Identification of new heterocyclic compounds synthesized from 4-aminopyridine and evaluation their antibacterial effect

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ABSTRACT

Diazotization of pyridine-4-amine (1) to form diazonium chloride salt (2): pyridine-4-diazenium chloride which undergo coupling reaction with various anions in DMF, and EtOH to give: 2-(pyridine-4-yldiazonium) isoidoline-1,3-dione (3), 2-(pyridine-4-yldiazenioion) isoidoline-1-one-3-sulphoxide (4), and ethyl 2-(pyridine-4-yldiazonium) acetate (5). The last ester was converted to the acid hydrazide: 2-(pyridine-4-yldiazonium) acetoxydiazide (6) which was condensed with 4-chlorobenzaldehyde in absolute ethanol and some drops of glacial acetic acid to give the Schiff’s base: N-[(4-chlorobenzylidene) -2-(pyridine-4-yldiazonium) acetoxydiazide (7). Schiff’s base was reacted with benzoic acid derivatives (2-aminobenzoic acid, 2-hydroxybenzoic acid, and 2-mercaptobenzoic acid) in ethanol to give: N-[2-(4-chlorophenyl)-4-oxo-1,2-dihydroquinazoline-3-(4H)-yl]-2-(pyridine-4-yldiazenioion)acetamide (8), N-[2-(4-chloro-phenyl)-4-oxo-2H-benzo[e][1,3]oxazine-3-(4H)-yl-2- (pyridine-4-yldiazonium)acetamide (9), and N-[2-(4-chlorophenyl)-4-oxo-2H-benzo[e][1,3]thiazine-3-(4H)-yl]-2-(pyridine-4-yldiazenioion)acetamide (10). The spectral methods of the prepared compounds were characterized by FTIR, ¹HNMR (for compounds (4, and 10), and Uv-Vis (for compounds (3,4,8,9, and 10), besides melting points were recorded and the purity was checked through T.L.C. technique. Antibacterial activity for some of the synthesized compounds was screened.

Keywords: 4-Aminopyridine, Acid hydrazide, Diazonium salt, Dihydroquinazoline, Heterocyclic compounds, Oxazine, Schiff’s, Thiazine.


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INTRODUCTION

Heterocyclic synthesis has emerged as a powerful technique for generating new chemical entities useful for drug discovery [1]. Synthetic heterocyclic compounds especially containing hetero atom N, O, S have enormous potential primarily as agrochemicals, drugs [2]. Isoindoline-1,3-dione derivatives have structural feature –CO-N(R)-CO- and an imide ring which help them to be biologically active and pharmaceutically useful [3]. Phthalimides have received much attention due to their anti bacterial, anti fungal [4], analgesic [5], anti-tumor [6], anti-HIV activities [3], anti-inflammatory [7], antioxidant, anti-proliferative [8], acetyl cholinesterase inhibitors [9] and inhibitor of human
neuronal nitric oxide synthase [10]. 1,2- Dihydroquinazolinone (DHQZ) derivatives are used as chemotherapeutic agents for the treatment of diseases resulting from different microorganisms and now there has been a major expansion in the number of quinazolinone derivatives as drugs [11]. DHQZ is a privileged scaffold because of its extensive pharmacological activities including anti-bacterial, anti-fertility, anti-tumor, anti-fungal, analgesic efficacy [12], hypnotic, sedative, analgesic, anticonvulsant, anti-tussive, antibacteria, anti-diabetic, anti-inflammatory, and anti-tumor agents [13]. In addition to this, some therapeutic agents containing the structure of quinazolinone have been on the market or are in clinical trials for the treatment of cancer [14]. 1,3- Oxazine derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis[15]. Due to the rapid development of bacterial resistant to antibacterial agents, it is vital to discover novel scaffold for the design and synthesis of the new antibacterial agents to help in the battle against pathogenic microorganisms [16]. In the last few years oxazine derivatives have proved to be valuable synthetic intermediates and also possess important biological activities like sedative, analgesic, antipyretic, anti-conversant, anti-tubercular, anti-tumor, anti-malarial, anti-fungal, anti-bacterial, anti-viral, and analgesic activity. Due to the rapid development of bacterial resistant to antibacterial agents, it is vital to discover novel scaffold for the design and synthesis of the new antibacterial agents to help in the battle against pathogenic microorganisms [17]. 1,3- Thiazine derivatives are used in various organic synthesis and transformation as reaction intermediates. They have been used as anti tubercular, anti bacterial, anti microbial, anti tumor, insecticidal, fungicidal, herbicidal agent, tranquilizers anti radiation agents and various dyes [18]. The study aims to prepare and characterize some of new heterocyclic derivatives starting from 4-amino-pyridine by using some strategies. The methods used offer some advantages such as good yields, simple procedure, low cost, and ease of work up, and were expected to have a biological activity.

