Protonation sites and hydrogen bonding in mono-hydrobromide salts of two N,4-diheteroaryl 2-aminothiazoles

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Abstract
The synthesis and structural characterization of N-(6-methoxypyridin-3-yl)-4-(pyridin-2-yl)thiazol-2-amine mono-hydrobromide monohydrate (3) and N-(6-methoxypyridin-3-yl)-4-(pyrazin-2-yl)thiazol-2-amine mono-hydrobromide 0.35 methanol solvate (4) are reported. The crystal structures of 3 (monoclinic, space group P21/n, Z = 4) and 4 (monoclinic, space group, C2/c, Z = 8) feature N,4-diheteroaryl 2-aminothiazoles showing similar molecular conformations but different sites of protonation and thus distinctly different intermolecular hydrogen bonding patterns. In 3, N-amine–H⋯Br−, N+pyridine–H⋯Owater, and Owater–H⋯Br− hydrogen bonds link protonated N-(6-methoxypyridin-3-yl)-4-(pyridin-2-yl)thiazol-2-amine and water molecules and bromide anions into a three-dimensional hydrogen-bonded network, whereas intermolecular N+methoxypyridine–H⋯Npyrazine hydrogen bonds result in hydrogen-bonded zigzag chains of protonated N-(6-methoxypyridin-3-yl)-4-(pyrazin-2-yl)thiazol-2-amine molecules in 4.

Keywords 2-Aminothiazoles · Hydrobromides · Hantzsch reaction · Hydrogen bonding · Crystal structure · DFT calculation

Introduction
The 2-aminothiazole unit is a synthetically versatile building block, which has been widely used in medicinal chemistry. A number of active pharmaceutical ingredients containing a 2-aminothiazole moiety with different pharmacological properties are on the market. They include, for example, the third-generation cephalosporin anti-infective cefdinir, the β3 adrenergic agonist mirabegron, the tyrosine kinase inhibitor dasatinib, and the recently approved phosphatidylinositol-3-kinase (PI3K) inhibitor alpelisib. Antiproliferative, antidiabetic, and antihypertensive, and anti-inflammatory properties as well as antiviral, antitubercular, antifungal, antileishmanial, and antiprion activities of 2-aminothiazoles have been reported [1].

Antiileishmanial properties of N,4-diaryl substituted 2-aminothiazoles have been studied based on a hit in a screening of 200,000 compounds [2], and growth inhibition of other microorganisms including plasmodia [3] and mycobacteria [4] by this compound class has also been described. A series of N,4-diaryl 2-aminothiazoles with activity against Mycobacterium tuberculosis were subject of a structure-activity relationship (SAR) study reported by Meissner et al. [5]. Makam and Kannan evaluated N,4-diaryl substituted 2-aminothiazoles for inhibitory potential against M. tuberculosis, H37Rv, and reported minimum inhibitory concentration (MIC) values of 6.25–12.50 μM [6]. In view of these results, N,4-dieteroaryl substituted 2-aminothiazoles attracted our interest in the course of our studies on new antimycobacterial agents. Recently, we have explored the structural chemistry of freebase N,4-dieteroaryl 2-aminothiazoles with a 4-methylpyridin-2-yl group bound to the amino group at the 2-position of the thiazole core [7, 8].

Herein, we report the synthesis and structural characterization of two N,4-dieteroaryl 2-aminothiazole hydrobromides. Bromide is among the anions that are currently available for salt formation of active pharmaceutical ingredients [9], and a number of hydrobromide drugs, for example, the antitussive
dextromethorphan hydrobromide, are widely used. To the best of our knowledge and based on the search of the Cambridge Structural Database (CSD) [10] via WebCSD in October 2020 [11], hydrobromide salts of 4,4-diaryl 2-aminothiazoles have not been structurally characterized so far. The structure of a related 4-phenyl-2-(2-phenylhydrazinyl)thiazol-3-ium bromide was, however, reported very recently [12]. Structural insight into molecular conformations, preferred sites of protonation, and hydrogen bonding patterns in pharmaceutical salt forms is important for drug design and formulation development.

