A theoretical study of the valence tautomerism of 1H-pyrazolium-4-olates (X = O) and related compounds (X = S, Se, NH): relative stabilities, protonation effects, and tautomerization barriers

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Abstract
The valence isomerism of a series of heterocyclic mesomeric betaines (HMBs) belonging to class 5, called pseudo-semiconjugated HMBs, has been studied theoretically both the neutral and the protonated species. These HMBs are 1H-pyrazol-2-ium-4-olates and related compounds where the oxygen atom has been replaced by S, Se atoms, and an NH group. The main conclusion of the present work is that the ring/open valence tautomerism is possible both for neutral and protonated although it has never been observed experimentally.

Keywords Pyrazoles · Pyrazolium salts · Mesoionic rings · Heterocyclic mesomeric betaines · Bis(arylimino)pentan-3-ones

Introduction
To facilitate the following discussion, the numbering of the studied structures is reported in Fig. 1; actually, for protonated molecules, the number of possible structures is larger, but this does not alter this introduction.

Mesoionic compounds occupy a singular place among the huge field of heterocyclic chemistry. Their structure and complex system of classification is due to Baker [1, 2], Ollis [3, 4], Potts [5–7], and Oziminski [8, 9], among others, although the main contribution is that of Ramsden [10–16]. Ramsden classification is reported in Fig. 2.

In 1988 [17], we used the SOS (Simulated Organic Synthesis) program due to Barone and Chanon [18–20] to find new ways to prepare pyrazoles, different from the classical ones [21–25]. In that paper, we reported a new method and calculated within the MNDO [26] method the minima and TS of the reaction A1 ⇌ TS1 ⇌ B1 (Fig. 3), corresponding to the present numbering of 1(O)c, 1(O)TS, and 1(O)c.

According to the MNDO calculations, it appeared that 1,3-diminopropan-2-one B1 was much more stable than 1H-pyrazol-2-ium-4-olate (also called 4-hydroxy-1H-pyrazolium inner salt); the barrier TS1 between A1 and the cyclic compound, B1, was very high.

In 2019 Ramsden and Oziminski studied a series of closely related reactions based on MP2 ab initio calculations [15]; in Fig. 3, we have reported one of their examples concerning their A2 compounds [our n = 2(O) compounds of Fig. 1]. Their results concerning the general solvation by water, PCM model [27], and the specific solvation by a water molecule show that the differences in stability can be strongly modified, to the point that A2·H2O (PCM) is more stable than B2·H2O (PCM). The corresponding TSs were not calculated.

A search for 1H-pyrazol-2-ium-4-olates and 2,4-bis(imino)pentan-3-ones in Scifinder [28] afforded compounds 6 to 20 gathered in Fig. 4 and Fig. 5 together with their CAS registered numbers. The simplest compound of Fig. 5 (14, R = H) is only a calculated compound [15].

Note that compounds 11 (Figs. 4) and 14 (Fig. 5) are valence tautomers. No experimental synthetic method that involve the creation of a N–N bond has any relationship with the procedure of Fig. 3; the reported methods correspond to oxidative synthesis using nitriles and creating simultaneously N–N and C–N bonds [29–31]. The synthesis of 1H-pyrazol-2-ium-4-olates uses hydrazines as starting materials [32–34].
Concerning the protonated species, only one structure has been reported and always only in patents [35], the perchlorate of 4-hydroxy-1,2-dimethyl-3,5-diphenyl-1H-pyrazol-2-ium \(10\text{H}^+\) \(\text{R}^1 = \text{R}^2 = \text{Me}, \text{R}^3 = \text{R}^5 = \text{Ph}, 4(\text{O})\) \(\text{cH}^+\) (Fig. 6); this compound was not prepared by protonation of 10 but by methylation of the corresponding N-methyl pyrazole [34]. These 4-hydroxy-pyrazolium salts were proposed by Begtrup in 1970 as intermediates but were not isolated [36].

