**Excited-State Intramolecular Proton Transfer in 2-(2′-Hydroxyphenyl)pyrimidines: Synthesis, Optical Properties, and Theoretical Studies**

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**ABSTRACT:** The development of fluorescence materials with switched on/off emission has attracted great attention owing to the potential application of these materials in chemical sensing. In this work, the photophysical properties of a series of original 2-(2′-hydroxyphenyl)pyrimidines were thoroughly studied. The compounds were prepared by following well-established and straightforward methodologies and showed very little or null photoluminescence both in solution and in the solid state. This absence of emission can be explained by a fast proton transfer from the OH group to the nitrogen atoms of the pyrimidine ring to yield an excited tautomer that deactivates through a nonradiative pathway. The key role of the OH group in the emission quenching was demonstrated by the preparation of 2′-unsubstituted derivatives, all of which exhibited violet or blue luminescence. Single crystals of some compounds suitable for an X-ray diffraction analysis could be obtained, which permitted us to investigate inter- and intramolecular interactions and molecular packing structures. The protonation of the pyrimidine ring by an addition of trifluoroacetic acid inhibited the excited-state intramolecular proton transfer (ESIPT) process, causing a reversible switch on fluorescence response detectable by the naked eye. This acidochromic behavior allows 2-(2′-hydroxyphenyl)pyrimidines to be used as solid-state acid−base vapor sensors and anticounterfeiting agents. Extensive density functional theory and its time-dependent counterpart calculations at the M06-2X/6-31+G** level of theory were performed to rationalize all the experimental results and understand the impact of protonation on the different optical transitions.

**KEYWORDS:** ESIPT, pyrimidines, fluorescence, TD-DFT, anticounterfeiting

**1. INTRODUCTION**

In the last years, the phenomenon of excited -state intramolecular proton transfer (ESIPT) has been widely studied both from a spectroscopic and theoretical point of view, since it is a fundamental process in different chemical and biological systems. Typical ESIPT molecules possess intramolecular hydrogen bonds because the geometric proximity between the proton donor and acceptor units is crucial for ESIPT to occur. ESIPT is usually accompanied by large Stokes shifts, very short lifetimes \( k \approx 10^{13} \text{ s}^{-1} \), and often low fluorescence quantum yields in solution. Photoexcitation triggers a fast proton transfer from the H-bond donor to the H-bond acceptor that leads to a tautomer (keton) with a different electronic and geometrical structure from the original excited form (enol). As a consequence, ESIPT chromophores are able to show two emission bands, the one with longer wavelength arising from the excited-state keto form (ESIPT emission). Because of the major structural...
reorganization, the fluorescence properties are highly sensitive to the microenvironment. Thus, the dual emission of the ESIPT molecules is finely tunable and has found numerous applications in fields such as UV photostabilizers, 13,14 fluorescent probes and imaging agents, 15−19 and organic optoelectronic devices, 20−25 among others.

Although the range of ESIPT emitters is wide, 2-(2′-hydroxyphenyl)-substituted derivatives of benzimidazole, benzoxazole, and benzothiazole are by far the most studied to date. In this type of compound, it is also possible to detect triple fluorescence, because luminescent phenolic anions can be generated in alkaline protic media. 2,26−28 In contrast, diazine-based fluorophores have been scarcely investigated in this context. 29,30 Recently, the first detailed account for quinazoline derivatives has been reported, in which the ESIPT emission was found to be completely quenched in solution but successfully restored via aggregation-induced emission (AIE). 31 Frustration of ESIPT luminescence is very common in solution, although it can sometimes be restored in the solid state due to the beneficial restriction of molecular motions. 3

On the other hand, the photophysical properties of conjugated molecules based on diazines and benzodiazines also respond to environmental stimuli. These molecules have demonstrated to be highly sensitive to changes in polarity, pH, and the presence of metal cations. 32−34 In this respect, the potential for protonation, complexation, and hydrogen bonding with the nitrogen atoms provides an excellent tool for developing new sensing and luminescent materials.

In this paper, we describe the synthesis, characterization, and a full investigation of the photophysical properties of a series of original 2-(2′-hydroxyphenyl)pyrimidines. Through first-principles calculations, we give an in-depth insight into the ESIPT process and nonradiative deactivation mechanism of this family of compounds. Time-dependent density functional theory (TD-DFT) has shown to be a suitable computational method for a deeper understanding of the ESIPT process, 1,35−44 in which the proton transfer takes place in the excited state but not in the ground state.

2. RESULTS AND DISCUSSION

2.1. Synthesis of 2-Aryl-4,6-bis(arylviny)pyrimidines. Two synthetic pathways can be envisaged for the synthesis of 2-aryl-4,6-bis(arylviny)pyrimidines, both based in a combination of Suzuki-Miyaura cross coupling and Knoevenagel condensation reactions. 2-Halo-4,6-dimethylpyrimidines 1 were used as starting materials to access 2-halo-4,6-bis(arylviny)pyrimidines 2 by condensation with the appropriate benzaldehyde in basic media. Chloro derivatives 2a and 2c were prepared in aqueous NaOH using Aliquat 336 as a phase-transfer catalyst. 45 Microwave irradiation allowed us to reduce drastically the reaction time for 2a. Meanwhile, the iodo derivative 2b was obtained in excellent yield by solvent-free condensation. 46 The subsequent coupling reaction of compound 2b with 2-hydroxyphenylboronic acid under standard conditions afforded 2-(2′-hydroxyphenyl)-4,6-bis(4′-methoxy styryl)pyrimidine (4a) with moderate yield (Scheme 1, top). Nevertheless, this methodology proved unsuccessful when 2-chloro derivatives were used because of the lower reactivity of aryl chlorides.