**Experimental section**

**General**

Starting materials were purchased from Sigma-Aldrich and used as received. Solvents were of analytical grade. The synthesis of 2-bromo-1-(pyridine-2-yl)ethanone hydrobromide was published by others [13].

**Physical methods**

Melting points (uncorrected) were determined on a Boëtius hot-stage microscope (VEB Kombinat NAGEMA, Dresden, GDR). NMR spectra were recorded at room temperature on an Agilent Technologies VNMRS 400 and a Varian INOVA 500 NMR spectrometer. The residual solvent signal of DMSO-$d_6$ ($\delta_H = 2.50$ ppm) was used to reference the spectra ($s = $ singlet, $bs = $ broad singlet, $d = $ doublet, $dd = $ doublet of doublets, $td = $ triplet of doublets). APCI mass spectrometry was carried out on an Advion Expression compact mass spectrometer. High-resolution ESI mass spectra were measured on a Bruker Daltonics Apex III FT-ICR mass spectrometer.

**Synthesis and crystallization**

$N$-(6-Methoxy pyridin-3-yl)-4-(pyridin-2-yl)thiazol-2-amine mono-hydrobromide 0.35 methanol solvate (4) Compound 4 was prepared in analogy to 3 from 2 (453 mg, 2.47 mmol) and 2-bromo-1-(pyrazine-2-yl)ethanone hydrobromide [16] (note that the compound is not denoted as hydrobromide therein), which was synthesized from acetylpyrazine (305 mg, 2.50 mmol) using 2-pyridolidone hydrotrifluorobromide (1.36 g, 7.47 mmol) as reagent and used in situ without purification. Yield (based on 2): 344 mg (0.91 mmol, 37%); m.p. 195–197 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta = 10.49$ (s, 1H), 9.18 (d, $J = 1.5$ Hz, 1H), 8.65 (dd, $J = 2.6$, 1.5 Hz, 1H), 8.63 (d, $J = 2.8$ Hz, 1H), 8.58 (d, $J = 2.5$ Hz, 1H), 8.19 (dd, $J = 9.0$, 2.8 Hz, 1H), 7.68 (s, 1H), 6.97 (d, $J = 9.0$ Hz, 1H), 3.88 (s, 3H), 3.16 (s, solvate methanol) ppm; HRMS (ESI): $m/z$ [M + H]$^+$ calcd. for $C_{14}H_{13}N_4O_2S^+$: 285.0805; found: 285.0800.

$N$-(6-Methoxy pyridin-3-yl)-4-(pyrazin-2-yl)thiazol-2-amine mono-hydrobromide 0.5 methanol solvate (4) Compound 4 was prepared in analogy to 3 from 2 (453 mg, 2.47 mmol) and 2-bromo-1-(pyrazine-2-yl)ethanone hydrobromide [16] (note that the compound is not denoted as hydrobromide therein), which was synthesized from acetylpyrazine (305 mg, 2.50 mmol) using 2-pyridolidone hydrotrifluorobromide (1.36 g, 7.47 mmol) as reagent and used in situ without purification. Yield (based on 2): 344 mg (0.91 mmol, 37%); m.p. 195–197 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta = 10.49$ (s, 1H), 9.18 (d, $J = 1.5$ Hz, 1H), 8.65 (dd, $J = 2.6$, 1.5 Hz, 1H), 8.63 (d, $J = 2.8$ Hz, 1H), 8.58 (d, $J = 2.5$ Hz, 1H), 8.19 (dd, $J = 9.0$, 2.8 Hz, 1H), 7.68 (s, 1H), 6.97 (d, $J = 9.0$ Hz, 1H), 3.88 (s, 3H), 3.16 (s, solvate methanol) ppm; HRMS (ESI): $m/z$ [M + H]$^+$ calcd. for $C_{14}H_{13}N_4O_2S^+$: 285.0758; found: 285.0753.