**Computational methods**

The geometry of the molecules has been optimized with the M06-2x [37] functional and the aug-cc-pVDZ basis set [38] in gas phase and with the continuum solvation model PCM [39] using the water parameters, PCM(H\(2\)O)-M06-2x. Frequency calculations at the same computational levels were carried out to verify that the structures obtained correspond to energetic minima (no imaginary vibrations).
frequencies) or to transition states (only one imaginary frequency). The IRC of some of the reactions studies has been explored. All these calculations have been carried out using the Gaussian-16 package [40]. Additional calculations at domain-based local pair natural orbital coupled cluster with single-, double-, and perturbative triple excitation level [41], DLPNO-CCSD(T)/aug-cc-pVDZ, have been performed with the Orca5 program [42]. This methodology provides similar results to those obtained with the standard CCSD(T) method [43].

The electron density of the molecules has been analyzed with the quantum theory of atoms in molecules (QTAIM).

Fig. 3 Valence tautomerism in the 1 and 2 series. All values in kJ·mol⁻¹. Data for A2 are from ref. [15] where the corresponding TSs were not calculated.

Fig. 4 1H-Pyrazol-2-ium-4-olates. 6 = 2(O)c; 7 = 3(O)c; 10 = 4(O)c; 11 = 5(O)c.
using the AIMAll program \cite{45}. The presence of (3,-1) critical points associated to interatomic interactions allows to classify such contact in covalent and non-covalent.

The analysis of the IRC profile has been carried out with the Eyringpy program \cite{46}.

\section*{Results and discussion}

\subsection*{Neutral molecules, comparison between n(X)c and n(X)o}

Energetic comparisons between closed (pyrazolium-olates and related compounds) and open structures [2,4-bis(arylimino)pentan-3-ones and related compounds] are reported in Fig. 7 and Table 1, and the geometries are listed in the Supplementary data.

Several of the 20 values of Table 1 columns are linearly related, and the simple linear regression equations, \(y = a + bx\), obtained from these values are reported in Table 2.

The square correlation coefficients are not very good, and that is also apparent in the relatively large errors of the coefficients. The first three equations are a consequence of the Hammond postulate, which states that \emph{the transition state resembles the structure of the nearest stable species}, in this case the cyclic compounds. Equation 4 corresponds to the fact that CCSD(T) calculations increase considerably the differences in stability between open and cyclic structures compared with M06-2x ones. General water solvation stabilizes the mesoionic compounds compared to the neutral open forms due to their high dipole moments (see Supplementary data), Eqs. 5. Equations 6 and 7 have slopes near 1.00; thus, the intercepts can be directly compared; the values are relatively small, +15.3 for the CCSD(T)/M06-2x pair, positive like in Eq. 4 but lower, and –11.4 for the PCM(H2O)/M06-2x comparison, again similar and lower to that of Eq. 5.

The solvent effect produces an elongation of the N–N distance in the TS between 0.03 and 0.12 Å (see Supplementary data, Table S2).

A clear relationship is found between the energetic values of the TS structures in gas phase and their N–N distances as can be observed in Fig. 8. The shorter the N–N distance in the TS, the larger is the barrier. Linear correlations between these two parameters show \(R^2\) values larger than 0.98 for each family of compounds (1–5) and a \(R^2\) value of 0.92 considering all the points together. A linear correlation is only the simplest model, for instance, a second order polynomial affords an \(R^2 = 0.936\). A similar relationship is obtained...
when the values in PCM(H2O) are considered (see Supplementary data, Fig. S1):

The analysis of the electron density of the structures within the QTAIM methodology [44] shows the presence of a bcp between the nitrogens involved in the reaction in the closed and TS structures but not in the open ones. The \(\rho_{\text{BCP}}\) in the closed structures range between 0.387 and 0.331 au with negative values of \(\nabla^2 \rho_{\text{BCP}}\) and \(H_{\text{BCP}}\) that are large. In contrast, the \(\rho_{\text{BCP}}\) for the TS structures range between 0.175 and 0.071 au with positive values of \(\nabla^2 \rho_{\text{BCP}}\) and negative values of \(H_{\text{BCP}}\) as indication of partial covalent character of this contact in the TS [47].