**EXPERIMENTAL**

**Instruments**

All melting points are uncorrected in degree centigrade and determined on Gallen kamp electric melting point apparatus. FTIR spectra were recorded on a SHIMADZU FTIR 8300 spectrophotometer in the range (4000 - 400)/ cm. UV/Vis spectra were recorded on UV /Vis Varian UV-Cary-100 spectrophotometers in DMSO as solvent. HNMR spectra were determined on a BRUKER-400 MHz operating 300 MHz spectrometer with tetramethyl-silane (TMS) as an internal standard, and the chemical shifts are in δ ppm using deuterated dimethylsulfoxide (DMSO-d6) as a solvent, measurements were done in Chemistry Department, AL-Al-Bayt University-Jordan. The reactions progress was monitored by thin-layer chromatography (TLC) using Fertigfollen precoated sheets type Polygram Silg, and the plates were developed with iodine vapor. The biological activity was performed by environmental laboratory, University of Baghdad, Baghdad, Iraq.

**Synthesis of diazonium salt (2) [19]**

Pyridine-4-amine (1) (0.02 mol, 1.8822 gm) was added to hydrochloric acid (10 ml, HCl +10 ml water) and cooled in ice-salt bath at (0-5) 0C with stirring and then added to cold sodium nitrite solution (1.38 gm in 5 ml) water was added slowly with stirring at 5 °C for 1 h to form diazonium salt. The mixture was diluted with water, neutralized by addition of ammonia.

**Synthesis of 2-(pyridine-4-yldiazonium) isoindoline-1, 3-dione (3) [20]**

To get stirred solution of formed, diazonium chloride salt (2) was added gradually (0.02 mol, 3.382 gm) of sodium phthalimide in DMF (20 ml) and stirring was continued for 30 min at 5 °C. The reaction temperature was then gradually raised to room temperature, then to 50 °C and after 15 min a clear yellow solution was obtained. The yielded mixture was refluxed with continuous stirring and then left to crystallize. Crystals were collected by filtrations, washed with 2% sodium bicarbonate solution and then with excess distilled water and re-crystallized from ethanol to give bright yellow crystals.

**Synthesis of 2-(pyridine-4-yldiazonium) isoindoline-1-one-3-sulphoxide (4) [21]**

To get stirred solution of formed diazonium chloride salt (2) was added gradually (0.02 mol, 4.103 gm) of sodium saccharin in DMF (20 ml) and stirring was continued for 30 min at 5 0C. The reaction temperature was then gradually raised to room temperature, then to 40-50 °C and after 15 min a clear yellow solution was obtained. The solution was then refluxed with continuous stirring, and then left to form crystals. Crystals were collected by filtrations, washed with (2%) sodium bicarbonate solution then with excess distilled water and re-crystallized from ethanol to give pale yellow crystals.