The preparation was more straightforward, and the overall yield was substantially improved when the functionalization pattern of the starting materials was inverted (Scheme 1, bottom). Thus, starting from commercially available 2-chloro-4,6-dimethylpyrimidine (1a), 2-(2′-hydroxyphenyl)-4,6-dimethylpyrimidine (3a) was easily accessed. The synthesis of this compound had been previously reported from hydroxybenzamidine and acetylacetone with a very low yield of 12%. 57
protons in the 1H NMR spectra indicated the selective role of the OH group in the emission quenching was observed (Figure S1, Supporting Information). Thus, in a first reaction with 2 equiv of the appropriate boronic acid, we were able to obtain the 2-chloro-4,6-diarylpyrimidines by selectively introducing two aryl groups under standard conditions at 50–65 °C. In a second step, a higher temperature (100 °C) was necessary to access the desired triarylsubstituted compounds 6 by reaction with a new molecule of boronic acid (Scheme 2). Under these conditions, no reaction was observed when 5c was treated with 2-hydroxyphenylboronic acid, probably due to the higher electron-donor character of the carbazolyl group, which prevents the oxidative addition of Pd to the C–Cl bond. The temperature needed to be raised up to 140 °C when 4-hydroxyphenyl boronic acid was used, obtaining 6e in moderate yield.

### 2.3. Photophysical Properties in Solution

The optical properties of compounds 4 and 6 were studied by UV/vis and fluorescence spectroscopy in CH2Cl2 solution at room temperature. The data obtained are summarized in Table 1. All compounds showed absorption maxima in the UV or visible region, which experienced a red shift on increasing the temperature. The data obtained are summarized in Table 1. All compounds showed absorption maxima in the UV or visible region, which experienced a red shift on increasing the temperature.

#### Table 1. UV/Vis and Photoluminescence (PL) Data of Compounds 4 and 6

| Compd | CH2Cl2 | CH2Cl2 + TFA | Solid (powder) |
|-------|--------|--------------|----------------|
| 4a    | 347 (41.3), 384 (45.4) | 408 (33.8)^f, 468 (55.4) | 457 |
| 5a    | 447 (55.2) | 483 (6.9)^f, 596 (27.4) | 471 |
| 4c    | 291 (39.9), 328 (34.2)^f | 440 | 0.08 |
| 4d    | 320 (69.9)^f, 371 (93.1), 384 (79.8)^f | 438 | 0.11 |
| 6b    | 270 (58.9), 327 (11.7)^f | 359 (36.9), 395 (42.2) | 444, 594 |
| 6c    | 283 (13.4), 333 (21.6) | 374 | 0.02 |
| 6e    | 293 (37.3), 331 (12.4) | 360, 371 | 0.01 |

^f All spectra were registered at room temperature (c = (0.38–5.80) × 10^{-6} M). ^ Data after the addition of TFA (3000 equiv for 4a, 1200 for 4b, and 6000 for 6a). ^ Fluorescence quantum yield determined relative to those of 9,10-diphenylanthracene in cyclohexane (Φ_F = 0.90) and quinine sulfate in 0.1 M H2SO4 (Φ_F = 0.54) for 4d and 4e (λ_exc = 373 nm); 2-aminopyridine in 0.1 M H2SO4 (Φ_F = 0.60) for 6c (λ_exc = 297 nm); anthracene in ethanol (Φ_F = 0.27) for 6d and 6e (λ_exc = 330 nm). ^ Fluorescence quantum yield determined relative to those of fluorescein in 0.1 M NaOH (Φ_F = 0.82) for 4a (λ_exc = 467 nm), and 9,10-diphenylanthracene in cyclohexane (Φ_F = 0.90) for 6a (λ_exc = 390 nm). ^ Fluorescence quantum yield calculated with a Jasco ILF-835/100 mm integrating sphere. ^ Shoulder. ^ Not determined (nd).

The final desired compounds 4a–4c were obtained by Knoevenagel condensation with the corresponding aromatic aldehyde. In this case, the reaction was performed in hot aqueous NaOH. This protocol could also be used for the successful preparation of higher reactivity of the C4 and C6 carbons over the C2 carbon allows one to perform Suzuki-Miyaura coupling reactions in a sequential manner. Thus, in a case, the reaction was performed in hot aqueous NaOH.

#### 2.2. Synthesis of 2,4,6-Triarylpyrimidines

Commercially available 2,4,6-trichloropyrimidine was chosen as starting material for the synthesis of 2,4,6-triarylpyrimidines because the higher reactivity of the C4 and C6 carbons over the C2 carbon allows one to perform Suzuki-Miyaura coupling reactions in a sequential manner. Thus, in a first reaction with 2 equiv of the appropriate boronic acid, we were able to obtain the 2-chloro-4,6-diarylpyrimidines by selectively introducing two aryl groups under standard conditions at 50–65 °C. In a second step, a higher temperature (100 °C) was necessary to access the desired triarylsubstituted compounds 6 by reaction with a new molecule of boronic acid (Scheme 2). Under these conditions, no reaction was observed when 5c was treated with 2-hydroxyphenylboronic acid, probably due to the higher electron-donor character of the carbazolyl group, which prevents the oxidative addition of Pd to the C–Cl bond. The temperature needed to be raised up to 140 °C when 4-hydroxyphenyl boronic acid was used, obtaining 6e in moderate yield.

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Lowest-Energy Transition Wavelengths (shown in Table S1). Figures S5 and S6 show some selected stable conformation in solution (the relative energies are and also in the crystal when available. Solvent effects were included using the polarizable continuum model (PCM) that accounts for implicit solvation (see the Supporting Information).

Table 1. Maximum Absorption (λ_{abs,max} eV) and Emission Wavelengths (λ_{em,max} eV) Determined in CH_2Cl_2 Solution. Calculated Lowest-Energy Transition Wavelengths (λ_{vert-cal} eV and λ_{vert-em} eV) and Oscillator Strengths (f) for These Transitions

| compd | λ_{abs,max} eV (nm) | λ_{vert-cal} eV (nm) | f   | % contribution | λ_{em,max} eV (nm) | λ_{vert-em} eV (nm) | f   |
|-------|---------------------|---------------------|-----|----------------|-------------------|-------------------|-----|
| 4a    | 3.23 (384)          | 3.45 (360)          | 1.86| H → L (90)     | 2.86 (434) E      | 1.44 (859) K      | 0.09|
| 4d    | 3.34 (371)          | 3.55 (350)          | 1.89| H → L (89)     | 2.82 (440)        | 2.88 (430)        | 1.54|
| 4f    | 3.32 (373)          | 3.54 (350)          | 1.78| H → L (89)     | 2.83 (438)        | 2.90 (428)        | 1.94|
| 6a    | 3.76 (330)          | 4.17 (297)          | 0.80| 1.03           | 2.83 (438) E      | 1.77 (702) K      | 0.12|
| 6c    | 3.81 (325)          | 4.28 (290)          | 0.90| 1.03           | 3.36 (369)        | 3.84 (323)        | 0.86|
| 6d    | 3.72 (333)          | 4.22 (294)          | 0.67| 1.03           | 3.32 (374)        | 3.76 (330)        | 0.86|
| 6e    | 3.75 (331)          | 4.23 (293)          | 0.70| 1.03           | 3.45 (360) 3.31 (371) | 3.75 (331) | 0.62|

*Calculations were performed at the M06-2X/6-31+G** level of theory. The absorption corresponds to S_0 → S_1, and the emission corresponds to the S_1 → S_0 transition.

