Synthesis and Antimicrobial, Antiplatelet, and Anticoagulant Activities of New Isatin Derivatives Containing a Hetero-Fused Imidazole Fragment

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Received October 18, 2021; revised November 10, 2021; accepted November 12, 2021

Abstract—A series of isatin derivatives containing an adenine or theophylline fragment have been synthesized. The corresponding \(N'\)-[2-(trimethylammonio)acetyl] and \(N'\)-(2-pyridinioacetyl) hydrazones have been found to exhibit neither cytotoxicity nor hemotoxicity. Quaternary salts based on adenine derivatives of 5-methyl- and 5-ethylisatins showed the highest antiplatelet activity which exceeded the activity of acetylsalicylic acid by a factor of 1.5.

Keywords: isatin, xanthines, hydrazones, antimicrobial activity, hemotoxicity, anticoagulants, antiplatelet activity

DOI: 10.1134/S1070428022030101

INTRODUCTION

Imidazole derivatives exhibit a broad spectrum of biological activity [1–3] (Fig. 1). Among them, 4-nitroimidazoles like A have been studied most thoroughly. A particular position in the series of functionally substituted imidazoles is occupied by 4,5-hetero-fused derivatives of natural and synthetic origins, namely purines and xanthines. Adenine (9\(H\)-purin-6-amine) is a natural compound whose derivatives are potential scaffolds for the design of compounds possessing antiviral [4] and antimicrobial activities [5, 6] (e.g., structure B in Fig. 1). Another important and interesting class of hetero-fused imidazoles is represented by xanthines that are referred to as privileged structures [7, 8]. Studies of xanthine derivatives containing methyl groups at different positions (theophylline, caffeine, theobromine) resulted in the discovery of pentoxifylline (D) which is an efficient drug in the therapy of cardiovascular diseases [9]. It has also been reported that combinations of caffeine (1,3,7-trimethylxanthine) with a number of antibiotics show enhanced antibacterial activity against \(P.\) aeruginosa and \(S.\) aureus [10].

The use of the isatin scaffold in searching for new antibacterial and antiviral drugs, including those active against SARS CoV-2 [11–16], and the synthesis of
hybrid compounds based on isatin and imidazole remain important problems. It should be noted that we have found no published data on antimicrobial properties of isatin derivatives containing an imidazole moiety nor data on their effect on hemostasis. Only antiviral activity of isatin thiosemicarbazone \( (\text{C}) \) containing a benzimidazole fragment at \( N^1 \) has been reported [17].

Our studies in the field of isatin-based ammonium salts indicated high potential of these compounds as efficient and nontoxic antimicrobial agents and hence the necessity of more profound structural modification of their molecules [18–23].

RESULTS AND DISCUSSION

Herein we describe the synthesis of a new series of isatin derivatives linked to a purine fragment through an ethylene bridge. The alkylation of isatins containing a substituent in the aromatic ring was carried out according to the procedure described in [22] using 9-(2-bromoethyl)adenine and 7-(2-chloroethyl)theophylline as alkylating agents (Scheme 1). Compounds \( 1a–1c, 2a, \) and \( 2b \) were obtained in high yields, and they required no further purification. The yields of theophylline derivatives \( 2a \) and \( 2b \) were slightly lower, presumably due to their better solubility in aqueous DMF; we failed to isolate additional amounts of these compounds therefrom. The structure of isatin derivatives \( 1a–1c, 2a, \) and \( 2b \) was unambiguously confirmed by IR and \( ^1H \) and \( ^{13}C \) NMR spectra.