**Synthesis of ethyl 2-(pyridine-4-yldiazonium) acetate (5) [22]**

To get a stirred solution of formed diazonium chloride salt (2) was added gradually a solution of 0.02 mol, 1.76 gm of ethyl acetate and 0.02 mol, 1.64 gm of sodium acetate into 25 ml ethanol with stirring for 30 min at 5 0C. The reaction temperature was then gradually raised to room temperature. The resulted mixture was refluxed with continuous stirring then cooled to room temperature. The formed precipitate was filtered, washed with (2%) sodium bicarbonate solution then with distilled water, dried and purified by re-crystallization from ethanol to give light brown crystals.

**Synthesis of 2-(pyridine-4-yldiazonium) acetohydrazide (6) [23,24]**

To get a solution of 0.006 mol, 1.159 gm of ethyl 2-(pyridine-4-yldiazonium) acetate (5), absolute ethanol (20 ml) was added (0.01 mol, 0.5 gm, 0.5 ml) to hydrazine hydrate (90%). The mixture was refluxed under anhydrous conditions for 6-7 h. Excess solvent was distilled off. The resulting solid was separated out on cooling filtered and re-crystallized from ethanol. The compound was separated as shining light yellow needle shaped crystals.
Synthesis of N - (4-chlorobenzylidene)-2-(pyridine-4-yldiazonium) acetohydrazide (7) [25]

Schiff's bases (7) have been prepared according to standard method. In absolute ethyl alcohol (20 ml), solution of 2-(pyridine-4-yldiazonium) acetohydrazide (6) (0.005 mol, 0.895 gm) were slowly added to a solution of 4-chlorobenzaldehyde (0.005 mol, 0.702 gm) + 2 drops of glacial acetic acid in absolute ethanol (20 ml). After stirring for 1 h, the mixture was refluxed for 4-5 h with stirring. The mixture was filtered after cooling and washed with cold ethanol and re-crystallized from ether.

Synthesis of N- [2-(4-chlorophenyl)-4-oxo-1,2-dihydroquinazoline-3-(4H)-yl] -2-(pyridine-4-yldiazonium) acetamide (8) [26]

To a solution of Schiff base N - (4-chlorobenzylidene)-2-(pyridine-4-yldiazonium) acetohydrazide (7) (0.002 mol, 0.602 gm) in absolute ethanol (20 ml) was added slowly to the solution (0.002 mol, 0.274 gm) of 2-aminobenzoic acid into absolute ethanol (15 ml). The mixture was stirred for 1 h then the mixture was refluxed for 9 h with stirring. The reaction mixture was poured into crushed ice water. The separated crystals were filtered, washed with ethanol, dried and re-crystallized using ethanol.

Synthesis of N-[2-(4-chlorophenyl)-4-oxo-2H-benzo[e][1,3]oxazine-3-(4H)-yl] -2-(pyridine-4-yldiazonium) acetamide (9) [27]

To a solution of schiff base: N - (4-chlorobenzylidene)-2-(pyridine-4-yldiazonium) acetohydrazide (7) (0.002 mol, 0.602 gm) in absolute ethanol (20 ml) was added slowly to solution (0.002 mol, 0.276 gm) of 2-hydroxybenzoic acid in absolute ethanol (15 ml). The mixture was stirred for 1 h then the mixture was refluxed for 9 h with stirring. The reaction mixture was poured into crushed ice water. The separated oxazine was filtered, washed with ethanol, dried and re-crystallized using ethanol.

Synthesis of N-[2-(4-chlorophenyl)-4-oxo-2H-benzo[e][1,3]thiazine-3-(4H)-yl]-2-(pyridine-4-yldiazonium) acetamide (10) [28]

To a solution of Schiff base: N - (4-chlorobenzylidene)-2-(pyridine-4-yldiazonium) acetohydrazide (7) (0.002 mol, 0.602 gm) in absolute ethanol (20 ml) was added slowly to solution (0.002 mol, 0.308 gm) of 2-mercaptobenzoic acid in absolute ethanol (15 ml). The mixture was stirred for 1 h then the mixture was refluxed for 9 h with stirring. The reaction mixture was poured into crushed ice water. The separated thiazine was filtered, washed with ethanol, dried and re-crystallized using ethanol.