The ESIPT process was thoroughly studied from a theoretical point of view by performing density functional theory (DFT) and TD-DFT calculations in CH_2Cl_2 solution and also in the crystal when available. Solvent effects were included using the polarizable continuum model (PCM) that accounts for implicit solvation (see the Supporting Information for computational details). Taking into account the similarity that exists both in the chemical structure and in the experimental photophysical properties, quantum-mechanical calculations were performed over compounds 4a, 4d, 4e, 6a, and 6c–6e. An initial conformational analysis was performed at the M06-2X/6-31G** level of theory to determine the most stable conformation in solution (the relative energies are shown in Table S1). Figures S5 and S6 show some selected parameters of the optimized molecular geometry for the ground and excited states. It is worth commenting on the variations of the molecular geometry in compounds 4a and 6a after excitation. Our calculations predict O–H···N hydrogen bonds in the ground state as moderate, according to the Jeffrey criteria, which could predispose the molecule to the proton transfer in the excited state. For 4a, a planar structure is predicted with dihedral angles along the molecular skeleton very close to zero for both S_0 and S_1 states. After excitation, these hydrogen-bond distances increases from 1.355 Å (S_0, O–H···N) to 1.360 Å (S_1, O–H···N), and the O–H···N bond angle decreases from 150° (S_0) to 138° (S_1), which would favor the stabilization of the keto form in the excited state. For compound 6a, the hydroxyphenyl ring is twisted relative to the pyrimidine ring by ~3°, and a significant deviation of the planarity is also found for the dihedral angles between the phenyl rings at the 4 and 6 positions and the central pyrimidine of ~27° and ~20° in the ground state. After excitation, these dihedral angles decrease up to 18° and 0.8°, while the ring at position 2 is twisted 19°. As in 4a, the hydrogen-bond distance increases from 1.681 Å (S_0, O–H···N) to 1.875 Å (S_1, O–H···N), and the O–H···N bond angle decreases from 148° (S_0) to 147° (S_1).
134° ($S_1$). Thus, the O−H···N hydrogen bond weakens in 6a after excitation, favoring the stabilization of the keto form in the excited state. Finally, compounds 4d and 4e are predicted to be almost planar in both ground and excited states. In contrast, compounds 6c−6e present deviations in the ground state of 21° between the phenyl rings at the 4 and 6 positions and at the central pyrimidine and less than 0.2° between the pyrimidine and the phenyl ring at position 2. Nevertheless, these molecules become completely planar in the excited state.

The relaxed potential energy scan (PES) from the enol form (E) to the keto form (K) were computed in CH2Cl2 solution for 2-(2'-hydroxyphenyl)pyrimidines 4a and 6a, enlarging the oxygen−hydrogen bond length of the OH group toward the nitrogen atom of the pyrimidine ring. As expected, the enol form is predicted to be more stable for both 4a and 6a in the ground state $S_0$ whereas the keto form becomes more stable in the first excited state $S_1$ (Figure 1, top; Table S1 lists the relative energies of the minima). As shown in Figure 1 (bottom), the height of the barrier for 4a from the enol to keto form in $S_1$ is 0.15 eV (3.4 kcal/mol), and the reversed barrier is 0.28 eV (6.5 kcal/mol). For 6a, the energy barrier from the enol to keto form in $S_1$ is 0.02 eV (0.5 kcal/mol), and the reversed barrier is 0.57 eV (13.3 kcal/mol). As a result, the low energy barriers from the enol to keto form and the high reversed-energy barriers would favor the ESIPT process in 4a and 6a and the fluorescence emission from the keto form.

Table 2 lists the vertical electronic transitions and oscillator strength ($f$) calculated at the M06-2X/6-31+G** level of theory in CH2Cl2 solution, considering both enol (E) and keto (K) tautomers (for more details see Table S2). There is a good agreement with the experimental absorption data, especially for compounds 4a, 4d, and 4e with differences in the range of 0.1−0.3 eV. However, the differences observed were greater (0.3−0.5 eV) for compounds 6a and 6c−6e. For all compounds studied, the lowest energy transition $S_0$ → $S_1$ is predicted to be the strongest with a high contribution of the highest occupied molecular orbital (HOMO) → lowest unoccupied molecular orbital (LUMO) and therefore charge-transfer character. Figure 2 plots the HOMO and LUMO molecular orbitals. For compounds 4a, 4d, and 4e, the HOMO is delocalized on the two styryl arms, while the LUMO is more localized on the pyrimidine ring. In 6a and 6c−6e, the HOMO is localized on the three phenyl rings, while the LUMO is localized on the pyrimidine ring.

A large red shift is predicted in the calculated $S_1$ → $S_0$ transition for the keto form compared to the enol form in compounds 4a and 6a. In addition, the predicted oscillator strength is significantly smaller in the keto form ($f = 0.09$ for 4a and $f = 0.12$ for 6a) compared to the enol form ($f = 2.06$ for 4a and $f = 1.18$ for 6a). Since the keto form is predicted to be more stable in the first excited state $S_1$, the emission will occur from this form and could therefore account for the absence of emission in solution for these compounds in the experimental spectra.

The nonradiative vibrational relaxation from the excited state was also studied by calculating the Huang–Rhys (HR) factors in CH2Cl2 solution (see Table S3; the corresponding reorganization energies are shown in Figure S7). Figure 3 shows that the largest values were calculated for compounds 4a and 6a, in agreement with the dark states observed by these compounds in solution. For 4a, the largest HR factor is found for the vibrational mode associated with the OH stretching, calculated at 3131 cm$^{-1}$ with an HR factor of 28. For 6a, this vibrational mode is calculated at 3176 cm$^{-1}$ with an HR factor of 1.4, and there are also two modes in the low-energy region predicted at 24 and 34 cm$^{-1}$ with HR factors of 3 and 6, respectively. In view of our calculations, we postulate that the proton transfer in the excited state will be assisted mainly by
the OH stretching mode in the high-energy region for 4a, by the low-energy modes at 24 and 34 cm$^{-1}$, and by the OH stretching mode for 6a.