Compounds \( 1a–1c, 2a, \) and \( 2b \) were then reacted with acetohydrazides containing a trimethylammonium, pyridinium, or 2,3-dimethylpyridinium cationic center (Scheme 2). The resulting ammonium salts \( 3a–3d, 4a, \) and \( 4b \) (yield 80–96%) were yellow solid powders. Their structure was confirmed by IR and NMR spectra. The IR spectra of all compounds \( 3 \) and \( 4a \) showed a broadened absorption band in the region 3318–3446 cm\(^{-1} \) due to stretching vibrations of the hydrazone \( N–H \) bond. The IR spectra of theophylline derivatives \( 4a \) and \( 4b \) contained an additional medium-intensity band at about 3540 cm\(^{-1} \), which indicated their existence in crystal as mixtures of two isomers with respect to the hydrazone \( C=N \) bond. Furthermore, in the far IR region of the spectra of adenine derivatives \( 3a–3d \) (3137–3205 cm\(^{-1} \)) we observed narrow absorption peaks corresponding to \( N–H \) stretchings of the primary amino group. The presence of two isomers of hydrazones \( 4a \) and \( 4b \) in solution was also confirmed by their \( ^1H \) NMR spectra recorded from solutions in DMSO-\( d_6 \)-D\(_2\)O, where the signals from methylene protons of the ethylene bridge (δ 4.16, 4.52 ppm) and methylene group linked to the quaternary nitrogen atom (δ 4.88 ppm) were broadened.

Biological testing of new hydrazones \( 3a–3d, 4a, \) and \( 4b \) against both sensitive and methicillin-resistant (MRSA-1, MRSA-2) strains of \( S. \) \textit{aureus} showed the absence of antimicrobial activity in combination with very low cytotoxicity and hemotoxicity (IC\(_{50}, HC_{50} > 600 \mu M \)). The cytotoxicity and hemotoxicity assays were carried out on human blood erythrocytes and normal liver cells (Chang liver cell line).

Being purine derivatives, adenine- and theophylline-based isatin hydrazones containing an ammonium moiety offer a significant potential as thrombolytic agents and anticoagulants [7, 24–29]. The presence in their molecules of an oxindole fragment which is con-
Considered a privileged structure enhances this potential [30–33]. Therefore, in this work we studied the effect of hydrazones $3a$–$3d$, $4a$, and $4b$ on the parameters of platelet aggregation and coagulation in hemostasis (Table 1). As follows from the data in Table 1, the examined compounds showed different antiplatelet aggregation activities. Adenine derivatives $3b$ and $3c$ containing an alkyl group at the 5-position of the indole fragment proved to be 1.5 times more active than acetylsalicylic acid with respect to platelet aggregation level, and the latent period of aggregation was prolonged by more than 30%. In addition, theophylline-based trimethylammonium salt $4b$ exhibited platelet aggregation activity which exceeded the activity of etamsylate more than twofold without affecting the latent period.

**EXPERIMENTAL**

The $^1$H and $^{13}$C NMR spectra were recorded on Bruker Avance-400 (400 MHz for $^1$H and 100.6 MHz) and Bruker Avance-600 (600 MHz for $^1$H and 150.9 MHz for $^{13}$C) spectrometers (Germany) using DMSO-$d_6$, CDCl$_3$–DMSO-$d_6$, or D$_2$O–DMSO-$d_6$ as solvent; the chemical shifts were measured relative to the residual proton and carbon signals of the deuterated solvent. Signals from hydrogen-bearing carbons were assigned on the basis of $^{13}$C DEPT spectra. The mass spectra (MALDI) were run on a Bruker UltraFlex III TOF/TOF mass spectrometer (Germany). The IR spectra were recorded on a Bruker Vector-22 spectrometer (Germany) from samples dispersed in mineral oil and placed between KBr plates. Elemental analysis was performed on a Euro Vector 2000 CHNS-O analyzer (Italy). The melting points were measured with a Stuart SMP10 melting point apparatus (UK).

Citrate blood was centrifuged on an OPN-3.02 centrifuge (DASTAN, Kyrgyzstan). Platelet aggregation was studied according to the procedure described in [34] using an AT-02 aggregometer (Medtekh, Russia). Anticoagulant activity was estimated using a Solar CGL 2110 turbidimetric hemocoagulometer (SOLAR, Russia). The results were processed using Statistica 10.0 (StatSoft, USA).
Commercially available DMSO-d$_6$ (99.9 atom % D, Acros Organics), CDCl$_3$ (99.8 atom % D, Acros Organics), D$_2$O (99.8 atom % D, Acros Organics), trifluoroacetic acid (98%, Acros Organics), isatin (98%, Acros Organics), 5-methylisatin (95%, Acros Organics), 7-(2-chloroethyl)theophylline (≥98.0%, TCI Chemicals), and adenine (>99.0%, TCI Chemicals) were used. 5-Ethylisatin [35] and 9-(2-bromoethyl)-adenine [36] were synthesized according to literature procedures.