**RESULTS and DESCUSION**

The infrared study of the important methods in identification of absorbed peaks of the result functional groups effective which found within the structural formula of the compounds prepared. The difference in the intensity of the main functional groups of absorption peaks indication of the occurrence of interaction. Aromatic diazonium salt: pyridine-4-diazonium chloride (2) was obtained by diazotization of pyridine-4-amine (1) with NaNO2 in dilute hydrochloric acid according to a published procedure [19,29] (Table 1).

The suggested mechanism of the diazotization reaction is known [30,31]. Compound (2) represents a stable aryl diazonium ion source and is a class of nitrogen-containing compounds useful for synthetic transformations [32]. Diazonium ions are weak electrophiles, however, they undergo coupling with activated aromatic nuclei such as aryl amines, phenols and aromatic heterocyclic compounds. However, the careful control of the pH of the reaction medium is necessary for the success of the process [33]. It is well-known classical synthesis of aromatic diazoaminoo system is formed in the reaction between a diazonium cation and the nucleophilic nitrogen atom of an amine or amide. Usually, the diazonium salt involved is not isolated, and an acidic aqueous solution of this reagent is exposed directly to the amine at low temperature in the presence of an excess of base to neutralize the acid used for diazotation [34].

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Molecular formula</th>
<th>Molecular Weight (gm/mol)</th>
<th>Yield %</th>
<th>M.P. (°C)</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>C11H10O2N4</td>
<td>252</td>
<td>74</td>
<td>127-129</td>
<td>Light yellow</td>
</tr>
<tr>
<td>4</td>
<td>C12H10O2N2S</td>
<td>288</td>
<td>69</td>
<td>117-120</td>
<td>Brown</td>
</tr>
<tr>
<td>5</td>
<td>C4H4O2N3</td>
<td>193</td>
<td>75</td>
<td>191-193</td>
<td>Light brown</td>
</tr>
<tr>
<td>6</td>
<td>C2H4O2S</td>
<td>179</td>
<td>61</td>
<td>153-155</td>
<td>Yellow</td>
</tr>
<tr>
<td>7</td>
<td>C14H12O2N2Cl</td>
<td>301.5</td>
<td>54</td>
<td>173-175</td>
<td>Dark yellow</td>
</tr>
<tr>
<td>8</td>
<td>C2H10O2N2Cl</td>
<td>420.5</td>
<td>59</td>
<td>219-221</td>
<td>Yellow</td>
</tr>
<tr>
<td>9</td>
<td>C2H16O2N2Cl</td>
<td>421.5</td>
<td>55</td>
<td>235-237</td>
<td>Brown</td>
</tr>
<tr>
<td>10</td>
<td>C2H16O2N2Cl</td>
<td>437.5</td>
<td>56</td>
<td>241-143</td>
<td>Greenish brown</td>
</tr>
</tbody>
</table>

Nitrogen containing nucleophiles that are not amines are known as amine surrogates like phthalimide, which reacted with diazonium cations to give covalent diazo-compounds. This nucleophile (N-) can be reacted with electrophiles to produce an N-substituted phthalimide [35-38]. Among the bicyclic nitrogen heterocycles phthalimides which classified as cyclic imides are an interesting class of compounds with a large range of applications, their molecules contain an imide ring and the general structure (-CO-N(R)-CO-) [39].
These cyclic imides are an important functionality which have important biological effects similar or even higher than known pharmacological molecules and so their biological activity is being a subject of biomedical research [40,41].

The action of aromatic diazonium salt with sodium phthalimide (the first step in the Gabriel synthesis of amines) in DMF is a nucleophilic substitution reaction type second order (SN2) to form 2-(pyridine-4-yl diazonium) isoindoline-1,3-dione (3) via a straightforward SN2 displacement [42].

