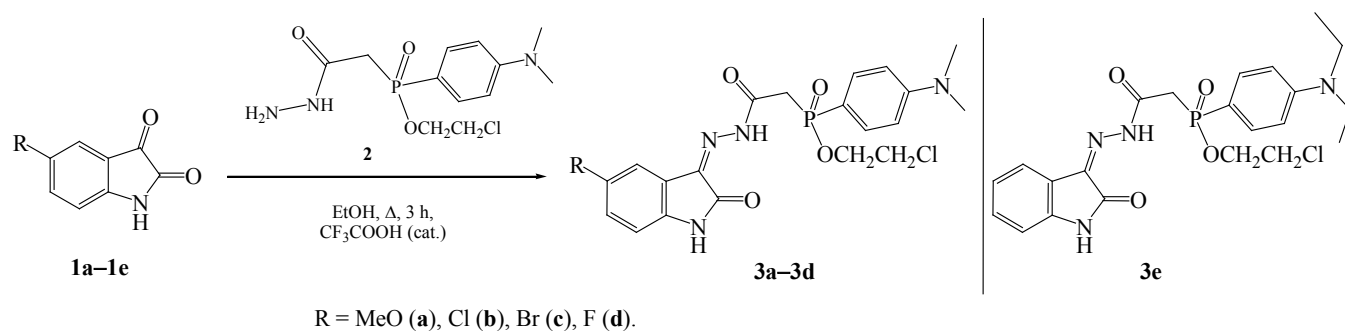
## INTRODUCTION

Indole, its mono- and dicarbonyl derivatives (oxindole and isatin) exhibit a wide range of practically useful properties [1–4]. Due to its high reactivity, isatin is of greatest interest to researchers, from which large libraries of polymeric, open-chain and heterocyclic structures can be obtained for use in organic synthesis, materials chemistry and pharmaceuticals [5–9].

Despite significant advances in the study of the properties of isatin, its phosphorus-containing derivatives remain one of the most poorly studied classes. For example, the synthesis and the structural features of a small series of isatin-based compounds containing phosphine oxide or phosphonate substituents at positions 1 or 3 of the heterocycle, respectively, have been published [10, 11]. Some of these compounds have found to possess high level of antiphytopathogenic activity [12, 13]. This work describes the synthesis and investigated the antitumor activity of new isatin derivatives containing a pharmacophore phosphorus-containing substituent on the periphery of the hydrazone fragment.

The method for obtaining target compounds **3a–3e** is based on the condensation reaction of 5-substituted isatins **1a–1e** with 2-chloroethyl [4-(dimethylamino)phenyl]-(2-hydrazinyl-2-oxoethyl)phosphinate (KAPAKh) **2** or its *N,N*-diethylamino analogue (Scheme 1). Hydrazones **3a–3e** were obtained in high yields after refluxing the reaction mixture in the presence of catalytic amounts of trifluoroacetic acid. This approach does not require the use of additional purification techniques, since the desired products precipitate from the reaction solution in pure form. Their structure and composition were confirmed by IR and NMR spectroscopy, elemental analysis and mass spectrometry. The presence of geometric isomerism relatively to the C=N–NH fragment is confirmed by NMR spectra. Thus, in the <sup>31</sup>P NMR spectra of acylhydrazones **3a–3e** solutions in DMSO there are two closely located signals at 36.9 ppm in a ratio of 2 : 1. Taking into account the literature data [14–18], it can be assumed that the *E,anti*-isomer is the main one. Using the example of chlorine derivative **3b**, this was confirmed by X-ray diffraction data, which will be published later.

Scheme 1.



Compounds **3a–3e** were tested for antitumor activity against duodenal adenocarcinoma (HuTu80) and cervical epithelioid carcinoma (M-HeLa) cell lines. Thus, it was found that, compared with Tamoxifen ( $IC_{50} = 28 \mu M$ ), the 5-bromo analogue **3c** ( $IC_{50} = 17.4 \mu M$ ) has the best activity against M-HeLa. For HuTu80 cell lines, the highest activity compared to 5-fluorouracil ( $IC_{50} = 16.6$  vs  $65.2 \mu M$ ) was observed for chlorine derivative **3b**. It should be especially noted that the entire series of obtained compounds does not have toxicity towards normal hepatocyte-like Chang liver cells ( $IC_{50} = 70 \rightarrow 100 \mu M$ ) and human erythrocytes ( $HC_{50} > 100 \mu M$ ).