Isatin derivatives 1a–1c, 2a, and 2b (general procedure). Isatin, 5-methylisatin, or 5-ethylisatin (10 mmol) was dissolved in 20 mL of DMF, and 0.42 g of sodium hydride (10 mmol, 60% suspension in mineral oil) was added with stirring on a magnetic stirrer at 10°C. The mixture was allowed to warm up to 25°C over a period of 30 min, and 7-(2-chloroethyl)theophylline (2.43 g, 10 mmol) or 9-(2-bromoethyl)-adenine (2.42 g, 10 mmol) was added. The resulting solution was stirred at 60°C for 3 h and poured into a mixture of 100 g of ice and 50 mL of water. The mixture spontaneously warmed up to 25°C, and the solid product was filtered off, washed with diethyl ether, and dried under reduced pressure (18 mm Hg, water-jet pump).

| Compound no. | Latent period | Maximum amplitude | Platelet aggregation rate | Time of achieving maximum amplitude | APTT$^b$ |
|-------------|---------------|-------------------|--------------------------|--------------------------------------|-----------|
| 3a          | +3.1 (2.4–6.4)$^c$ | −5.8 (4.7–6.4)$^c$ | −11.4 (10.5–15.7)$^c$ | +14.7 (12.9–15.3)$^{d,e}$ | +3.7 (2.9–5.4)$^c$ |
| 3b          | +5.6 (4.3–8.5)$^c$ | −19.3 (17.4–21.8)$^c$ | −28.3 (24.5–30.1)$^{d,e,f}$ | +21.3 (15.3–24.7)$^{d,e,f}$ | +6.5 (4.9–8.3)$^{c,e}$ |
| 3c          | +9.4 (7.2–12.4)$^c$ | −20.2 (18.4–23.5)$^c$ | −31.5 (26.9–34.3)$^{d,e,f}$ | +1.5 (0.8–3.4)$^{e,f}$ | +5.3 (4.1–9.6)$^{c,e}$ |
| 3d          | +6.3 (4.5–8.9)$^c$ | −4.2 (3.7–5.6)$^c$ | −3.1 (2.4–4.5)$^c$ | +2.7 (1.3–4.5)$^c$ | +2.5 (1.8–4.3)$^c$ |
| 4a          | +3.2 (1.5–5.6)$^c$ | −6.3 (5.4–7.1)$^c$ | −15.4 (11.7–19.4)$^c$ | +21.6 (17.4–25.3)$^{d,e,f}$ | +8.4 (7.3–10.4)$^{c,e}$ |
| 4b          | +1.1 (0.4–2.3)$^{c,g}$ | +8.3 (7.4–10.5)$^{c,f,g}$ | +12.7 (10.6–15.3)$^c$ | −10.5 (7.4–13.3)$^{c,g}$ | +7.3 (5.6–9.4)$^{c,e}$ |
| Acetylsalicylic acid | −2.1 (1.1–2.6) | −13.7 (10.8–16.4)$^c$ | −10.5 (7.6–12.3)$^c$ | +10.5 (8.7–13.4)$^c$ | +1.1 (0.5–1.9)$^c$ |
| Etamsylate | −16.7 (13.5–18.4)$^{d,f}$ | +3.4 (2.7–4.4)$^{c,e,f}$ | +16.7 (14.3–20.1)$^{d,f}$ | +14.2 (10.3–15.6)$^{c,f}$ | − |
| Sodium heparin | − | − | − | − | +20.3 (19.7–21.4)$^d$ |

$^a$ The latent period is given for collagen-induced platelet aggregation, and the other parameters correspond to ADP-induced platelet aggregation.

$^b$ APTT is activated partial thromboplastin time.

$^c$ $p \leq 0.05$.

$^d$ $p \leq 0.001$ (compared to control).

$^e$ $p \leq 0.05$ (compared to sodium heparin).

$^f$ $p \leq 0.001$ (compared to acetylsalicylic acid).

$^g$ $p \leq 0.05$ (compared to etamsylate).

$^h$ “−” stands for no data; $n = 6$.