In contrast to the null emission observed for 4a−4c, quantum yields of 8% and 11% were measured in solution for 4d and 4e, respectively (see Table 1). These results are consistent with the small vibrational relaxation predicted for these compounds, with 0.64 and 0.67 being the highest HR factors calculated for the vibrational modes 25 cm$^{-1}$ (4d) and 24 cm$^{-1}$ (4e), respectively. Furthermore, higher HR factors (~6) were obtained for 6c−6e, which could justify the lower quantum yields measured for these derivatives in solution ($\Phi_F \leq 1\%$). Thus, our calculations predict two vibrational modes at 24 and 38 cm$^{-1}$ for 6c, at 21 cm$^{-1}$ for 6d, and at 23 and 35 cm$^{-1}$ for 6e, with HR factors around 5−6. Figures S8 and S9 show the atomic displacements for some of these vibrational modes.

2.4. Photophysical Properties in Solid State. Single crystals of 4a, 4e, and 6c−6e suitable for X-ray diffraction analysis were obtained by vapor diffusion in CH$_2$Cl$_2$/CH$_3$CN and CHCl$_3$/MeOH solvent systems. This allowed us to investigate inter- and intramolecular interactions and molecular packing structures, which directly impact the emissive properties of the compounds in the solid state.$^{34}$ Data processing and refinement parameters are given in Table 3.

The compounds adopt monoclinic crystal systems, except 4a, which prefers an orthorhombic structure with two crystallographically independent molecules in the asymmetric unit. Figure S10 shows the crystal structures for all compounds. In general, intramolecular C−H···N weak hydrogen bonds (2.48−2.83 Å) exist between the central pyrimidine and the adjacent phenyl rings, which could restrict the intramolecular distortion and increase the molecular stability. Crystal structures show that the compounds adopt a planar geometry: the dihedral angle between the plane of the rings and the molecular plane exhibits values between 5.1° and 18.1°, with the compound 6c showing the greatest deviation (18.1°). For compounds 4a and 6e, the presence of the OH group in ortho (4a) and para (6e) position permits intra- and intermolecular hydrogen bonds, respectively. In the structure of 4a, it can be observed an intramolecular interaction O2C−H2C···N3 (O2−N3 distance of 2.545(6) Å), whereas 6e exhibits an intermolecular bond O4C−H4C···N1 (O4−N1 distance of 2.905(1) Å).

The molecular packing patterns of the less-emissive compounds in solid 4a and in 6c−6e are similar. Crystal structures of 4a and 6d show the molecules stacked in parallel, while in 6c and 6e the arrangement is antiparallel. All the interactions were stabilized by π−π interactions through the pyrimidine ring and one of the neighboring rings (Figure 4, top). Geometrical parameters defining the π−π interactions indicate the existence of a π-stacking arrangement with centroid distances that range between 3.5 and 4.0 Å. As it is known, these interactions quench the emission,$^{36}$ which would
agree with the low quantum yield measured for compounds 6c and 6d in the solid state (10% and 3%, respectively) and the null emission for 4a and 6e. Meanwhile, multiple weak interactions such as C−H···π interactions and no classical hydrogen bonds promote three-dimensional structures in which the stacking of molecules shows an angular disposition (Figure 4, bottom), with angular dihedral angles between 40.73° in 4a and 73.10° (quasi parallel disposition) in 6d. In contrast, the three-dimensional structure of 4e shows isolated molecules and exhibits only an intramolecular weak bond (C42−H42···N3; 2.841(2) Å). Moreover, the intermolecular interactions are weaker than in the other structures; for

| Table 3. Crystallographic and Refinement Data for 4a, 4e, and 6c–6e |
|------------------------|------------------------|------------------------|------------------------|------------------------|
| compound               | 4a                     | 4e                     | 6c                     | 6d                     | 6e                     |
| CCDC number            | 2113241                | 2113242                | 2113243                | 2113244                | 2113245                |
| formula                | C28H24N2O3             | C29H26N2O3             | C24H20N2O2             | C25H22N2O3             | C24H20N2O3             |
| FW (g·mol⁻¹)           | 436.49                 | 450.52                 | 368.42                 | 398.44                 | 384.42                 |
| color, habit           | white needle           | yellow prism           | white prismatic        | white prismatic        | white prismatic        |
| crystal size (mm³)     | 0.030 × 0.035 × 0.300  | 0.20 × 0.15 × 0.06     | 0.27 × 0.23 × 0.07     | 0.190 × 0.185 × 0.035  | 0.228 × 0.150 × 0.123  |
| crystal system         | orthorhombic           | monoclinic             | monoclinic             | monoclinic             | monoclinic             |
| space group            | P a 21                 | P 21/c                 | P 21/n                 | P 21                   | P 21/n                 |
| unit cell dimens. a (Å)| 22.569(1)              | 15.917(1)              | 13.460(1)              | 6.483(1)               | 13.755(1)              |
| b (Å)                  | 5.140(1)               | 13.881(1)              | 7.515(1)               | 8.533(1)               | 7.797(1)               |
| c (Å)                  | 37.999(1)              | 10.594(1)              | 18.609(1)              | 18.029(1)              | 17.927(1)              |
| α (deg)                | 90                     | 90                     | 90                     | 90                     | 90                     |
| β (deg)                | 90                     | 98.99(1)               | 104.27(1)              | 95.01(1)               | 102.42(1)              |
| volume (Å³)            | 4408.2(2)              | 2312.1(1)              | 1824.2(1)              | 993.5(1)               | 1877.9(2)              |
| density (calc. Mg·m⁻³) | 1.315                  | 1.294                  | 1.341                  | 1.332                  | 1.360                  |
| μ (mm⁻¹)               | 0.086                  | 0.084                  | 0.086                  | 0.088                  | 0.091                  |
| F(000)                 | 1840                   | 952                    | 776                    | 420                    | 808                    |
| θ range (deg)          | 2.099–27.177           | 1.96–27.12             | 2.14–7.51              | 2.27–27.19             | 2.33–28.76             |
| index ranges           | 0 ≤ h ≤ 6              | −20 ≤ h ≤ 20           | −17 ≤ h ≤ 16           | −8 ≤ h ≤ 8             | −18 ≤ h ≤ 18           |
|                        | 0 ≤ k ≤ 28             | −17 ≤ k ≤ 17           | 0 ≤ k ≤ 9              | −10 ≤ k ≤ 10           | −9 ≤ k ≤ 10            |
|                        | −48 ≤ l ≤ 48           | −13 ≤ l ≤ 13           | 0 ≤ l ≤ 24             | 0 ≤ l ≤ 23             | −24 ≤ l ≤ 23           |
| reflcs. collected      | 9721                   | 18.962                 | 4185                   | 4409                   | 46.689                 |
| indep. / I > 2σ(I)     | 9721                   | 5113                   | 4185                   | 4409                   | 4872                   |
| R <sub>exp</sub>       | 0.086                  | 0.0381                 | 0.047                  | 0.035                  | 0.0429                 |
| weighting scheme       | w⁻¹ = σ²(F<sub>c</sub>²) + (σP)² + yP (P = (F<sub>c</sub>² + 2F<sub>e</sub>²)/3) |
| x/y                    | 0.0624/0.8168          | 0.0513/0.3935          | 0.0379/1.1602          | 0.0419/0.1246          | 0.0573/1.0741          |
| data/restraints/parameters | 9721/1/636             | 5113/0/411             | 4185/0/333             | 4409/1/359             | 4872/0/342             |
| goodness-of-fit on F²  | 1.036                  | 1.037                  | 1.077                  | 1.061                  | 1.061                  |
| R1/wR2 [I > 2σ(I)]    | 0.0619/0.1325          | 0.0391/0.0968          | 0.0474/0.1120          | 0.0347/0.0854          | 0.0409/0.1092          |
| R1/wR2 (all data)     | 0.0850/0.1485          | 0.0539/0.1032          | 0.0544/0.1154          | 0.0403/0.0876          | 0.0516/0.1186          |
| largest Δρ (e·Å⁻³)    | 0.844/−0.365           | 0.322/−0.205           | 0.957/−1.143           | 0.156/−0.239           | 0.390/−0.283           |