In this work anticoagulant and antiaggregation properties of novel hydrazones were studied. The findings show that compounds **3a**, **3b** and **3e** exhibit antiaggregational activity at the level of acetylsalicylic acid (13.7 vs 11.7 for **3a**, 17.4 for **3b** and 8.2 for **3e**). However, one should note that all compounds in addition to antiaggregational activity, lengthen the lag period, which characterizes the process of release of endogenous agonists of aggregation from platelets. This effect is absent in acetylsalicylic acid, which indicates a potentially wide antithrombotic potential of the studied compounds. With respect to the coagulation link of hemostasis, these compounds showed an effect exclusively on the APTT (activated partial thromboplastin time) index. Therefore, the resulting compounds have high potential as a scaffold for the development of effective anticoagulant and antiaggregation agents.

## CONCLUSIONS

In conclusion, it was found that hybrid compounds based on isatin and 2-chloroethyl (4-(dimethylamino)-phenyl)(2-hydrazinyl-2-oxoethyl)phosphinate (KAPAKh)

possess high activity against HuTu80 and M-HeLa cancer cell lines. Wherein, the selectivity and level of their activity depends on the nature of the substituent in the oxindole fragment. Low hemo- and cytotoxicity and the absence of a negative effect on the hemostatic system point to the high potential of phosphorus-containing isatin-3-acylhydrazones in the search for novel antitumor drug candidates.

## EXPERIMENTAL

$^1H$  and  $^{13}C$  NMR spectra were recorded on a Bruker Avance-400 (400 and 100 MHz, respectively) and Bruker Avance-600 (600 and 150 MHz, respectively) instruments. The chemical shift values are given relative to the residual signals of the deuterated solvent. MALDI spectra were recorded on UltraFlex III TOF/TOF mass-spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrometer for suspensions of substances in KBr pelettes. Elemental analysis was carried out using a CHNS-3 analyzer. The halogens content was determined by pyrolysis in an oxygen flow. Melting points are determined in glass capillaries on the Stuart SMP 10 apparatus.

Compounds **1a–1d** are commercially available.

**General procedure for the synthesis of compounds 3a–3e.** To a mixture of 1.1 mmol of isatin derivative **1a–1e** and 1.1 mmol of 2-chloroethyl [4-(dimethylamino)-phenyl](2-hydrazinyl-2-oxoethyl)phosphinate **2** or 2-chloroethyl [4-(diethylamino)phenyl](2-hydrazinyl-2-oxoethyl)phosphinate in 7 mL of ethanol, 3 drops of trifluoroacetic acid were added. The reaction mixture was refluxed for 3 h, then left at room temperature for 8 h. The resulting precipitate was filtered off, washed with diethyl ether and dried under reduced pressure (20 Torr).

**2-Chloroethyl [4-(dimethylamino)phenyl]{2-[2-(5-methoxy-2-oxoindolin-3-ylidene)hydrazinyl]-2-oxoethyl}phosphinate (3a).** Yield 85%, light-orange powder, mp 223°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3432, 3210, 2999, 2922, 1686, 1599, 1523, 1485, 1306, 1194, 1163, 1125, 1028.  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta$ , ppm: 2.78 s (6H,  $\text{CH}_3$ ), 3.68–3.76 m (5H,  $\text{CH}_2$ ,  $\text{OCH}_3$ ), 3.79–3.83 m (2H,  $\text{CH}_2\text{Cl}$ ), 4.07–4.28 m (2H,  $\text{CH}_2\text{O}$ ), 6.58 d. d (1H, ArH,  $^3J_{\text{HH}} = 8.7$ ,  $^4J_{\text{PH}} = 2.6$  Hz), 6.81 d (1H, ArH,  $^3J_{\text{HH}} = 8.3$  Hz), 6.87 d (1H, ArH,  $^4J_{\text{HH}} = 1.9$  Hz), 6.93 d. d (1H, ArH,  $^3J_{\text{HH}} = 8.4$ ,  $^4J_{\text{HH}} = 2.4$  Hz), 7.48 d. d (1H, ArH,  $^3J_{\text{HH}} = 9.0$ ,  $^3J_{\text{PH}} = 11.4$  Hz), 10.98 s (1H, NH), 12.43 s (1H, NH).  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta_{\text{C}}$ , ppm: 35.3 d ( $^1J_{\text{PC}} = 83.9$  Hz), 39.1, 43.9 d ( $^3J_{\text{PC}} = 5.7$  Hz), 55.6, 64.1 d ( $^2J_{\text{POC}} = 3.2$  Hz), 106.3, 110.9 d ( $^3J_{\text{PC}} = 14.1$  Hz), 111.6, 113.9 d ( $^1J_{\text{PC}} = 138.6$  Hz), 117.2, 120.3, 132.4 d ( $^2J_{\text{PC}} = 11.3$  Hz), 134.0, 135.8, 152.4, 155.1, 162.4, 167.8.  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum ( $\text{DMSO}-d_6$ ):  $\delta_{\text{P}}$  36.02 ppm. Mass spectrum (MALDI),  $m/z$ : 501  $[M + \text{Na}]^+$ . Found, %: C 52.47; H 4.85; Cl 7.20; N 11.50; P 6.27.  $\text{C}_{21}\text{H}_{24}\text{ClN}_4\text{O}_5\text{P}$ . Calculated, %: C 52.67; H 5.05; Cl 7.40; N 11.70; P 6.47.