$N$-(6-Methoxy pyridin-3-yl)-4-(pyridin-2-yl)thiazol-2-amine mono-hydrobromide 0.35 methanol solvate (4) Compound 4 was prepared in analogy to 3 from 2 (453 mg, 2.47 mmol) and 2-bromo-1-(pyrazine-2-yl)ethanone hydrobromide [16] (note that the compound is not denoted as hydrobromide therein), which was synthesized from acetylpyrazine (305 mg, 2.50 mmol) using 2-pyridolidone hydrotrifluorobromide (1.36 g, 7.47 mmol) as reagent and used in situ without purification. Yield (based on 2): 344 mg (0.91 mmol, 37%); m.p. 195–197 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta = 10.49$ (s, 1H), 9.18 (d, $J = 1.5$ Hz, 1H), 8.65 (dd, $J = 2.6$, 1.5 Hz, 1H), 8.63 (d, $J = 2.8$ Hz, 1H), 8.58 (d, $J = 2.5$ Hz, 1H), 8.19 (dd, $J = 9.0$, 2.8 Hz, 1H), 7.68 (s, 1H), 6.97 (d, $J = 9.0$ Hz, 1H), 3.88 (s, 3H), 3.16 (s, solvate methanol) ppm; HRMS (ESI): $m/z$ [M + H]$^+$ calcd. for $C_{14}H_{13}N_4O_2S^+$: 285.0805; found: 285.0800.

**X-ray crystallography**

The X-ray intensity data for 3 were measured on a Bruker AXS II diffractometer and those for 4 on an Enraf-Nonius KappaCCD diffractometer, both equipped with a FR591 rotating anode radiation source. Data reductions were performed using the SAINT software [17] for 3 and EvalCCD [18] for 4. In both cases, face-indexed absorption corrections were carried out using SADABS [19]. The crystal structures were solved with SHELXT-2018/1 [20] and refined with SHELXL-2018/3 [21]. The methanol molecule of crystallization in 4 is disordered about a crystallographic twofold...
rotation axis, and the occupancy was refined freely to yield 0.70(1), using isotropic displacement parameters for the carbon and oxygen atoms. Carbon-bound hydrogen atoms were placed in geometrically calculated positions with C aromatic–H = 0.95 Å and C methyl–H = 0.98 Å and refined with the appropriate riding model. Methyl groups (apart from methanol) were allowed to rotate to match the underlying electron density maxima. Hydrogen atoms attached to nitrogen were localized in difference electron density maps and refined with the N–H bond lengths restrained to a target value of 0.88(2) Å. $U_{	ext{iso}}(H) = 1.2$ $U_{	ext{eq}}$(C, N, O) (1.5 for methyl groups) was applied for all hydrogen atoms. We note that the highest difference electron density peak of 1.90 eÅ$^{-3}$ in 4 is located 0.65 Å from Br1. Crystal data and refinement details for 3 and 4 are summarized in Table 1. Structure pictures were generated with Diamond [22].

### Computational methods

DFT calculations were undertaken using the program ORCA (version 4.2) [23] with a B3LYP hybrid functional (20% HF exchange) [24, 25] using a def2-TZVPP basis set [26].

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**Table 1 Crystal data and refinement details for 3 and 4**

|       | 3                          | 4                          |
|-------|---------------------------|---------------------------|
| **Empirical formula** | C$_{14}$H$_{15}$BrN$_4$O$_2$S | C$_{13.35}$H$_{13.41}$BrN$_4$O$_{1.35}$S |
| $M_r$  | 383.27                    | 377.50                    |
| $T$ (K) | 100(2)                    | 100(2)                    |
| $\lambda$ (Å) | 1.54178                   | 0.71073                   |
| **Crystal system** | Monoclinic                | Monoclinic                |
| **Space group** | $P2_1/n$                  | $C2/c$                    |
| $a$ (Å) | 9.6904(4)                 | 17.4497(4)                |
| $b$ (Å) | 17.6873(8)                | 12.2030(5)                |
| $c$ (Å) | 9.9215(4)                 | 15.3912(8)                |
| $\beta$ (°) | 117.286(2)               | 116.998(4)                |
| $V$ (Å$^3$) | 1511.30(11)            | 2920.2(2)                 |
| $Z$    | 4                         | 8                         |
| $\rho_{\text{calc}}$ (g cm$^{-3}$) | 1.684                     | 1.717                     |
| $\mu$ (mm$^{-1}$) | 5.118                     | 2.968                     |
| $F(000)$ | 776                       | 1523                      |
| **Crystal size (mm)** | 0.152×0.101×0.080       | 0.110×0.090×0.050         |
| $\theta$ range (°) | 5.00–72.28              | 2.91–33.18                |
| **Reflections collected/unique** | 56,808/2956              | 36,295/5581               |
| $R_{	ext{int}}$ | 0.0611                   | 0.0804                    |
| **Observed reflections $[I>2\sigma(I)]$** | 2670                      | 3747                      |
| **Goodness-of-fit on $R^2$** | 1.168                     | 1.040                     |
| $R_1$ [I$>2\sigma(I)$] | 0.0322                    | 0.0517                    |
| $wR_2$ (all data) | 0.0855                   | 0.1136                    |
| $\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ (eÅ$^{-3}$) | 0.62, −1.19             | 1.90, −2.01               |