The IRCs (Intrinsic Reaction Coordinate) of some selected transformations have been calculated. Using these values, the reaction force profile along the reaction has been derived. One example is given in Fig. 9. The reaction force divides the IRC in three regions: (i) from the reactant to the minimum (\(\xi_1\)) which is associated to structural reordering, (ii) from \(\xi_1\) to the maximum \(\xi_2\) where the electronic variation dominates, and (iii) between \(\xi_2\) and the products that corresponds to a structural relaxation. It should be noted that the TS (\(\xi_{\text{TS}}\)) is located between \(\xi_1\) and \(\xi_2\) allowing to divide the reaction in four regions. Table 3 shows the energetic values between the critical points in the IRC and reaction force along the reaction coordinate for some of the reactions. The structural reorderings (W1 and W4) are larger in the processes of reaching the TS from the products and the reactants than the electronic reorganization (W2 and W3). Good linear correlations \(R^2 > 0.96\) of each term with the corresponding TS have been obtained when the two families (1 and 3) are considered separately.

### Table 1: Energies (in kJ·mol\(^{-1}\)) of the valence tautomerization between \(n(X)c\) and \(n(X)o\).

| X   | Code | Gas phase M06-2x | Gas Phase-CCSD(T) | PCM(H2O)-M06-2x |
|-----|------|-----------------|-------------------|------------------|
|     |      | n(X)c TS | n(X)c TS | n(X)c TS | n(X)c TS |
| H   | H    | O   | 1(O)c | 68.1 | 179.5 | 107.6 | 190.9 | 3.1 | 168.1 |
| H   | H    | S   | 1(S)c | 19.3 | 155.8 | 67.8 | 168.2 | -75.3 | 138.8 |
| H   | H    | Se  | 1(Se)c | -4.1 | 142.7 | 56.7 | 163.9 | -102.2 | 125.6 |
| H   | H    | NH  | 1(NH)c | 157.7 | 245.6 | 195.6 | 255.6 | 90.3 | 227.8 |
| CH₃ | H    | O   | 2(O)c | 61.7 | 173.8 | 93.2 | 181.0 | -2.7 | 156.9 |
| CH₃ | H    | S   | 2(S)c | 7.3 | 146.8 | 47.2 | 155.6 | -86.5 | 122.3 |
| CH₃ | H    | Se  | 2(Se)c | -16.6 | 133.2 | 35.3 | 152.9 | -113.6 | 108.3 |
| CH₃ | H    | NH  | 2(NH)c | 144.9 | 235.5 | 176.6 | 240.8 | 79.6 | 214.3 |
| CH₃ | CH₃  | O   | 3(O)c | 46.3 | 156.0 | 74.4 | 159.8 | -6.7 | 144.7 |
| CH₃ | CH₃  | S   | 3(S)c | -30.8 | 112.5 | 10.0 | 119.3 | -108.5 | 99.4 |
| CH₃ | CH₃  | Se  | 3(Se)c | -57.9 | 97.8 | -6.1 | 111.6 | -137.9 | 85.3 |
| CH₃ | CH₃  | NH  | 3(NH)c | 117.4 | 204.3 | 146.1 | 208.7 | 66.0 | 190.8 |
| CH₃ | C₅H₅  | O   | 4(O)c | 15.8 | 141.2 | 53.1 | 150.4 | -28.2 | 128.9 |
| CH₃ | C₅H₅  | S   | 4(S)c | -37.5 | 118.2 | 9.2 | 126.3 | -106.2 | 102.5 |
| CH₃ | C₅H₅  | Se  | 4(Se)c | -61.6 | 105.5 | -3.4 | 120.2 | -132.9 | 90.4 |
| CH₃ | C₅H₅  | NH  | 4(NH)c | 72.7 | 175.7 | 111.9 | 188.4 | 41.0 | 173.0 |
| C₆H₅ | CH₃  | O   | 5(O)c | 64.8 | 160.1 | 78.0 | 153.8 | 23.8 | 188.0 |
| C₆H₅ | CH₃  | S   | 5(S)c | -7.1 | 108.8 | 17.19 | 106.9 | -66.1 | 97.1 |
| C₆H₅ | CH₃  | Se  | 5(Se)c | -33.8 | 91.3 | 3.4 | 101.6 | -94.4 | 80.7 |
| C₆H₅ | CH₃  | NH  | 5(NH)c | 134.6 | 205.4 | 146.5 | 196.8 | 96.2 | 193.7 |