**2-Chloroethyl {2-[2-(5-chloro-2-oxoindolin-3-ylidene)hydrazinyl]-2-oxoethyl}[4-(dimethylamino)phenyl]phosphinate (3b).** Yield 80%, yellow crystals, mp 201°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3400, 3126, 3081, 2992, 2947, 1686, 1629, 1598, 1521, 1489, 1317, 1190, 1122, 1025.  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta$ , ppm: 2.79 s (6H,  $\text{CH}_3$ ), 3.70 d (2H,  $\text{CH}_2$ ,  $^2J_{\text{PH}} = 18.6$  Hz), 3.79–3.82 m (2H,  $\text{CH}_2\text{Cl}$ ), 4.06–4.26 m (2H,  $\text{CH}_2\text{O}$ ), 6.58 d. d (1H, ArH,  $^3J_{\text{HH}} = 8.4$ ,  $^4J_{\text{PH}} = 2.0$  Hz), 6.90 d (1H, ArH,  $^3J_{\text{HH}} = 8.3$  Hz), 7.25 s (1H, ArH), 7.28 br. d (1H, ArH,  $^3J_{\text{HH}} = 8.4$  Hz), 7.48 d. d (1H, ArH,  $^3J_{\text{HH}} = 8.8$ ,  $^3J_{\text{PH}} = 11.1$  Hz), 11.28 s (1H, NH), 12.31 s (1H, NH).  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta_{\text{C}}$ , ppm: 35.5 d ( $^1J_{\text{PC}} = 84.9$  Hz), 39.1, 43.9 d ( $^3J_{\text{PC}} = 7.1$  Hz), 64.1 d ( $^2J_{\text{POC}} = 5.2$  Hz), 110.9 d ( $^3J_{\text{PC}} = 14.0$  Hz), 112.4, 113.8 d ( $^1J_{\text{PC}} = 148.2$  Hz), 120.5, 121.2, 126.5, 130.7, 132.5 d ( $^2J_{\text{PC}} = 13.7$  Hz), 132.7, 140.8, 152.4, 162.0, 167.9 d ( $^2J_{\text{PC}} = 4.4$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum ( $\text{DMSO}-d_6$ ):  $\delta_{\text{P}}$  36.85 ppm. Mass spectrum (MALDI),  $m/z$ : 483  $[M + \text{H}]^+$ . Found, %: C 49.51; H 4.18; Cl 14.47; N 11.39; P 6.21.  $\text{C}_{20}\text{H}_{21}\text{Cl}_2\text{N}_4\text{O}_4\text{P}$ . Calculated, %: C, 49.71; H, 4.38; Cl 14.67; N 11.59; P 6.41.