Figure 4. Pattern of the π−π interactions between molecules (top) and crystal packing (bottom) of compounds 4a, 6c, and 4e. For clarity, neither hydrogen atoms (top) nor atom labels are displayed (crystal packing of 6d and 6e are shown in Figure S11).
instance, the distances between planes to form the π−π stacking are larger (ca. 4.54 Å). These weaker interactions could lead to improved emission, thus increasing the photoluminescence quantum yield in the solid state for 4e up to 21%.

The possibility of ESIPT in the crystal was also investigated by performing TD-DFT calculations for compound 4a. For 6e, we analyzed the possibility of an intermolecular proton transfer in the excited state in a dimer. In both cases, we built a cluster of 15 molecules from the crystal structure. The relaxed PES from the enol form (E) to the keto form (K) were computed by enlarging the oxygen–hydrogen bond length of the OH group to the nitrogen atom of the pyrimidine ring in compound 4a and to the neighboring molecule in dimer 6e, leaving the surrounding molecules frozen. As expected, the enol form is more stable for both 4a and 6e in the ground state S0 (Figure 5). For compound 4a, the energy barrier for the ESIPT process disappears, and the keto form becomes more stable in the first excited state S1. However, the energy barrier for the intermolecular proton transfer in 6e is 0.49 eV (11.1 kcal/mol), and the ESIPT process in the solid state would be less favored than in solution (Figure S12). In any case, this result should be taken with caution due to the simplicity of our model, which considers only the excitation of one dimer in the crystal. Table S4 lists the calculated emission for the enol (E) and keto (K) forms of the central molecule of 4a and the dimer 6e. The calculated oscillator strength for the keto form of 4a is almost zero (f = 0.008), which is in agreement with the lack of

Figure 5. (a) PES curves computed for the central molecule of 4a (top) and the dimer of 6e (bottom) in the ΔE scale at the M06-2X/6-31G** level of theory. The enol (E) and keto (K) forms are indicated at short and long O–H distances, respectively. (b) Molecular clusters computed at the QM/MM level. The central molecule is treated as high level (M06-2X/6-31G**) and the surrounding molecules as low level (UFF41).

Figure 6. Changes in the absorption (left) and emission (right, λexc = 384 nm) spectra of a CH2Cl2 solution of 4a (c = 4.12 × 10−6 M) upon addition of TFA.
emission of this compound in the solid state. Although the enol form is more stable than the keto form for the dimer of 6e, the oscillator strength is also very small ($f = 0.4$), which could account for the absence of emission in the solid state.

2.5. Effect of Protonation: Experimental Results and Computational Insights. The effect of protonation of the pyrimidine ring on the photophysical properties was also studied by titration of CH$_2$Cl$_2$ solutions with trifluoroacetic acid (TFA). The changes observed in the absorption and emission spectra for compound 4a are illustrated in Figure 6. The UV/vis spectra showed the progressive attenuation of the absorption band for the neutral compound on increasing the concentration of acid, whereas a new red-shifted absorption band progressively appeared. The spectra showed an isosbestic point at 402 nm, and this is characteristic of an equilibrium between two species (Figure 6, left). The bathochromic shift is explained by the higher degree of intramolecular charge transfer (ICT) due to an increase in the electron-withdrawing character of the pyrimidine ring, as observed previously. More than 3000 equiv of TFA was required for a complete protonation.

As mentioned above, the neutral solution of 4a did not exhibit luminescence. Nevertheless, the addition of acid resulted in the progressive appearance of a green-yellow emission band ($\lambda_{\text{max}} = 550$ nm) whose intensity increased with the concentration of acid (Figure 6, right). The addition of acid should inhibit the ESIPT process, effectively interrupting the nonradiative deactivation pathway of the excited state. This fact accounts for the observed switch on fluorescence response, which was also readily detectable by the naked eye (Figure 7, left).

![Figure 7](image-url). Change in the color of a CH$_2$Cl$_2$ solution of 4a (left) and 6a (right) after the addition of TFA (3000 equiv for 4a and 1500 equiv for 6a). The pictures were taken in the dark upon irradiation with a UV hand-held lamp ($\lambda_{\text{exc}} = 365$ nm, 24 W).