The suggested mechanism of the reaction is shown in scheme 3. The FT-IR spectrum of compound (3), showed disappearance of (−NH2) stretching bands at $\nu$ (3437, 3379)/cm, and (NH) bending at $\nu$ (1587)/cm of the starting material, and appearance stretching bands of (C=O cyclic amide) at $\nu$ (1651)/cm, (N=N trans azo) at $\nu$ (1586)/cm, (Table 2) (Fig 1).

The 1HNMR spectrum of compound (4) shows the several characteristic chemical shifts; protons of pyridine ring at $\delta$ (7.736-7.887) ppm, and protons of benzene ring appeared (Table 1). Ethyl acetate suffered coupling reaction with aromatic diazonium salt in absolute ethanol in presence of sodium acetate to form the ester: ethyl 2-(pyridine-4-yl diazonium) acetate (5) via a straight forward SN2 nucleophilic substitution reaction [46].
Fig 1. FT.IR spectrum of compound (3).

Fig 2. FT.IR spectrum of compound (4).

Fig 3. FT.IR spectrum of compound (5).

Table 2. FT.IR spectral data of the synthesized compounds (3-10).

<table>
<thead>
<tr>
<th>Comp.</th>
<th>δCH ar.</th>
<th>δCH al.</th>
<th>δC=O</th>
<th>δS=O</th>
<th>δN=H₂, NH</th>
<th>δC=C ar.</th>
<th>δN=N trans azo</th>
<th>Others ˢ</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3054</td>
<td>-</td>
<td>1651</td>
<td>-</td>
<td>-</td>
<td>1534, 1589</td>
<td>1586</td>
<td>C-N 1254</td>
</tr>
<tr>
<td>4</td>
<td>3082</td>
<td>-</td>
<td>1659</td>
<td>1356, 1063</td>
<td>-</td>
<td>1556, 1585, 1639</td>
<td>C-N 1269</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3068</td>
<td>2986, 2947</td>
<td>1765</td>
<td>-</td>
<td>-</td>
<td>1529, 1576</td>
<td>C=O 1247</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3057</td>
<td>2976</td>
<td>1710</td>
<td>-</td>
<td>3443-3351</td>
<td>1527, 1579</td>
<td>N-H bend 1625.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3054</td>
<td>2926, 2859</td>
<td>1684</td>
<td>-</td>
<td>3346</td>
<td>1553, 1563</td>
<td>C=N imine 1675</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C=Cl 856 N-H bend. 1565</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3082</td>
<td>2924</td>
<td>1763</td>
<td>-</td>
<td>3418</td>
<td>1567, 1527</td>
<td>C-N 1253</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C=Cl 867 N-H bend. 1622</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>3091</td>
<td>2982, 2856</td>
<td>1767</td>
<td>-</td>
<td>3447</td>
<td>1585, 1536</td>
<td>C-N 1251</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-O 1237 C=Cl 871 N-H bend. 1627</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3064</td>
<td>2931</td>
<td>1735</td>
<td>-</td>
<td>3422</td>
<td>1559, 1531</td>
<td>C-N 1254 C-S 1271</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-Cl 874 N-H bend. 1623</td>
<td></td>
</tr>
</tbody>
</table>
The reaction of hydrazine hydrate with ester is one of the most common reactions to synthesize the acid hydrazide, it is a tetrahedral nucleophilic substitution reaction[47,48].

The titled compounds were synthesized from the condensation reaction of equimolar amounts of acid hydrazide (6) with 4-chlorobenzaldehyde in absolute ethanol and drops of glacial acetic acid; It is the major method to prepare Schiff bases [49-51]. The mechanism of this condensation is known and is acid catalyzed [52]. The FT-IR spectrum of compound (7), showed disappearance of (−NH2) stretching band, and appearance stretching band of imine (C=N) at υ (1675) cm⁻¹, and stretching band of aromatic (C-Cl) at υ (856) cm⁻¹ (Table. 2) (Fig.5).