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**Scheme 1** Synthesis of N,4-diheteroaryl 2-aminothiazole hydrobromides 3 and 4 from 2 and the respective α-bromoketone hydrobromide. Solvent molecules of crystallization are not included.
Optimization of the structures used the BFGS method from an initial Hessian according to Almoef’s model with a very tight self-consistent field convergence threshold [27]. Calculations were made on the free cations of 3 and 4 as well as their corresponding free bases. Avogadro was used as a model editor and visualization tool [28]. The results of the DFT calculations are summarized in the Supplementary Material. The optimized structures exhibited no negative frequencies. Natural atomic charges were calculated using NBO analysis [29]. Structure overlay pictures were drawn with Mercury [30].

Results and discussion

The N,4-diheteroaryl 2-aminothiazole mono-hydrobromide salts investigated in this study were prepared using the Hantzsch thiazole synthesis [31, 32], as summarized in Scheme 1. Reactions of 2-bromo-1-(pyridine-2-yl)ethanone mono-hydrobromide and 2-bromo-1-(pyrazine-2-yl)ethanone mono-hydrobromide with 2 in ethanol afforded 3 and 4 after recrystallization from methanol. The compounds were structurally characterized by X-ray crystallography. Figure 1 depicts the molecular structures in the solid state.

In both 3 and 4, the structure of the central five-membered 1,3-thiazole heterocycle is as expected [33]. The N-(pyridin-3-yl)thiazol-2-amine unit adopts the same conformation in 3 and 4 with the sulfur atom and the pivot atom of the pyridine ring C9 in an antiperiplanar arrangement around the C2–N2 bond. A molecular conformation with a similar orientation of the two aryl rings was observed previously in some crystal structures of N,4-diaryl 2-aminothiazoles [34–36]. The thiazole and pyridine rings in 3 and 4 are not entirely coplanar. The angle between the respective mean planes is 10.43(7)° in 3 and 12.6(1)° in 4. The mean planes of the heteroaryl rings

### Table 2 Hydrogen bonds for 3 and 4

| D–H⋯A | d(D–H) | d(H⋯A) | d(D⋯A) | <(DHA) |
|-------|--------|--------|--------|--------|
| N2–H2⋯Br1 | 0.863(17) | 2.467(18) | 3.3226(18) | 171(2) |
| N4–H4⋯O2 | 0.858(17) | 1.94(2) | 2.704(2) | 147(2) |
| O2–H2A⋯Br1a | 0.830(17) | 2.483(18) | 3.3128(17) | 179(3) |
| O2–H2B⋯Br1b | 0.829(18) | 2.531(18) | 3.3539(17) | 173(3) |
| C14–H14⋯N1c | 0.95 | 2.43 | 3.368(3) | 168 |
| N1–H1⋯N5a | 0.884(18) | 1.931(19) | 2.808(3) | 171(3) |
| N2–H2⋯Br1 | 0.874(18) | 2.355(18) | 3.228(2) | 177(3) |

a Symmetry codes: (a) x–1/2, –y+1/2, z–1/2; (b) –x+3/2, y+1/2, –z+3/2; (c) x–3/2, –y+1/2, z–1/2