**2-Chloroethyl [4-(dimethylamino)phenyl]{2-[2-(5-fluoro-2-oxoindolin-3-ylidene)hydrazinyl]-2-oxoethyl}phosphinate (3c).** Yield 95%, light-orange powder, mp 195°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3410, 3128, 3077, 2995, 1689, 1599, 1522, 1483, 1373, 1314, 1189,

1123, 1026.  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta$ , ppm: 2.79 s (6H,  $\text{CH}_3$ ), 3.69 d (2H,  $\text{CH}_2$ ,  $^2J_{\text{PH}} = 15.6$ ), 3.80–3.83 m (2H,  $\text{CH}_2\text{Cl}$ ), 4.08–4.26 m (2H,  $\text{CH}_2\text{O}$ ), 6.58 br. d (1H, ArH,  $^3J_{\text{HH}} = 6.6$  Hz), 6.89 d. d (1H, ArH,  $^3J_{\text{HH}} = 8.4$ ,  $^4J_{\text{FH}} = 3.9$  Hz), 7.06 d (1H, ArH,  $^3J_{\text{FH}} = 7.3$  Hz), 7.17–7.20 m (1H, ArH), 7.48 d. d (1H, ArH,  $^3J_{\text{HH}} = 8.9$ ,  $^3J_{\text{PH}} = 11.0$  Hz), 11.18 s (1H, NH), 12.36 s (1H, NH).  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta_{\text{C}}$ , ppm: 35.5 d ( $^1J_{\text{PC}} = 84.7$  Hz), 39.1, 44.0 d ( $^3J_{\text{PC}} = 6.9$  Hz), 64.2 d ( $^2J_{\text{POC}} = 6.0$  Hz), 108.1 d ( $^2J_{\text{FC}} = 25.6$  Hz), 111.0 d ( $^3J_{\text{PC}} = 14.2$  Hz), 112.0 d ( $^3J_{\text{FC}} = 7.5$  Hz), 113.7 d ( $^1J_{\text{PC}} = 148.4$  Hz), 117.7 d ( $^2J_{\text{FC}} = 23.6$  Hz), 120.8 d ( $^3J_{\text{FC}} = 9.2$  Hz), 132.6 d ( $^2J_{\text{PC}} = 11.5$  Hz), 133.0, 138.4, 152.5, 158.2 d ( $^1J_{\text{FC}} = 238.1$  Hz), 162.4, 168.0 d ( $^2J_{\text{PC}} = 4.3$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum ( $\text{DMSO}-d_6$ ):  $\delta_{\text{P}}$  36.89 ppm. Mass spectrum (MALDI),  $m/z$ : 467  $[M + \text{H}]^+$ . Found, %: C 51.26; H 4.33; Cl 7.39; F 3.87; N 11.80; P 6.43.  $\text{C}_{20}\text{H}_{21}\text{ClFN}_4\text{O}_4\text{P}$ . Calculated, %: C 51.46; H 4.53; Cl 7.59; F 4.07; N 12.00; P 6.63.

**2-Chloroethyl {2-[2-(5-bromo-2-oxoindolin-3-ylidene)hydrazinyl]-2-oxoethyl}[4-(dimethylamino)phenyl]phosphinate (3d).** Yield 87%, yellow powder, mp 250°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3410, 3128, 3077, 2995, 1689, 1599, 1522, 1483, 1373, 1314, 1189, 1123, 1026.  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta$ , ppm: 2.80 s (6H,  $\text{CH}_3$ ), 3.70 d (2H,  $\text{CH}_2$ ,  $^2J_{\text{PH}} = 18.4$  Hz), 3.79–3.82 m (2H,  $\text{CH}_2\text{Cl}$ ), 4.06–4.26 m (2H,  $\text{CH}_2\text{O}$ ), 6.58 d. d (1H, ArH,  $^3J_{\text{HH}} = 8.3$ ,  $^4J_{\text{PH}} = 2.2$  Hz), 6.86 d (1H, ArH,  $^3J_{\text{HH}} = 8.3$  Hz), 7.41 s (1H, ArH), 7.45–7.53 m (3H, ArH), 11.29 s (1H, NH), 12.31 s (1H, NH).  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta_{\text{C}}$ , ppm: 35.5 d ( $^1J_{\text{PC}} = 84.4$  Hz), 38.9, 43.9 d ( $^3J_{\text{PC}} = 7.4$  Hz), 64.1 d ( $^2J_{\text{POC}} = 4.7$  Hz), 110.9 d ( $^3J_{\text{PC}} = 13.9$  Hz), 112.8, 113.8 d ( $^1J_{\text{PC}} = 148.6$  Hz), 121.6, 123.3, 132.5 d ( $^2J_{\text{PC}} = 10.8$  Hz), 133.4, 141.1, 152.4, 161.8, 167.9 d ( $^2J_{\text{PC}} = 4.5$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum ( $\text{DMSO}-d_6$ ):  $\delta_{\text{P}}$  36.84 ppm. Mass spectrum (MALDI),  $m/z$ : 528  $[M + \text{H}]^+$ . Found, %: C 45.32; H 3.81; Br 14.94; Cl 6.52; N 10.32; P 5.37.  $\text{C}_{20}\text{H}_{21}\text{BrClN}_4\text{O}_4\text{P}$ . Calculated, %: C 45.52; H 4.01; Br 15.14; Cl 6.72; N 10.62; P 5.87.

