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S_NAr Reactions on 2-Amino-4,6-dichloropyrimidine-5-carbaldehyde

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Abstract: We report the experimental results of unexpected aromatic nucleophilic substitution reaction products on 2-amino-4,6-dichloropyrimidine-5-carbaldehyde. The isolated compounds are products of amination, solvolysis, and condensation processes under mild and environmentally friendly conditions, due to the influence of structural factors of the starting pyrimidine and a high concentration of alkoxide ions. This method allows the building of pyrimidine-based compound precursors of *N*-heterocyclic systems.

Keywords: amination; dichloropyrimidines; aromatic substitution

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Citation: Trilleras, J.; Pérez-Gamboa, A.; Quiroga, J. S_NAr Reactions on 2-Amino-4,6-dichloropyrimidine-5-carbaldehyde. *Molbank* **2022**, *2022*, M1426. https://doi.org/10.3390/M1426

Academic Editor: Ian R. Baxendale

Received: 30 June 2022
Accepted: 10 August 2022
Published: 12 August 2022

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1. Introduction

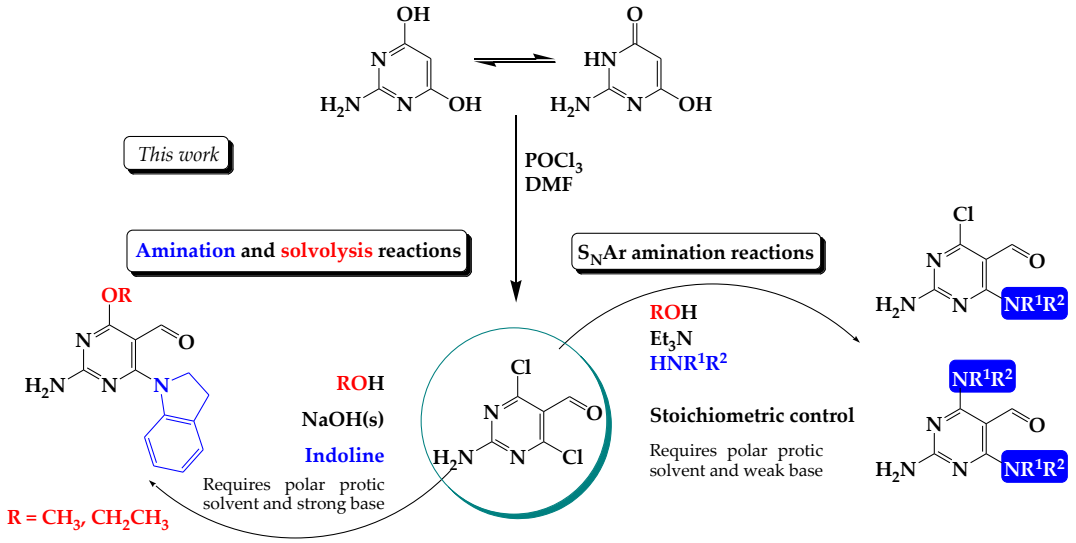
After the pyridine scaffold, the pyrimidine core is regarded as the second heteroaromatic ring present in pharmaceutically active compounds [1,2]. The main justification for this work is researching and exploring synthetic methods to produce this significant class of heterocyclic systems. In particular, functionalized pyrimidines with amino and halogen groups become suitable precursors for a number of structural alterations in the synthesis of pyrimidine-based compounds [3–7]. Halopyrimidines can be made by the Vilsmeier–Haack reaction, which efficiently converts 4,6-dihydroxypyrimidines to 4,6-dichloropyrimidines [8,9]. Another regioselective synthetic strategy is to obtain 2-chloropyrimidines from available 2,4-dichloropyrimidines through regioselective dechlorination [10]. These synthetic protocols are complementary to the conventional synthesis of pyrimidines and analogues through the reaction between β-dicarbonyl compounds (and its synthons) and components with an N–C–N fragment (urea, thiourea, amidine, or guanidine) [11,12]. The halogenated pyrimidines can incorporate nucleophiles regioselectivity via S_NAr reaction, unlike other nitrogen heterocycles such as pyridine and imidazole [4]. Substitution reactions that include Grignard agents [13], cross-coupling reactions to build aryl-heteroaryl or heteroaryl-heteroaryl bonds [4,14,15], and alkoxy and amino groups [16–19]. In this work, we report a sequence of reactions of S_NAr, solvolysis, and Claisen–Schmidt condensation on symmetrically substituted 2-amino-4,6-dichloropyrimidine-5-carbaldehyde.