1-[2-(6-Amino-9H-purin-9-yl)ethyl]-2,3-dihydro-1H-indole-2,3-dione (1a). Yield 2.74 g (89%), orange powder, mp 242°C (decomp.). IR spectrum, $\nu$, cm$^{-1}$: 3442, 3318, 3160, 3104, 1732, 1732, 1652, 1611, 1596, 1473, 1362, 1300, 1186, 1150, 1096. $^1$H NMR spectrum (CDCl$_3$–DMSO-d$_6$, 1:1), $\delta$, ppm: 4.13 t (2H, CH$_2$, $J_3 = 5.7$ Hz), 4.50 t (2H, CH$_2$, $J_3 = 5.7$ Hz), 6.83 d (1H, $J_3 = 8.4$ Hz), 7.01 d (1H, $J_3 = 7.5$, 7.5 Hz), 7.44 d (1H, $J_3 = 7.5$, 7.5 Hz), 7.82 s (2H, NH$_2$), 8.10 s (1H), 8.20 s (1H). Mass spectrum: $m/z$ 309 [M + H]$^+$. Found, %: C 58.30; H 3.78; N 27.09. C$_{15}$H$_{12}$N$_6$O$_2$. Calculated, %: C 58.44; H 3.92; N 27.26.

1-[2-(6-Amino-9H-purin-9-yl)ethyl]-5-methyl-2,3-dihydro-1H-indole-2,3-dione (1b). Yield 2.54 g (79%), orange powder, mp 254°C (decomp.). IR spectrum, $\nu$, cm$^{-1}$: 3564, 3360, 3160, 3108, 2925, 1732, 1682, 1656, 1618, 1601, 1492, 1420, 1345, 1302, 1157, 1130. $^1$H NMR spectrum (CDCl$_3$–DMSO-d$_6$, 1:1), $\delta$, ppm: 2.21 s (3H, CH$_3$), 4.09 t (2H, CH$_2$, $J_3 = 5.8$ Hz), 4.48 t (2H, CH$_2$, $J_3 = 5.8$ Hz), 6.62 d (1H, $J_3 = 8.0$ Hz), 7.20 br.d (1H, $J_3 = 8.4$ Hz), 7.22 br.s (1H, 4-H), 7.49 s (2H, NH$_2$), 8.06 s (1H), 8.10 s (1H). Mass spectrum: $m/z$ 323 [M + H]$^+$. Found, %: C 59.50; H 4.23; N 25.89. C$_{16}$H$_{14}$N$_6$O$_2$. Calculated, %: C 59.62; H 4.38; N 26.07.
1-[2-(6-Amino-9H-purin-9-yl)ethyl]-5-ethyl-2,3-dihydro-1H-indole-2,3-dione (1c). Yield 2.65 g (79%), orange powder, mp 228°C. IR spectrum, v, cm⁻¹: 3363, 3166, 2929, 1742, 1723, 1653, 1616, 1418, 1342, 1306, 1255, 1128, 1081. ¹H NMR spectrum (DMSO-d₆), δ, ppm: 1.12 t (3H, CH₃, 3J = 7.7 Hz), 2.54 q (2H, CH₂, 3J = 7.6 Hz), 4.08 t (2H, CH₂, 3J = 5.3 Hz), 4.41 t (2H, CH₂, 3J = 5.3 Hz), 6.82 d (1H, 3J = 8.0 Hz), 7.09 s (2H, NH₂), 7.32 brs (1H, 4-H), 7.35 brd (1H, 3J = 7.8 Hz), 7.96 s (1H), 8.13 s (1H). Mass spectrum, m/z 337 [M + H]⁺. Found, %: C 60.52; H 4.63; N 24.79. C₁₇H₁₆N₆O₂. Calculated, %: C 60.71; H 4.79; N 24.99.