A similar behavior was observed for compounds 4b and 6a (Figure 7 right and Figures S13 and S14), although the protonated form of 4b showed a poor fluorescence signal because of a greater ICT. In contrast, the optical properties of 4c and 6b remained almost unaltered in the presence of an excess of TFA, which denoted an ineffective protonation. The strong electron-withdrawing character of the CF$_3$ groups should decrease the basicity of the pyrimidine nitrogen atoms. Titrations of acetonitrile solutions of 4a and 6a with aqueous HCl gave similar results to those obtained with TFA, although less acid was required for complete protonation due to the higher acidity of HCl. All these data seem to rule out the formation of a dication at least at the concentration of acid used.

Protonation of 4a and 6a was also studied by $^1$H NMR spectroscopy. Upon addition of an excess of TFA to a CDCl$_3$ solution of 4a, most of the signals were shifted downfield, except proton H6' of the -hydroxyphenyl group, which experienced an upfield shift (Figure 8). A similar behavior was observed for the protonation of 6a (Figure S15). The addition of acid should lead to an equilibrium between the two possible monoprotonated species (Figure 9). This equilibrium is fast on the NMR time scale, and the only set of signals observed is an average of both species. If only one of these species was formed, each branch at positions 4 and 6 of the pyrimidine ring would give a different set of signals.

TD-DFT calculations were also performed on protonated compounds 4a and 6a in order to investigate the origin of the emission after protonation. The molecular geometry for the ground and excited states were optimized at the M06-2X/6-31+G** level of theory in CH$_2$Cl$_2$ solution exploring the two possibilities of protonation as shown in Figure 9 (see geometrical parameters in Figure S16). Protonation leading to 4aH$^+$-(2) and 6aH$^+$-(2) provides further stabilization and lack of ESIPT. These protonated species are slightly more stable ($\Delta E \approx 1$ kcal/mol) than 4aH$^+$-(1) and 6aH$^+$-(1) (relative energies are listed in Table S5).

Table 4 lists the vertical electronic transitions along with the experimental absorption and emission data (see also Table S6 for more transitions). The theoretical predictions are in good agreement with the experimental observations, with deviations in the range of 0.1—0.4 eV for 4aH$^+$-(1) and 6aH$^+$-(1) and up to 0.5 eV for 4aH$^+$-(2) and 6aH$^+$-(2). The lowest-energy $S_0 \rightarrow S_1$ transition is predicted to be the strongest with a high contribution of the HOMO $\rightarrow$ LUMO transition and therefore charge-transfer character. Figure S17 plots the HOMO and LUMO molecular orbitals for the protonated compounds.

The relaxed PES from the enol form (E) to the keto form (K) were also computed for 4aH$^+$-(1) and 6aH$^+$-(1), enlarging the oxygen--hydrogen bond length of the OH group to the nitrogen atoms of the pyrimidine ring. As shown in Figure 10, the enol form is more stable for both protonated species in the ground state $S_0$. The calculated energy barrier predicts the stabilization of the enol form of 4aH$^+$-(1) in the first excited state $S_1$ that is, the ESIPT would not occur in 4aH$^+$-(1) (Table S5 lists the relative energies of the minima). As shown in Table 4, a significant oscillator strength ($f = 2.39$) is predicted not only for the $S_1 \rightarrow S_0$ electronic transition of the enol form of 4aH$^+$-(1) but also for 4aH$^+$-(2) ($f = 2.37$), which could account for the observed emission after the addition of acid ($\Phi_F = 11\%$). Namely, according to our calculations, both protonation positions would result in emissive species in the case of compound 4a.

With regard to 6aH$^+$-(1), the keto form in $S_1$ is 1.6 kcal/mol more stable than the enol form (Figure S18 shows an enlarged view of the calculated energy barrier in the excited state $S_1$). The energy barrier from the enol to keto form in $S_1$ is 0.17 eV (3.9 kcal/mol), and the reversed barrier is 0.24 eV (5.5 kcal/mol). These results do not justify the emission increase observed for compound 6a after protonation ($\Phi_F = 34\%$). Nevertheless, the calculated oscillator strength for the $S_1 \rightarrow S_0$ transition of 6aH$^+$-(2) ($f = 1.47$) does explain the observed emission.

Furthermore, small HR factors were calculated for protonated 4a and 6a, which supported the switch on
fluorescence response observed for these compounds after protonation (Figure 11, Table S7). The largest HR factor for $4aH^+-(1)$ was $\sim 1$ for the vibrational mode at 23 cm$^{-1}$ in the low-frequency region. The calculated values for $4aH^+-(2)$ were even smaller than those for $4aH^+-(1)$. Therefore, both protonation positions would favor the radiative relaxation. In $6aH^+-(1)$, if the relaxation occurs from the enol form, there are several modes in the low-energy region with HR $< 1$, which could favor the radiative relaxation. In contrast, if the molecule relaxes from the keto form (predicted more stable than the enol form), a large value of HR $= 30$ is calculated in the high-frequency region for the mode at 3474 cm$^{-1}$ in detriment of the emission. For $6aH^+-(2)$, small HR factors ($\sim 2$) were obtained in the low-energy region, thus clearly favoring the radiative relaxation.

Table 4. Maximum Absorption ($\lambda_{\text{ab}}^{\text{max}}$) and Emission Wavelengths ($\lambda_{\text{em}}^{\text{max}}$) Determined for Protonated Compounds $4a$ and $6a$. Calculated Lowest-Energy Transition Wavelengths ($\lambda_{\text{vert}}^{\text{-abs}}$ and $\lambda_{\text{vert}}^{\text{-em}}$) and Oscillator Strengths ($f$) for These Transitions$^a$

| compd  | $\lambda_{\text{ab}}^{\text{max}}$ eV (nm) | $\lambda_{\text{vert}}^{\text{-abs}}$ eV (nm) | $\%$ contr. | $\lambda_{\text{em}}^{\text{max}}$ eV (nm) | $\lambda_{\text{vert}}^{\text{-em}}$ eV (nm) | $f$ |
|--------|------------------------------------------|-------------------------------------------|-------------|------------------------------------------|------------------------------------------|-----|
| $4aH^+-(1)$ | 2.65 (468) | 2.76 (450) | 2.06 | $H \rightarrow L$ (92) | 2.25 (550) | 2.61 (476) | E | 2.39 |
| $4aH^+-(2)$ | 2.92 (425) | 2.04 | $H \rightarrow L$ (91) | 2.72 (456) | 2.37 |
| $6aH^+-(1)$ | 3.14 (395) | 3.46 (359) | 1.09 | $H \rightarrow L$ (90) | 3.33 (396) | 1.47 |
| $6aH^+-(2)$ | 3.62 (342) | 3.62 (342) | 1.12 | $H \rightarrow L$ (89) | 3.33 (372) | 1.47 |

$^a$Calculations were performed at the M06-2X/6-31+G** level of theory in CDCl$_3$ solution. The absorption corresponds to S$_0 \rightarrow$ S$_1$, and the emission corresponds to S$_1 \rightarrow$ S$_0$ transition.