2. Results

Chemistry

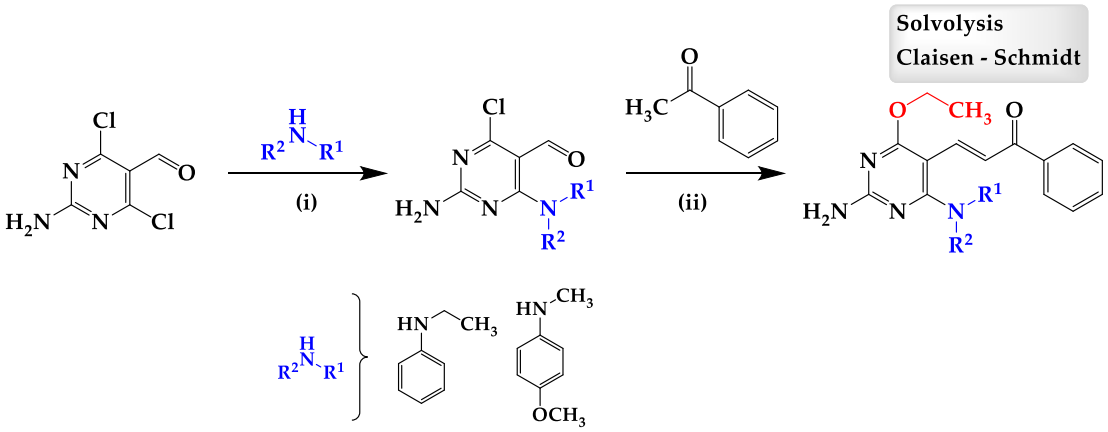
Unlike the reactions of S_NAr on 2,4-dichloropyrimidine derivatives—in which Lewis acid atoms, functional groups, or catalysts are required to enhance the ratio of isomers and favor substitutions at the C-2 position when weak nucleophilic amines are used—S_NAr reactions on symmetrically substituted 4,6-dichloropyrimidine derivatives under conventional conditions and stoichiometric control of reactants work well with different types of nucleophilic amines [19]. However, by increasing the alkalinity on the medium in which

the reaction takes place under stoichiometric control of reactants' reactions, both S_NAr amination and solvolysis reactions are observed (Scheme 1).



Scheme 1. Amination and solvolysis reactions on 2-amino-4,6-dichloropyrimidin-5-carbaldehyde.

Similar behavior was observed in derivatization reactions to produce heterocyclic analogs of chalcones by the conventional Claisen–Schmidt condensation method between pyrimidines mono-aminated (prepared following the reported methodology [19]) and acetophenone (Scheme 2).



Scheme 2. (i) Ethanol, TEA, HNR^1R^2, reflux for 3 h [19]; (ii) Ethanol, $NaOH_{(s)}$, reflux for 3 h.

3. Discussion

Conventional synthetic protocols without requiring regio- and chemoselective control using 2-amino-4,6-dichloropyrimidine-5-carbaldehyde as starting material should generate the expected products. In our study, exploring the conditions for incorporating complexity and molecular diversity on 2-amino-4,6-dichloropyrimidine-5-carbaldehyde, several conditions were tested—including changes in solvents, bases, and heating sources— to find the best reaction conditions for the synthesis of pyrimidine derivatives. We found that using triethylamine (TEA) in refluxing ethanol provides suitable conditions for S_NAr amination reactions with different amines (aliphatics, cyclic and alicyclic amines, aromatic, and heteroaromatic and benzylic amines) and to provide the mono-substituted compounds [19]. The increase in alkalinity on the reaction medium influences the isolated products (**I–IV**) (Figure 1), unlike previously reported results [19]. The alcohols used as solvents favor

the S_NAr reaction and at the same time, with NaOH in the medium, the formation of alkoxide ions.