7-[2-(2,3-Dioxo-2,3-dihydro-1H-indol-1-yl)ethyl]-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (2a). Yield 2.58 g (73%), orange powder, mp >300°C. IR spectrum, v, cm⁻¹: 3466, 3107, 2961, 1746, 1700, 1659, 1611, 1550, 1474, 1407, 1373, 1350, 1233, 1157. ¹H NMR spectrum (DMSO-d₆), δ, ppm: 3.14 s (3H, CH₃), 3.38 s (3H, CH₃), 4.10 t (2H, CH₂, 3J = 5.4 Hz), 4.51 t (2H, CH₂, 3J = 5.4 Hz), 6.82 d (1H, 3J = 8.1 Hz), 7.05 d.d (1H, 3J = 7.5, 7.5 Hz), 7.52–7.48 m (2H), 8.10 s (1H). Mass spectrum: m/z 376 [M + Na]⁺. Found, %: C 57.58; H 4.03; N 19.72. C₁₇H₁₅N₅O₄. Calculated, %: C 57.79; H 4.28; N 19.82.

1,3-Dimethyl-7-[2-(5-methyl-2,3-dihydro-1H-indol-1-yl)ethyl]-1H-purine-2,6(3H,7H)-dione (2b). Yield 2.75 g (75%), orange powder, mp >300°C. IR spectrum, v, cm⁻¹: 3467, 3135, 2923, 2855, 1739, 1699, 1659, 1598, 1543, 1494, 1447, 1349, 1227, 1136. ¹H NMR spectrum (DMSO-d₆), δ, ppm: 2.23 s (3H, CH₃), 3.14 s (3H, CH₃), 3.38 s (3H, CH₃), 4.07 t (2H, CH₂, 3J = 5.5 Hz), 4.49 t (2H, CH₂, 3J = 5.5 Hz), 6.82 d (1H, 3J = 8.1 Hz), 6.73 d (1H, 3J = 8.7 Hz), 7.33–7.31 m (2H), 8.08 s (1H). Mass spectrum: m/z 368 [M + H]⁺. Found, %: C 58.72; H 4.50; N 19.83. C₁₈H₁₇N₅O₄. Calculated, %: C 58.85; H 4.66; N 19.06.

Ammonium salts 3a–3d, 4a, and 4b (general procedure). Isatin derivative 1a–1c, 2a, or 2b (0.28 mmol) was dissolved in 10 mL of anhydrous ethanol, the corresponding hydrazide (0.28 mmol) was added in one portion, and 2 drops of trifluoroacetic acid were added. The mixture was refluxed for 1.5 h and allowed to cool down to room temperature, and the precipitate was filtered off, washed with anhydrous diethyl ether, and dried under reduced pressure (12 mm Hg).

2-(2-[1-(2-(6-Amino-9H-purin-9-yl)ethyl]-5-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylidene)hydrazinyl]-N,N-trimethyl-2-oxoethan-1-aminium chloride (3a). Yield 0.12 g (91%), yellow powder, mp 270°C (decomp.). IR spectrum, v, cm⁻¹: 3318, 3137, 3050, 2968, 1690, 1635, 1514, 1488, 1418, 1366, 1260, 1201, 1133, 1057. ¹H NMR spectrum (DMSO-d₆), δ, ppm: 1.17 t (3H, CH₃, 3J = 7.6 Hz), 2.62–2.59 m (2H, CH₂), 4.23 t (2H, CH₂, 3J = 5.5 Hz), 4.52 t (2H, CH₂, 3J = 5.5 Hz), 6.20 brs [2H, CH₂C(O)], 6.97 d (1H, 3J = 6.6 Hz), 7.23 d (1H, 3J = 7.7 Hz), 7.38 brs (1H), 7.99 brs (2H, NH₂), 8.18 s (1H), 8.27 d.d (1H, 3J = 6.9, 6.7 Hz), 8.30 s (1H), 8.73 d.d (1H, 3J = 7.9, 7.9 Hz), 9.12–9.09 m (2H), 12.53 s (1H, NH). Mass spectrum: m/z 470 [M – Cl]⁻. Found, %: C 56.83; H 4.59; N 24.80. C₂₄H₂₄ClN₅O₂. Calculated, %: C 56.97; H 4.78; N 24.92.