Figure 8. Expanded regions of the $^1$H NMR spectrum of $4a$ before (bottom) and after (top) the addition of an excess of TFA (CDCl$_3$, 500 MHz).

Figure 9. Possibilities of protonation for compounds $4a$ and $6a$.

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2.6. Hydrogen-Bonding Strength. The potential energy barrier of the C–C–C–N dihedral angle between the pyrimidine and the phenyl ring at position 2 was calculated in the ground state in order to estimate the ease of rotation of the phenyl ring. As expected, the highest rotational energy barrier was obtained for compounds 4a and 6a (~11 kcal/mol), which is indicative of the strength of the hydrogen bond (Figure S19). The phenyl ring may undergo twisting motions more easily for the rest of the compounds. With regard to the protonated species, the height of the barrier correlates well with the strength of the hydrogen bond; that is, 4a > 4aH+(1) > 4aH+(2), and 6a > 6aH+(1) > 6aH+(2) (see below).

Additionally, to confirm the relative strength of the intramolecular hydrogen bonds predicted in compounds 4a and 6a, before and after protonation, we performed Quantum Theory of Atoms In Molecules (QTAIM) calculations in the context of Bader’s theory using the ground-state optimized molecular geometry of 4a and 6a in CH2Cl2 solution as well as the molecular geometry derived from the crystal structure of 4a and 6a. Figure S20 shows the distribution of critical points (CPs) and bond paths for inter- and intramolecular hydrogen bonds. Table S8 lists the calculated QTAIM parameters of the hydrogen bonds. The dissociation energy (EDis) was calculated to evaluate the strength of the hydrogen bonds by using the methodology proposed by Espinosa et al.11 Figure 12 plots the EDis versus the hydrogen bond (HB) distance. The QTAIM analysis revealed that EDis for compounds 4a and 6a are higher and that, consequently, the intramolecular HBs are stronger than those of the corresponding protonated species. These results indicate that the ESIPt process is more favored before protonation. EDis is also higher for 4aH+(1) (45.1 kJ/mol) and 6aH+(1) (42.7 kJ/mol) compared to 4aH+(2) (38.7 kJ/mol) and 6aH+(2) (37.8 kJ/mol). In fact, the keto form of 6aH+(1) becomes more stable than the enol form in the excited state, thus favoring the ESIPt process and the absence of emission. Although the hydrogen bonds for 4aH+(2) and 6aH+(2) are weaker than for 4aH+(1) and 6aH+(1), these intramolecular interactions cause a rigidification in that part of the molecule (see Figure S16), preventing the ESIPt process and increasing the fluorescence emission. Regarding the crystal data, the weakest HB corresponds to the intermolecular HB in the dimer of 6e (EDis = 23.0 kJ/mol), while the intramolecular HB for compound 4a (EDis = 57.7 kJ/mol) is close to that in solution (EDis = 64.4 kJ/mol), which again favors the ESIPt process and the loss of emission in the solid state.

2.7. Anticounterfeiting Applications. The illicit trafficking of counterfeit goods is one of the largest money-making sources for organized crime and is a global serious concern.62 Fluorescent security inks are among the most widely used techniques to prevent counterfeiting. A higher level of security can be achieved simply by implementing a passive invisible ink as a tag.63,64 On the basis of the remarkable luminescence response aroused by acid, the fluorescence probes 4a and 6a look to be appropriate for anticounterfeiting applications. Thus, three drops of a solution of 4a (4.12 × 10−5 M in CH2Cl2) were deposited on a piece of Whatman filter paper, which were invisible both under daylight and under UV light. Upon exposure to acid vapors (HCl), the droplets were prominent as greenish-yellow circles under UV light (Figure 13) with a response time of a few seconds (1–5 s). The paper was further exposed to triethylamine vapor to check for reversibility. The emission could be switched on and off for at least 10 cycles allowing the material to be used multiple times. The fluorescent color on the paper also slowly faded over time. A similar phenomenon was observed for 6a (Figure S21).

3. EXPERIMENTAL SECTION

All experimental methods and materials as well as the synthesis and characterization of all compounds are fully described in detail in the Supporting Information. Here we include a few representative examples.

3.1. 2-(2′-Hydroxyphenyl)-4,6-dimethylpyrimidin (3a)58,59 2-Chloro-4,6-dimethylpyrimidin (1000 mg, 7.02 mmol), 2-hydroxyphenylboronic acid (1065 mg, 7.72 mmol), and sodium carbonate (3720 mg, 35.1 mmol, dissolved in a minimum amount of water) were mixed with 1,2-dimethoxyethane (8 mL). Palladium acetate (79 mg, 0.35 mmol, dissolved in a minimum amount of water) added. The mixture was bubbled with argon for 5 min and heated at 100 °C for 22 h. After this mixture was cooled, the precipitated yellow solid was collected by washing with boiling methanol (200 mg, 92%). mp: 175 °C (EtOAc/MeOH). 1H NMR (CDCl3, 500 MHz) δ: 7.42–7.49 (m, 1H, ArH), 7.38 (m, 1H, ArH), 8.54 (dd, 1H, J = 1.5 Hz, ArH), 7.38 (m, 1H, ArH), 8.54 (dd, 1H, J = 8.0 Hz, J = 1.5 Hz, ArH, ArH). 13C NMR and distortionless enhancement by polarization transfer (DEPT) (CDCl3, 125 MHz) δ: 165.9 (C), 164.2 (C), 160.7 (C), 158.6 (C), 133.0 (CH), 129.2 (CH), 118.9 (CH), 118.6 (C), 117.8 (CH), 117.5 (CH), 23.9 (CH3). IR (ATR) v: 1561, 1434, 1366, 1250, 848, 759 cm−1.