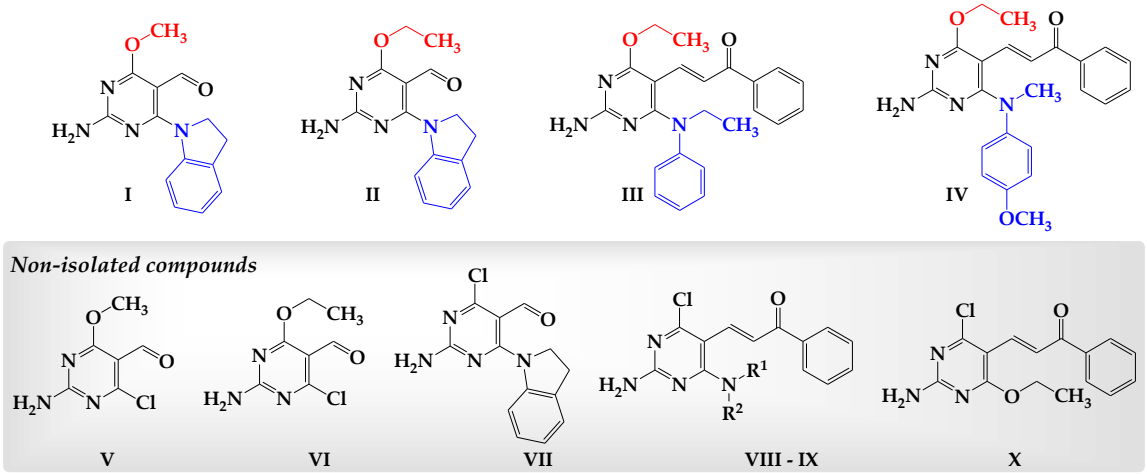


Figure 1. Isolated (**I**–**IV**) and expected (**V**–**X**) compounds.

The 2-amino-4,6-dichloropyrimidine-5-carbaldehyde is a symmetric compound in which all positions, except for the position at C–5, are α and/or γ to a nitrogen inside the ring. Consequently, when undergoing S_NAr amination reactions, the second nitrogen atom of the ring decreases electron density and contributes to the stabilization of anionic intermediates, increasing reactivity.

Based on these results, the structural characteristics of the compounds obtained moderate yield and incorporation of alkoxide ions, the formation of compounds (**I**–**IV**) results from competition between soft (amine) and hard (alkoxide) nucleophiles present. Equimolar addition of the amine is expected to control the mono-substitution on the pyrimidine ring, but the formation of alkoxide ions—which are stronger bases and better nucleophiles—compete towards substitution even if they are not in equal proportions.

Compounds **I**–**IV** were isolated, purified by recrystallization from ethanol, and their structures were ascertained by IR, MS, and NMR (^{1}H and ^{13}C) analysis. Copies of the spectra are included in supporting information. In the ^{1}H-NMR spectrum of the isolated compounds **I**–**IV**, the inclusion of the respective alkoxide ions is evidenced. Low field signals, with displacement and multiplicity characteristics for groups –OCH_3 and –OCH_2CH_3, were observed. In compound **I**, the signal for the methoxy group appear as a singlet at 3.92 ppm; for compound **II**, the signals at 1.34 and 4.37 ppm associated with protons the ethoxy group.

In the ^{1}H-NMR spectrum for the pyrimidine-based chalcones, the signals for the ethoxy groups appear at 1.13 and 4.37 ppm for compound **III**, and at 1.38 and 4.39 ppm for compound **IV**. Additionally, the doublets associated with the α,β-vinyl protons in *E* configuration of the new C=C bond formed at 7.17 ppm (J = 15 Hz, Hα) and 7.31 ppm (J = 15.5 Hz, Hβ) for compound **III**; and at 7.15 (J = 15.5 Hz, Hα) and 7.35 (J = 15.5 Hz, Hβ) for compound **IV**.