2-(2-[1-(2-(6-Amino-9H-purin-9-yl)ethyl]-5-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylidene)hydrazinyl]-N,N-trimethyl-2-oxoethan-1-aminium chloride (3b). Yield 0.12 g (91%), yellow powder, mp 270°C (decomp.). IR spectrum, v, cm⁻¹: 3446, 3205, 3149, 2941, 1723, 1691, 1665, 1491, 1440, 1350, 1308, 1242, 1153, 1086. ¹H NMR spectrum (DMSO-d₆, 1:3), δ, ppm: 2.26 s (3H, CH₃), 3.31 brs (9H, NMe₃), 4.16 t (2H, CH₂, 3J = 5.0 Hz), 4.52 t (2H, CH₂, 3J = 5.0 Hz), 4.88 brs [2H, CH₂C(O)], 6.83 d (1H, 3J = 8.1 Hz), 7.15 brd (1H, 3J = 8.1 Hz), 7.37 brs (1H), 8.18 s (1H), 8.33 s (1H). ¹³C NMR spectrum (DMSO-d₆, 1:3), δ, ppm: 20.7 (CH₃), 40.0 (CH₂), 41.8 (CH₃), 54.1 (CH₂), 62.3 (CH₂), 109.7 (CH), 118.3, 118.8, 121.7 (CH), 132.9 (CH), 133.0, 135.5, 141.1, 143.6 (CH), 147.5 (CH), 149.5, 151.9, 161.2, 166.4. Mass spectrum: m/z 436 [M – Cl]⁻. Found, %: C 53.29; H 5.41; N 26.58. C₂₁H₂₆ClN₉O₂. Calculated, %: C 53.44; H 5.55; N 26.71.
drazinyl)-2-oxoethyl]-2,3-dimethylpyridinium bromide (3d). Yield 0.14 g (90%), yellow powder, mp 218°C (decomp.). IR spectrum, ν, cm⁻¹: 3368, 3179, 3019, 2971, 1691, 1655, 1626, 1596, 1492, 1364, 1249, 1215, 1147, 1127, 1050. ¹H NMR spectrum (DMSO-d₆), δ, ppm: 2.30 s (3H, CH₃), 2.54 s (3H, CH₃), 2.65 s (3H, CH₃), 4.21 t (2H, CH₂, J = 5.3 Hz), 4.51 t (2H, CH₂, 3J = 5.3 Hz), 6.18 brs [2H, CH₂C(O)], 6.92 d (1H, 3J = 7.2 Hz), 7.20–7.19 m (1H), 7.38 br.s (1H), 7.77 brs (2H, NH₂), 7.96 d.d (1H, 3J = 7.2, 6.7 Hz), 8.13 s (1H), 8.23 s (1H), 8.49 d (1H, 3J = 7.1 Hz), 8.87 br.s (1H), 12.54 s (1H, NH). ¹³C NMR spectrum. ¹H NMR spectrum (D₂O–DMSO-d₆, 1:3), δ, ppm: 20.6 (CH₃), 27.7 (CH₃), 29.7 (CH₃), 30.7 (CH₂), 31.8 (CH₂), 41.5 (CH₂), 59.3 (CH₃), 109.7 (CH), 118.4 (CH), 118.9, 121.6, 124.9 (CH), 123.8, 130.9, 131.5, 138.9, 141.1 (CH), 142.6 (CH), 144.9, 147.0 (CH), 149.7 (CH), 153.5, 161.2, 167.1. Mass spectrum: m/z 481 [M + Cl]⁺. Found, %: C 53.30; H 5.47; N 22.17. C₂₅H₂₆BrN₉O₂. Calculated, %: C 53.43; H 5.65; N 21.67.

CONCLUSIONS

The proposed approach makes it possible to synthesize in two steps isatin derivatives containing an adenine or theophylline fragment in high yields. All newly synthesized compounds showed antiplatelet aggregation activity, and the activity of adenine derivatives of 5-methyl- and 5-ethylisatins exceeded the activity of acetylsalicylic acid by a factor of 1.5. The low toxicity of the obtained hydrazones to human erythrocytes and normal liver cells suggests prospects of using them as antiplatelet aggregation agents, as well as for preventing and terminating bleeding.

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ACKNOWLEDGMENTS

The authors thank the joint spectral and analytical center (Kazan Scientific Center, Russian Academy of Sciences) for technical support. Study of antiplatelet aggregation activity was performed according to the cooperation agreement between the Kazan Scientific Center (Russian Academy of Sciences) and Bashkir State Medical University (Ministry of Health of the Russian Federation).

FUNDING

This study was financially supported by the Program for Strategic Academic Leadership of Kazan (Volga Region) Federal University.
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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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