### Table 2: Statistical analyses of Table 1 data

| y | x | Method | Intercept a | Slope b | \(R^2\) | Eq |
|---|---|--------|-------------|---------|---------|-----|
| Cyclic minimum | TS | M06-2x | 133.6±2.8 | 0.63±0.04 | 0.94 | 1 |
| Cyclic minimum | TS | CCSD(T) | 114.1±3.5 | 0.68±0.04 | 0.94 | 2 |
| Cyclic minimum | TS | PCM(H2O) | 159.6±3.8 | 0.54±0.05 | 0.88 | 3 |
| Cyclic minimum | Cyclic minimum | CCSD(T)/M06-2x | 41.8±2.7 | 0.88±0.04 | 0.97 | 4 |
| Cyclic minimum | Cyclic minimum | PCM(H2O)/M06-2x | -71.4±4.9 | 1.14±0.07 | 0.95 | 5 |
| TS | TS | CCSD(T)/M06-2x | 15.3±6.2 | 0.95±0.04 | 0.97 | 6 |
| TS | TS | PCM(H2O)/M06-2x | -11.4±9.2 | 0.99±0.06 | 0.94 | 7 |
Protonated molecules, comparison between n(X)cH⁺ and n(X)oH⁺/n(X)o'H⁺

The situation for cations is much more complex than in neutral molecules because instead of two minima, now they are five. In Fig. 10 are represented the five minima of protonated structures and in Table 4 the corresponding energy results.

In Table 4 are reported the same results as in Sect. 2.1 for protonated species, but only for X = O, the remaining X groups are reported in the Supplementary data. Here the most stable is the cyclic compound and no longer the open compound like in neutral molecules. Note that open compounds a and c are related by a proton transfer, while structure d present a new N–H···N HB.

There are five minima and four TS. TS-co corresponds to the N–N bond breaking, TS-ab to the rotation about a CC single bond, TS-bc to an intramolecular proton transfer between X and N, and TS-cd to a second rotation about a 

### Table 3

Energy decomposition (kJ·mol⁻¹) using the reaction coordinate and the reaction force critical points. W1–W4 are the energy difference (kJ·mol⁻¹) between the corresponding stationary points.

| X         | Code  | W1   | W2       | W3       | W4    |
|-----------|-------|------|----------|----------|-------|
| R¹=R²     | X     | Code | ε₁       | ε₅ₛ      | ε₅ₛ → ε₂  | ε₂ → P  |
| H         | H     | O    | 1(O)c   | 59.4     | 51.9   | -61.1  | -118.4  |
| H         | H     | S    | 1(S)c   | 72.8     | 63.6   | -50.6  | -105.5  |
| H         | H     | Se   | 1(Se)c  | 78.7     | 68.2   | -44.8  | -97.9   |
| H         | H     | NH   | 1(NH)c  | 49.0     | 38.9   | -97.5  | -48.1   |
| CH₃       | CH₃   | O    | 3(O)c   | 70.7     | 41.0   | -28.0  | -145.6  |
| CH₃       | CH₃   | S    | 3(S)c   | 88.7     | 51.0   | -26.4  | -120.5  |
| CH₃       | CH₃   | Se   | 3(Se)c  | 96.2     | 53.6   | -25.9  | -107.5  |
| CH₃       | CH₃   | NH   | 3(NH)c  | 59.4     | 31.4   | -37.2  | -173.6  |
Fig. 10 The ring opening sequence in protonated 1H-pyrazol-2-ium-4-olates and related compounds. c-o means cyclic-open

Table 4 Energies (in kJ·mol⁻¹) of the valence tautomeration between n(O)cH⁺ and n(O)oH⁺ (open a and open d); the TS-co correspond to the ring opening of the closed structure to yield the open compound of type a. Relative energies to the cyclic n(O)cH⁺ structures

| Code   | n(O)cH⁺ open a | n(O)cH⁺ open d | Gas phase M06-2x | Gas Phase-CCSD(T) | PCM(H₂O)-M06-2x |
|--------|----------------|----------------|------------------|-------------------|------------------|
| 1(O)H⁺ | 258.2          | 258.2          | 204.0            | 163.4             | 219.0            |
| 2(O)H⁺ | 246.0          | 246.0          | 196.5            | 172.4             | 218.7            |
| 3(O)H⁺ | 247.4          | 247.4          | 209.0            | 185.0             | 220.4            |
| 4(O)H⁺ | 242.0          | 242.0          | 200.9            | 185.0             | 211.6            |
| 5(O)H⁺ | 247.4          | 247.4          | 209.0            | 185.0             | 211.6            |