Compounds **V**–**X** were not isolated under these reaction conditions. The excess of NaOH added increases the alkoxide ions and the solvolysis reactions, making it difficult to direct towards the exclusive obtention of the S_NAr amination product. No study was conducted with equimolar, lesser, or catalytic quantities of NaOH. Pyrimidine-based chalcones **III**–**IV** were prepared under the conventional method of cross-aldol condensation. The Claisen–Schmidt condensation reaction uses excess solid basic catalyst and polar solvent, generating conditions in which the 2-amino-4,6-dichloropyrimidine-5-carbaldehyde undergoes solvolysis and condensation via the 'one pot' process. These reaction conditions can lead to byproduct formation due to Michael addition; although they were not identified, it could be a factor that affects the low yield of the isolated products [20].

4. Materials and Methods

4.1. General Remarks

The 2-amino-4,6-dichloropyrimidine-5-carboxaldehyde was prepared according to Vilsmeier–Haack formylation methodology reported in the literature, starting from the commercially acquired 2-amino-4,6-dihydroxypyrimidine [19]. The reagents and solvents used in the S_NAr and Claisen–Schmidt reactions were commercially purchased (Sigma-Aldrich (St. Louis, MO, USA) or Merck (Kenilworth, NJ, USA)), without further purification.

Monitoring of the reactions was carried out with silica gel TLC plates (Merck (Kenilworth, NJ, USA) silica 60 F254). Spots were visualized with UV light at 254 and 365 nm. Melting points (uncorrected) were determined with a Thermo Scientific melting point apparatus, model IA 9100/Capillary. Infrared spectra (FT–IR) were collected at resolution of 2 cm^{-1} and 16 scans, (transmission mode 4000–500 cm^{-1}) using a Shimadzu FTIR 8400 spectrophotometer (Scientific Instruments Inc., Seattle, WA, USA) and KBr disks. NMR spectra ^1H and ^{13}C (DEPT—135) were recorded on a Bruker Advance spectrophotometer operating at 400 and 100 MHz, respectively, using TMS as internal standard (d, 0.0 ppm) and DMSO–d_6 as solvents. The NMR signals are reported in ppm and coupling constants (*J*) are reported in Hertz. Mass spectra were recorded in a Thermo Fisher Scientific (Waltham, MA, USA) GC–MS spectrometer model DSQII (Thermo Fisher Scientific Inc., Waltham, MA, USA) using a direct insertion probe and the electron impact ionization technique (70 eV). HRMS was recorded in an Agilent Technologies QTOF 6520B spectrometer coupled to a HPLC Agilent–1200 equipped with an Agilent Zorbax extend C18 (2.1 × 50 × 1.8 mm) PN 727700-902 column, via electrospray ionization (ESI) and analyzed in a positive mode. HPLC method: 0,4 mL/min, gradient from acetonitrile/water (10%, with 0.1% of formic acid) to acetonitrile (with 0.1% of formic acid). Microanalysis was performed on an Agilent CHNS elemental analyzer (Thermo Fischer Scientific Inc., Madison, WI, USA) and the values are within ±0.4% of the calculated values.

4.2. Synthesis and Characterization

Synthesis of 2-amino-4-(indolin-1-yl)-6-alkoxypyrimidine-5-carbaldehydes (**I**–**II**). To a mixture between 2-amino-4,6-dichloropyrimidin-5-carbaldehyde and indoline—in equimolar amounts (1 mmol)—in ethanol or methanol (5.0 mL), NaOH (0.2 g, 5 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. TLC was used to monitor the progress of the reaction. The solid obtained was isolated by filtration and recrystallized from ethanol. The purity of the product was confirmed by TLC test.

2-amino-4-(indolin-1-yl)-6-methoxypyrimidine-5-carbaldehyde **I**. White solid. M.p. 173–174 °C, 60% yield. ^1H-NMR (400 MHz DMSO–d_6) δ (ppm): 3.02 (t, 2H, CH_2), 3.92 (m, 5H, NCH_2, OCH_3), 6.91 (t, 1H, CH, *J* = 7.4 Hz), 7.07 (t, 1H, CH, *J* = 7.5 Hz), 7.21 (d, 1H, CH, *J* = 7.5 Hz), 7.27 (s, 2H, NH_2), 7.40 (d, 1H, CH, *J* = 8.1 Hz), 9.84 (s, 1H, CHO). ^{13}C-NMR δ (ppm): 28.2 (CH_2), 52.8 (CH_2), 53.8 (CH_3), 95.6 (C5), 116.8 (CH), 122.3 (CH), 124.6 (CH), 126.1 (CH), 132.8, 143.8, 160.1 (C6), 162.6 (C2), 172.7 (C4), 181.9 (CHO). IR, KBr (cm^{-1}): 3486–3461 (NH_2, st), 1663 (C=O, st). MS (70 eV) *m/z* (%): 270 (M^+, 100), 252 (30), 253 (30), 227 (23), 118 (63), 117 (36), 91 (40), 77 (26), 68 (30), 43 (59). Anal. calcd. for $C_{14}H_{14}N_4O_2$ (270.11): C, 62.21; H, 5.22; N, 20.73. Found: C, 62.45; H, 5.12; N, 20.86.