b Symmetry code: (a) x+1/2, –y+1/2, z+1/2
attached to C4 of the 1,3-thiazole ring are tilted out of its mean plane by only 1.88(6)° in 3 and 6.8(1)° in 4. Both mono-
hydrobromide salts have in common a hydrogen bond formed by the secondary amino group to the bromide anion (Table 2).
Moreover, the S1⋯Br1 short contacts of 3.5891(7) and 3.8344(8) Å as well as the C5⋯S1⋯Br angles of 177.96(8)° and 170.84(9)° in 3 and 4, respectively, provide structural evidence for chalcogen bonding [37, 38]. This arrangement appears not to be unusual. A survey of the CSD (version 5.41 with August 2020 updates) revealed that of 24 crystal structures containing the 2-aminothiazole unit and a bromide anion, where coordinates were available, 17 structures exhibited a short (< 4.0 Å) S⋯Br distance and C⋯S⋯Br angles in the range of 152–175° (see Supplementary Material).

The protonation sites in both 3 and 4 were identified in difference electron density maps. The observed respective C–N–C bond angles in the six-membered heterocycles (Table S1 in the Supplementary Material) corroborate the assignments made. The C12–N4–C11 and C6–N1–C10 bond angles at the protonated N4 in 3 and N1 in 4, respectively, are significantly larger than 120°. In contrast, the C–N–C bond angles at the unprotonated pyridine and pyrazine nitrogen atoms are within 116–117° and thus significantly smaller than 120°. In 3, the pyridine ring attached to C4 of the 1,3-thiazole ring is protonated, whereas the 2-methoxypyridine ring bonded to the amino group remains unprotonated. Since pyrazine is a weaker base than pyridine, protonation of the 2-methoxypyridine ring is preferred to protonation of the pyr-
azine ring in 4 as expected.

It is worth noting that in the crystal structure of 3, the bromide anion is involved in a hydrogen bond with H2 at the amine nitrogen atom; although H4 attached to the pyridinium nitrogen atom, the site of protonation of the free base exhibits the larger natural charge in the cation calculated by DFT methods and subsequent NBO analysis (Table 3). Similarly, in the crystal structure of 4, the bromide anion is involved in a hydrogen bond with H2; although H1 attached to the methoxypyridinium nitrogen atom, here the site of protonation has the larger natural charge in the calculated cation. Natural atomic charge or the site of protonation of the free base does therefore not appear to be an indicator of why the bromide anion is hydrogen-bonded to the amine H atom. In the crystal structures of both 3 and 4, the N\textsubscript{amine}–H⋯Br angles

| Table 3 | Selected natural atomic charges (e) for calculated free cations and free bases of 3 and 4 |
|----------|-------------------------------------------------|---------------------------------|----------------|----------------|
| Atom number\textsuperscript{a} | 3 (cation) | 4 (cation) | 3 (free base) | 4 (free base) |
| Positive | | | | |
| S1 | 0.43867 | 0.42585 | 0.34563 | 0.34574 |
| H1 | – | 0.44402 | – | – |
| H2 | 0.41178 | 0.41185 | 0.39616 | 0.39634 |
| H4 | 0.46263 | – | – | – |
| Negative | | | | |
| N1 | −0.47051 | −0.42745 | −0.47122 | −0.47341 |
| N2 | −0.55164 | −0.52947 | −0.54077 | −0.53978 |
| N3 | −0.53797 | −0.48917 | −0.49794 | −0.47084 |
| N4 | −0.42127 | −0.37532 | −0.41571 | −0.36370 |
| N5 | – | −0.36709 | – | −0.37629 |

\textsuperscript{a} Atom labelling scheme corresponding to the crystal structures

Fig. 2 Structure overlays of the thiazole units of the DFT-optimized structures of the cations (green) and free bases (orange) of 3 (top) and 4 (bottom). Sulfur and nitrogen atoms are highlighted with yellow and blue, respectively
are close to 180° (Table 2), indicating that the main interaction is with the amine H atom, although it is worth noting that the second highest positively charged atom in both cases is the sulfur atom (3 cation 0.43867 e and 4 cation 0.42585 e). In contrast, the amine nitrogen atom is the atom with the most negative natural atomic charge of all atoms in the calculated free cations of 3 (−0.55164 e) and 4 (−0.52947 e). For the calculated free bases, the largest positive natural atomic charge resides on the amine H atom (3 free base 0.39616 e and 4 free base 0.39634 e) closely followed by the sulfur atom (3 free base 0.34563 e, 4 free base 0.34574 e), whereas the atom with the most negative natural atomic charge is the amine nitrogen atom in both cases (3 free base −0.54077 e, 4 free base −0.53978 e), as for the calculated cations.