Fig. 11 The energy profile of 2(O)H⁺ in the gas-phase. a 2(O)H⁺. b 2(S)H⁺. c 2(Se)H⁺. d 2(NH)H⁺
There are two groups of structures, before proton transfer, a and b, and after proton transfer, c and d. Taking into account that some b structures have not been localized because they evolve spontaneously to type c structures, b is always more stable than a (mean = 39.6 kJ·mol⁻¹, extreme values 6.5 kJ·mol⁻¹, 4(Se)H⁺ and 55.5 kJ·mol⁻¹, 5(O)H⁺; even for 4(NH)H⁺, the differences is much lower, 13.0 kJ·mol⁻¹, respectively than the mean (see Table S5)).

The different character of 4 series is probably due to a hydrogen bond between the acidic OH and the adjacent N atom (Fig. 12); the three other X⁺–H groups are less acidic, NIST gas basicity values in kJ·mol⁻¹ H₂O (660.0), H₂S (673.8), H₂Se (676.4), and H₂N (819.0) [48].

After proton transfer, d is always more stable than c due to the very favorable structure for a strong hydrogen bond, pseudo-six membered ring. The mean value is smaller than in the preceding case (10.4 kJ·mol⁻¹).

Statistical analyses of Table 4 data similar to those of Table 2 are much more complicated due to the existence of four open cations. Only the correlation relating the TSs calculated by two methods was acceptable (Table 5).

### Table 5

| Comp | y    | Method                  | Intercept a | Slope b | R²     | Eq |
|------|------|-------------------------|-------------|---------|--------|----|
| cations | TS   | TS CCSD(T)/M06-2x       | 25.1 ± 18.1 | 0.79 ± 0.08 | 0.86  | 8  |
| neutrals | TS   | TS CCSD(T)/M06-2x       | 15.3 ± 6.2  | 0.95 ± 0.04 | 0.97  | 6  |

Fig. 12 Comparison of the types a and c of structures 3(O)OH⁺ and 4(O)OH⁺

Fig. 13 Comparison of the 2(NH)OH⁺ and 2(O)OH⁺ series
When the four profiles of Fig. 11, illustrated for the series, are compared, it appears that those of $X=O$ (Fig. 11a), $X=S$ (Fig. 11b), and $X=Se$ (Fig. 11c) are similar but that of $X=NH$ (Fig. 11d) is different. A closer look indicated that the amino profile has two parts both similar to the other profiles but different between them (Fig. 13).

The three values of the left side (blue) and the two values of the right side (red) are correlated with the black values of the $2(O)\cdot H^+$ series: $2(NH)\cdot H^+ = (1.07 \pm 0.07) 2(O)\cdot H^+ - (68 \pm 13)$, $n=5$, $R^2=0.9995$; the value $-68$ kJ·mol$^{-1}$ corresponds to the difference between both sides, the red minus the blue, and it is related to the much larger basicity of NH compared with that of O (see previously NIST data [48]).

To estimate protonation effects, i.e., the basicity of the compounds of Table 1, the latter and Table 4 and Supplementary data should be compared; some relationships could be found. For instance for the M06-2x calculations between n(X)H$^+$ type $c=(188.6 \pm 3.5) - (0.63 \pm 0.04)$ n(X) c $-(101.6 \pm 6.3)$ b series, $n=20$, $R^2=0.98$ (Eq. 10). Equation 10 shows the energetic difference between the a (0) and the b (1) series, the b series being in average 102 kJ·mol$^{-1}$ more stable than the a series.

When the four profiles of Fig. 11, illustrated for the a series, are compared, it appears that those of $X=O$ (Fig. 11a), $X=S$ (Fig. 11b), and $X=Se$ (Fig. 11c) are similar but that of $X=NH$ (Fig. 11d) is different. A closer look indicated that the amino profile has two parts both similar to the other profiles but different between them (Fig. 13).

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The TS ring opening shows barriers bigger than in the neutral systems and N–N distance systematically larger (0.35 Å in average) in the protonated ones. As in the cases, of the neutral systems, linear correlations are obtained between the barriers and the interatomic N–N distances for each family of compounds with $R^2>0.97$.