2-amino-4-ethoxy-6-(indolin-1-yl)pyrimidine-5-carbaldehyde **II**. Yellow solid. M.p. 234–236 °C, 60% yield. ^1H-NMR (400 MHz DMSO–d_6 RT) δ (ppm): 1.34 (t, 3H, CH_3), 3.03 (t, 2H, CH_2), 3.91 (t, 2H, CH_2), 4.37 (q, 2H OCH_2), 6.91 (t, 1H, CH, *J* = 7.5 Hz), 7.08 (t, 1H, CH, *J* = 7.5 Hz), 7.22 (s, 3H, CH, NH_2), 7.42 (d, 1H, CH, *J* = 8.06 Hz), 9.86 (s, 1H, CHO). ^{13}C-NMR δ(ppm): 14.4 (CH_3), 28.2 (CH_2), 52.8 (CH_2), 62.2 (OCH_2), 95.5 (C5), 116.9 (CH), 122.3 (CH), 124.6 (CH), 126.1 (CH), 132.8, 143.7, 160.1 (C4), 162.7 (C2), 172.4 (C6), 182.1 (CHO). IR, KBr (cm^{-1}): 3429–3380 (NH_2, st), 1632 (C=O, st). HR–MS calculated for $C_{15}H_{16}N_4O_2$: 284.1273, found: 284.1263. Anal. calcd. for $C_{15}H_{16}N_4O_2$ (284.13): C, 63.37; H, 5.67; N, 19.71. Found: C, 63.52; H, 5.52; N, 19.87.

Synthesis of (*E*)-3-(2-amino-4-ethoxy-6-(amino)pyrimidin-5-yl)-1-phenylprop-2-en-1-one **III**–**IV**. (i) S_NAr amination reactions: 2-amino-4,6-dichloropyrimidin-5-carbaldehyde (1 mmol),

amine (1 mmol), and triethylamine (1 mmol) in EtOH (5.0 mL) was heated under reflux for 3 h [19]. (ii) Pyrimidine-based chalcones are obtained under classical Claisen–Schmidt conditions. To an equimolar mixture of 2-amino-4-chloro-6-(ethyl(phenyl)aminopyrimidine-5-carbaldehyde (or 2-amino-4-ethoxy-6-((4-methoxy-phenyl)(methyl)amino)pyrimidin-5-carbaldehyde) and acetophenone in ethanol (8,0 mL), NaOH (0.2 g, 5 mmol) was added. Then, the reaction mixture was refluxed for 3 h. TLC was used to monitor the progress of the reaction. The precipitate obtained was isolated by filtration and recrystallized from ethanol to produce a yellow solid. The purity of the product was confirmed by TLC test.