For a long time imines have been used successfully in the synthesis of nitrogen containing heterocyclic [53]. Guinazoline (8), oxazine (9), and thiazine (10) were synthesized by refluxing equimolar amounts from the imine (7) with benzoic acid derivatives in absolute ethanol. Cyclization occur where functional group in (2-aminobenzoic acid, 2-hydroxybenzoic acid and 2-mercaptobenzoic acid) attack as a nucleophile the carbon of (C=N) bond [54,55]. These compounds were characterized by FT-IR, 1HNMR spectra, besides the TLC and physical properties (Table 2).

The FT-IR spectra of compounds (8, 9, and 10), showed the appearance of stretching band of carbonyl group at υ (1767-1735) cm⁻¹ due to Guinazoline, oxazine, and thiazine rings and this was the most characteristic evidence for the success of cyclization step.

The FT-IR spectra of compounds (8, 9, and 10), showed disappearance of (C=N) stretching band of imine, and appearance stretching band at υ (1237) cm⁻¹ due to (C-O) bond in oxazine ring, and stretching band at υ (1271) cm⁻¹ due to (C-S) bond in thiazine ring, (table-2) (figs.-6-8). The 1HNMR spectrum of compound (10) (Fig.10) shows the following characteristic chemical shifts (DMSO-d6) ppm., Protons of methylene (CH2) appeared at δ (2.046), Proton of methine (CH) appeared at (δ 2.467), Proton of (NH) of secondary amide group appeared atδ (3.301); Protons of aromatic rings appeared at the range δ (7.436-8.133) as a multiple overlapping peaks.
The proposed mechanism of this reaction is shown in scheme 11. UV-Vis absorption peaks values for compounds (3,4,8,9, and 10) were shown in (Table 3). The physical properties of all synthesized compounds are shown in (Table 1).

Table 3. Ultra violate (UV)- Visible spectral data for some synthesized compounds.

<table>
<thead>
<tr>
<th>Compounds No.</th>
<th>λMax (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>236</td>
</tr>
<tr>
<td>4</td>
<td>298, 306</td>
</tr>
<tr>
<td>8</td>
<td>345, 368</td>
</tr>
<tr>
<td>9</td>
<td>329, 361</td>
</tr>
<tr>
<td>10</td>
<td>340, 359</td>
</tr>
</tbody>
</table>

Microbiological examination

The disc diffusion method was used for study the antibacterial activity in this work. The prepared compounds (3,4,8,9, and 10) were assayed for antimicrobial activity in vitro against Gram negative bacteria (Escherichia coli) and Gram positive bacteria (Staphylococcus aurous). The sterilized petri dishes and agar were prepared by autoclaving for 15 min at 121 °C. The solvent DMSO was used for dissolving the compounds. Both bacteria were inoculated onto sterile plates and incubated at 37 °C for 24 h. The various prepared compounds which were examined cause inhibition zones. Table 4 shows results of the initial examination tests. Biological effectiveness test showed that prepared compounds sulphur (S) have high antibacterial effect on both used bacteria (E. coli and S. aureus). In case of S. aureus, compounds (4,8and 9) showed slightly antibacterial activity, and compound 10 showed highly activity, while compound 3 showed no activity. For E. coli, compound 9 have no effect on this bacteria because this bacteria is highly resistant to wide spectrum of antibiotic, their slim polysaccharides blocks antibiotics from enter the bacterial cells and also there are genetic factor, while compounds 3, 4, and 8 have no effect on this bacteria, compound 10 showed the highest antibacterial activity.

Table 4. Antimicrobial activity of some synthesized compounds. -, no inhibition = inactive; +, 5-10mm = slightly active; ++, 11-20 mm = moderately active.

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>Escherichia coli</th>
<th>Staphococcus aureus</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Fig 4. FT.IR spectrum of compound (6).

Fig 5. FT.IR spectrum of compound (7).
Conflict of interest
The authors declare that they have no conflict of interests.

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