The analysis of the electron density between both nitrogen atoms in the TS(c-o) shows a BCP like in the case of the neutral molecules. The representation of $\rho$BCP and $\nabla^2 \rho$BCP vs. the interatomic N–N distances. The fitted curves (blue) show $R^2$ values larger than 0.999.

Table 6 IRC analysis of the ring opening through the TS-co for molecules 1 and 3

| $R^1 = R^2$ | $R^3 = R^5$ | X   | Code C | W1  | W2  | W3  | W4  |
|------------|------------|-----|--------|-----|-----|-----|-----|
| H          | H          | O   | 1(O)cH$^+$ | 119.7 | 138.5 | -21.8 | -32.6 |
| H          | H          | S   | 1(S)cH$^+$ | 122.2 | 141.8 | -18.0 | -27.2 |
| CH$_3$     | CH$_3$     | O   | 3(O)cH$^+$ | 142.7 | 102.9 | -13.8 | -36.0 |
| CH$_3$     | CH$_3$     | S   | 3(S)cH$^+$ | 149.4 | 109.2 | -11.3 | -26.4 |

Fig. 14 $\rho$BCP and $\nabla^2 \rho$BCP vs. the interatomic N–N distances. The fitted curves (blue) show $R^2$ values larger than 0.999.
(W2 and W3) in analogy to what was observed for the neutral systems. In contrast, \(1(O)\text{H}^+\) and \(1(S)\text{H}^+\) shows a larger electronic reorganization W2 than the geometrical reordering W1.

**Comparison with geometries calculated and experimental X-ray data**

Unfortunately there are no experimental geometries of \(1\text{H}-\text{pyrazol-2-ium-4-olates and related compounds (CSD)}\) [53]. However, of the structures reported in Table 5 that of compound 21 has been determined (COPLAV) [54] and COPLAV01 [55]), this compound is related to \(5(O)o\), but the presence of two \(i\)-propyl at positions 2 and 6 of the phenyl rings should modify the conformation (Fig. 15).

The calculated structure has a symmetry axis (\(C_2\)) that is lost in the experimental structures that are different; the main difference between experimental and calculated geometries concerns one of the OCCN angles that are rotated to values (105.3° and 76.6°) much lower than the other \(N\)-phenyl group (169.6° and 176.2°) and to our calculated angles (178.0°).

**Conclusions**

Our conclusions agree with those of Ramsden and Oziminski [15] taking into account that protonation produces the same effect that hydrogen bonds with a water molecule but stronger.

Selecting for the conclusion, the two experimentally studied X atoms or groups, \(X = \text{O and X = NH (X = S and X = Se were not included in Fig. 16)}\), it is possible to summarize the calculated energy of the stationary states, minima, and transitions states, in Fig. 16. The values for the “open” protonated compounds correspond to “open-d”.

While in the neutral molecules the open structure is the most stable, in the cations, it is the opposite, the pyrazoliums are the most stable; although nobody has reported an example of ring-chain isomerization in these series, it should be possible by protonation/deprotonation, i.e., by simply changing the pH. The values reported in Fig. 16 indicate that solvation by water decreases the difference in stability between valence isomers so the experiments should be carried in the gas phase (by mass spectrometry, the open structure should be transformed in the cyclic structure of the cation) or in aprotic non-dipolar solvents, like benzene or other aromatic solvents.

The isomerization barriers lie in the range 162.1–237.6 (M06-2x), 167.2–218.1 [CCSD(T)], and 157.3–245.5 kJ·mol\(^{-1}\) (PCM water). These are high barriers that correspond to slow processes, in the order of \(10^{-3}\) to \(10^{-2}\) s\(^{-1}\) [56]. Even so, a \(1\text{H}-\text{pyrazol-2-ium-4-olate like 11 = 5(O)c}\) in an aprotic solvent (e.g., 1,4-dichlorobenzene-\(d_6\)) and heating the solution at 400 K for 2 weeks, or shorter in a microwave oven, should open it (the reaction can be followed by NMR).
Fig. 16  Energy means values (for the five \( n \) values, from 1 to 5) in \( \text{kJ mol}^{-1} \) units
Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s11224-022-01962-8.

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Data availability The data that support this research are available in the article and supporting information material.

Code availability Not applicable.

Declarations Conflict of interest The authors declare no competing interests.

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