**2-Chloroethyl [4-(diethylamino)phenyl]{2-oxo-2-[2-(2-oxoindolin-3-ylidene)hydrazinyl]ethyl}phosphinate (3e).** Yield 78%, yellow powder, mp 170°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3125, 3070, 2971, 2932, 1678, 1623, 1597, 1520, 1469, 1311, 1226, 1127, 1028.  $^1\text{H}$  NMR spectrum ( $\text{DMSO}-d_6$ ),  $\delta$ , ppm: 0.96 t (6H,  $\text{CH}_3$ ,  $^3J_{\text{HH}} = 6.9$  Hz), 3.19 q (4H,  $\text{CH}_2$ ,  $^3J_{\text{HH}} = 6.8$  Hz), 3.68 d. d (2H,  $\text{CH}_2$ ,  $^2J_{\text{PH}} = 18.7$ ,  $^2J_{\text{HH}} = 9.5$  Hz), 3.81 d. d (2H,  $\text{CH}_2\text{Cl}$ ,

$^3J_{\text{HH}} = 10.2$ ,  $^4J_{\text{PH}} = 4.2$  Hz), 4.08–4.26 m (2H, CH<sub>2</sub>O), 6.54 d. d (1H, ArH,  $^3J_{\text{HH}} = 8.8$ ,  $^4J_{\text{PH}} = 2.5$  Hz), 6.72 br. d (1H, ArH,  $^3J_{\text{HH}} = 6.1$  Hz), 6.79 d (1H, ArH,  $^3J_{\text{HH}} = 8.1$  Hz), 7.05 d. d (1H, ArH,  $^3J_{\text{HH}} = 7.5$ ,  $^3J_{\text{HH}} = 7.6$  Hz), 7.44 d. d (1H, ArH,  $^3J_{\text{HH}} = 8.9$ ,  $^3J_{\text{PH}} = 11.4$  Hz), 7.48–7.52 m (1H, ArH), 11.15 s (1H, NH), 12.40 s (1H, NH).  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum (DMSO-*d*<sub>6</sub>),  $\delta_{\text{C}}$ , ppm: 12.0, 35.2 d ( $^1J_{\text{PC}} = 85.1$  Hz), 43.4, 43.9 d ( $^3J_{\text{PC}} = 7.1$  Hz), 64.0 d ( $^2J_{\text{POC}} = 5.4$  Hz), 110.3 d ( $^3J_{\text{PC}} = 14.0$  Hz), 110.9, 112.8 d ( $^1J_{\text{PC}} = 149.3$  Hz), 119.4, 120.8, 122.2, 131.3, 132.8 d ( $^2J_{\text{PC}} = 11.6$  Hz), 133.7, 142.2, 150.0, 162.2, 167.8 d ( $^2J_{\text{PC}} = 4.4$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum (DMSO-*d*<sub>6</sub>):  $\delta_{\text{P}}$  36.80 ppm. Mass spectrum (MALDI), *m/z*: 477 [*M* + *H*]<sup>+</sup>. Found, %: C 55.21; H 5.30; Cl 7.13; N 11.55; P 6.29. C<sub>22</sub>H<sub>26</sub>ClN<sub>4</sub>O<sub>4</sub>P. Calculated, %: C 55.41; H 5.50; Cl 7.43; N 11.75; P 6.49.

#### AUTHOR INFORMATION

A.V. Bogdanov, ORCID: <https://orcid.org/0000-0002-2483-4742>

A.D. Voloshina, ORCID: <https://orcid.org/0000-0002-3540-8554>

S.V. Bukharov, ORCID: <https://orcid.org/0000-0002-5130-9441>

A.V. Samorodov, ORCID: <https://orcid.org/0000-0001-9302-499X>

I.D. Krylova, ORCID: <https://orcid.org/0000-0001-8979-9135>

Z.A. Valiullina, ORCID: <https://orcid.org/0009-0006-9107-0435>

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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