3.2. (E,E)-2-(2′-Hydroxyphenyl)-4,6-bis(4′-methoxystyryl)-pyrimidin (4a). A stirred mixture of 2-(2′-hydroxyphenyl)-4,6-dimethylpyrimidin (100 mg, 0.5 mmol), 4-methoxybenzaldehyde (136 mg, 1 mmol), Aliquat 336 (22 mg, 0.05 mmol), and 5 M NaOH (8 mL) was heated at 50 °C for 22 h. After this mixture was cooled, the precipitated yellow solid was collected by filtration and purified by washing with boiling methanol (200 mg, 92%), mp: 175–177 °C (EtOH/MeOH). 1H NMR (CDCl3, 500 MHz) δ: 8.36 (s, 6H, 2 × 24974
OCH₃), 6.94 (A of ABq, J = 8.5 Hz, ArH), 6.97 (A of ABq, 2H, J = 16.0 Hz, 2 × CH=), 6.99−7.02 (m, 1H, ArH), 7.07 (dd, J = 8.0 Hz, ArH), 7.10 (s, 1H, pyr), 7.39−7.43 (m, 1H, ArH), 7.58 (B of ABq, 4H, J = 8.5 Hz, ArH), 7.84 (B of ABq, 2H, J = 16.0 Hz, 2 × CH=), 8.67 (dd, J = 8.0 Hz, J = 1.5 Hz, ArH), 13.95 (br s, 1H, OH). ¹³C NMR and DEPT (CDCl₃, 125 MHz) δ: 164.1 (C), 161.9 (C), 161.0 (C), 160.8 (C), 137.5 (CH), 133.0 (CH), 129.4 (CH), 128.2 (C), 122.8 (CH), 119.0 (C), 118.9 (CH), 117.7 (CH), 114.4 (CH), 113.1 (CH), 55.4 (CH₃). Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (2,5-dihydroxybenzoic acid (DHB)) m/z: 437.3 [M + H]+. IR (attenuated total reflectance (ATR)) ν: 1526, 1593, 1560, 1508, 1367, 1242, 1161, 1022, 972, 840, 754 cm⁻¹. Anal. Calcd for C₂₈H₂₄N₂O₃: C, 77.04; H, 5.54; N, 6.42. Found: C, 76.86; H, 5.39, N, 6.62%.

3.3. 2-Chloro-4,6-bis(4'-methoxyphenyl)pyrimidine (5a).⁶⁶,⁶⁷ 2,4,6-Trichloropyrimidine (500 mg, 2.73 mmol), 4-methoxyphenylboronic acid (830 mg, 5.46 mmol), and sodium carbonate (1810 mg, 17.1 mmol, dissolved in a minimum amount of...
Figure 12. Dependence of the dissociation energy ($E_{\text{diss}}$) vs H–O distance.

Figure 13. Digital photographs of the reversible color change of Whatman filter paper under UV light (365 nm) using compound 4a as an anticounterfeiting agent.

developed for the synthesis of a new family of 2-('hydroxyphenyl')pyrimidines. These compounds exhibited very little or no luminescence both in solution and in the solid state, which is explained by an ESIPT process from the OH group to the nitrogen atoms of the pyrimidine ring and confirmed by the emissive properties of analogous 2-unsaturated derivatives. A single-crystal X-ray structure analysis determined inter- and intramolecular interactions and molecular packing structures, which helped us to rationalize the different luminescent behaviors in the solid state. The compounds could be easily protonated at the nitrogen atom of the pyrimidine ring. Protonation provided a substantial enhancement in the fluorescence response of 2-('hydroxyphenyl')pyrimidines and, consequently, allowed us to use these pyrimidines as solid-state acid–base vapor sensors and anticounterfeiting agents. All of the results were interpreted with the aid of extensive DFT and TD-DFT calculations.

Additional experimental details, material, and methods; synthesis of compounds; values of relative energies for the conformers of compounds 4a, 4d, 4e, 6a, and 6c–6e; maximum absorption wavelengths, calculated lowest-energy transition wavelengths, oscillator strength, and Huang–Rhys factors for 4a, 4d, 4e, 6a, and 6c–6e; wavenumber, reorganization energy, and Huang–Riggs factors calculated for protonated 4a and 6a; atomic displacements of selected vibrational modes calculated for compounds 4a, 4d, 4e, 6a, and 6c–6e; reorganization energy versus normal mode wavenumbers calculated for the ground state of compounds 4a, 4d, 4e, 6a, and 6c–6e; molecular structure of compounds 4a, 4e, and 6c–6e extracted from X-ray analysis; pattern of the $\pi$–$\pi$ interactions between molecules and crystal packing of 6d and 6e; potential energy surface of the excited state $S_1$ for the dimer 6e; absorption and emission spectra of 4b and 6a upon addition of TFA; 1H NMR spectrum of 6a before and after the addition of an excess of TFA; bond lengths and dihedral angles in the S0 and S1 states for the dimer 6e; atomic displacements of selected vibrational modes calculated for compounds 4a, 4d, 4e, 6a, and 6c–6e; molecular structure of compounds 4a, 4e, and 6c–6e extracted from X-ray analysis; pattern of the $\pi$–$\pi$ interactions between molecules and crystal packing of 6d and 6e; potential energy surface of the excited state $S_1$ for the dimer 6e; absorption and emission spectra of 4b and 6a upon addition of TFA; 1H NMR spectrum of 6a before and after the addition of an excess of TFA; bond lengths and dihedral angles in the S0 and S1 states for protonated 4a and 6a; frontier molecular orbitals calculated for protonated 4a and 6a in the ground state S0 and excited state $S_1$; potential energy surface of the excited state $S_1$ state for protonated 6a; relative rotational energy barrier of the phenyl ring in the ground state; molecular graphs from the QTAIM.
analysis; photographs of the reversible color change of 6a as an anticounterfeiting agent; and $^1$H and $^{13}$C NMR spectra of all compounds (PDF)

Three-dimensional molecular structures (ZIP)

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Notes
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**NOTE ADDED AFTER ISSUE PUBLICATION**

This article originally published with an inaccurate version of Figure 13. The corrected file published May 18, 2022.