In 4, the methoxy group in ortho-position to N1 is rotated by approximately 180° compared with 3, which appears to be associated with the protonation state of N1. This observation is mirrored in the DFT-optimized structures of the free cations and free bases of 3 and 4 (Fig. 2), whereby the methoxy group in the ortho-position to N1 only points away from N1 when it is protonated (cation of 4).

As shown in Fig. 3, N_amine–H⋯Br⁻, N⁺_pyridine–H⋯O_water and O_water–H⋯Br⁻ hydrogen bonds dominate the supramolecular structure of 3 in the solid state. Two solvate water molecules and two bromide anions form a centrosymmetric R₂⁺(8) hydrogen bond motif [39], which is surrounded by protonated N-(6-methoxypyridin-3-yl)-4-(pyridin-2-yl)thiazol-2-amine molecules. The protonated pyridin-2-yl group forms a hydrogen bond to the solvate water molecule and, as mentioned above, the amino group to a bromide anion, affording a three-dimensional hydrogen-bonded structure. In addition, the unprotonated pyridine nitrogen atom N1 appears to accept a weak C–H⋯N hydrogen bond from C14 of an adjacent molecule (Figure S1 in the Supplementary Materials).
Material. The centroid-centroid distance between face-to-face stacked methoxypyridine rings and thiazole rings is 3.51 Å. The hydrogen bonding scheme in 4 is distinctly different from that in 3. In 4, protonated N-(6-methoxypyridin-3-yl)-4-(pyrazin-2-yl)thiazol-2-amine molecules are joined via N$^+$–H⋯N hydrogen bonds between the protonated methoxypyridine ring and the pyrazine nitrogen atom N5 of an adjacent molecule, resulting in zigzag chains extending in the [101] direction in the crystal (Fig. 4). The second pyrazine nitrogen atom remains without a hydrogen bond donor in the crystal structure. The disordered solvate methanol molecule is also not involved in significant hydrogen bonding interactions. Geometric parameters of hydrogen bonds in 3 and 4, as summarized in Table 2, are within expected ranges [40].

Conclusions

We have prepared the two related N,4-diheteroaryl 2-aminothiazoles 3 and 4 using the Hantzsch thiazole synthesis and structurally characterized their mono-hydrobromide salts. The N,4-diheteroaryl 2-aminothiazole cations exhibit similar molecular conformations in the solid state but different sites of protonation. The intermolecular hydrogen bonding patterns in the crystal structures are markedly different. Despite the different solid-state supramolecular structures, a similar N$_\text{amine}$–H⋯Br⋯S association is encountered in both 3 and 4, indicating a preferred interaction of these groups, even though the site of protonation of the free base is elsewhere. With regard to the hitherto limited knowledge of N,4-diheteroaryl 2-aminothiazole mono-hydrobromide salts, structural information gained from the present study should be conducive for further investigations of this compound class in medicinal chemistry.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11224-021-01730-0.

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Authors’ contributions Conceptualization: PI and RWS; data curation: RWS, RG, and AR; formal analysis: RWS, RG, and AR; investigation: DB, AB, and RG; methodology: RG and RWS; project administration: PI and RWS; supervision: PI; validation: RWS, RG, and AR; visualization: RWS and RG; writing—original draft: RWS and RG; writing, review, and editing: RWS, RG, and PI.

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Data availability Results of the DFT calculations have been placed in the electronic Supplementary Material. CCDC 2043373 (3) and 2043374 (4) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication All co-authors have seen and approved the manuscript.

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