(*E*)-3-(2-amino-4-ethoxy-6-(ethyl(phenyl)amino)pyrimidin-5-yl)-1-phenylprop-2-en-1-one **III**. Yellow solid. M.p. 157–159 °C, 20% yield. ^{1}H—NMR (400 MHz DMSO–d_6 RT) δ (ppm): 1.13 (t, 3H, CH_3), 1.39 (t, 3H, CH_3), 3.93 (q, 2H, NCH_2), 4.37 (q, 2H, OCH_2), 6.91–7.00 (m, 5H, CH), 7.17–7.23 (m, 3H, H*o*, Hα *J* = 15 Hz), 7.31 (d, 1H, Hβ, *J* = 15.5 Hz), 7.45 (t, 2H, H*m*, *J* = 7.2 Hz), 7.54 (t, 1H, H*p*, *J* = 7.2 Hz), 7.62 (s, 2H, NH_2). ^{13}C–NMR δ (ppm): 13.3 (CH_3), 14.5 (CH_3), 46.8 (NCH_2), 62.2 (OCH_2), 93.0 (C5), 118.0 (Cα), 123.1 (C*o*), 123.2 (C*p*), 127.6 (C*m*), 128.5 (C*o*), 129.3 (C*m*), 131.9 (C*p*), 137.7 (Cβ), 138.5 (C*i*), 146.9 (C*i*), 161.9 (C6), 166.1 (C2), 169.6 (C4), 189.4 (CHO). IR, KBr (cm^{-1}): 3457–3407 (NH_2, st), 1641 (C=O, st). MS (70 eV) *m*/*z* (%): 388 (M^+, 7), 283 (49), 270 (13), 269 (64), 255 (21), 241 (28), 105 (79), 77 (100), 43 (30). Anal. calcd. for $C_{23}H_{24}N_4O_2$ (388.19): C, 71.11; H, 6.23; N, 14.42. Found: C, 70.92; H, 6.11; N, 14.57.

(*E*)-3-(2-amino-4-ethoxy-6-((4-methoxyphenyl)(methyl)amino)pyrimidin-5-yl)-1- phenylprop-2-en-1-one **IV**. Yellow solid. M.p. 154–156 °C, 20% yield. ^{1}H-NMR (400 MHz DMSO–d_6 RT) δ (ppm): 1.38 (t, 3H, CH_3), 3.31 (s, 3H, NCH_3), 3.64 (s, 3H, OCH_3), 4.39 (q, 2H, CH_2), 6.77 (d, 2H, H*m*, N-aryl, *J* = 8.9 Hz), 6.96–6.99 (m, 4H, H*p*, NH_2), 7.15 (d, 1H, Hα, *J* = 15.5 Hz), 7.35 (d, 1H, Hβ, *J* = 15.5 Hz), 7.46 (t, 2H, H*m*, *J* = 7.2 Hz), 7.55 (t, 1H, H*p*, *J* = 7.2 Hz), 7.64 (d, 2H, H*o*, *J* = 8.1 Hz). ^{13}C—NMR δ (ppm): 14.5 (CH_3), 41.6 (NCH_3), 55.2 (OCH_3), 62.1 (CH_2), 92.0 (C5), 114.6 (C*m*, N-aryl), 117.9 (Cα), 124.8 (C*o*, N-aryl), 127.6 (C*o*), 128.5 (C*m*), 131.8 (C*p*), 137.8 (Cβ), 138.6 (C*i*), 142.2 (C*i*, N-aryl), 155.7 (C*p*, N-aryl), 161.6 (C4), 166.7 (C6), 169.5 (C2), 189.5 (CHO). IR, KBr (cm^{-1}): 3432–3322 (NH_2, st), 1625 (C=O, st). HR–MS calculated for $C_{23}H_{24}N_4O_3$: 404.1848, found: 404.1832. Anal. calcd. for $C_{23}H_{24}N_4O_3$ (404.18): C, 68.30; H, 5.98; N, 13.85. Found: C, 68.10; H, 5.81; N, 14.05.

5. Conclusions

The compounds obtained, despite being unexpected, follow the parameters of the S_NAr reactions and demonstrate how changes in any of the factors that govern these reactions affect the expected result or product. These mild and environmentally friendly S_NAr reaction conditions on 2-amino-4,6-dichloropyrimidine-5-carbaldehyde represent an alternative protocol to functionalize them through S_NAr amination with a variety of amines, an important intermediate for the investigation of *N*-heterocyclic compounds and potential applications.

Supplementary Materials: Spectroscopic data of the isolated compounds **I**–**IV** are available online.

Author Contributions: Experimental execution and spectroscopic analysis J.T and A.P.-G.; Technical support, data analysis and interpretation, J.Q.; Writing—original draft preparation, J.T.; Writing—review and editing, A.P.-G. and J.Q. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors express their gratitude to the Universidad del Atlántico and Universidad del Valle.

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

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