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Synthesis of Pyrrolo[2,3-*c*]isoquinolines via the Cycloaddition of Benzyne with Arylideneaminopyrroles: Photophysical and Crystallographic Study

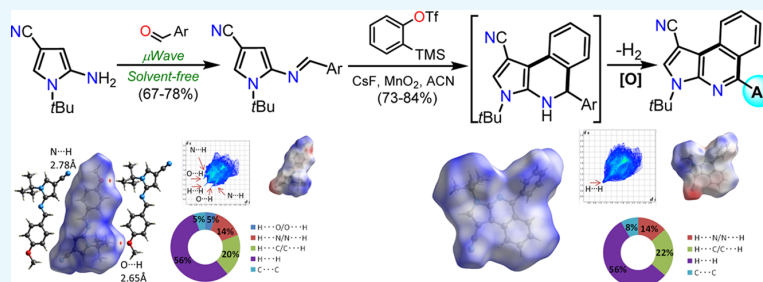
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ABSTRACT: An efficient and quick access toward a series of (*E*)-2-arylideneaminopyrroles **6** and to their benzyne-promoted aza-Diels–Alder cycloaddition products is provided. These products are three pyrrolo[2,3-*c*]isoquinolines **8a–c** substituted in position 5 with different electron-acceptor (A) or electron-donor (D) aryl groups. Intermediates and products were obtained in good yields (up to 78 and 84%, respectively), and their structures were determined on the basis of NMR measurements and HRMS analysis. Photophysical properties of **8a–c** were investigated, finding good Stokes shift in different solvents, but only the product **8c** showed appreciable fluorescence intensity since its 5-aryl group (2,4-Cl₂Ph) could favor the twisted intramolecular charge transfer effect. In addition, a riveting relationship between solvent viscosity and fluorescence intensity was found. Structures of **6** and **8** were studied and confirmed by single-crystal X-ray diffraction, observing that their electronic distributions effect the supramolecular assembly but with only long-distance hydrophobic interactions. A CE-B3LYP model was used to study the energetic topology and understand the crystal architecture of compounds as well as find a connection with both the synthetic and photophysical results.

INTRODUCTION

The development of simple and atom-economical approaches for the construction of fused *N*-heterocycles is very important because of their broad range of applications in medicinal chemistry and, nowadays, also in chemosensor design.^{1–3} In particular, isoquinoline derivatives are found in a plethora of natural products, pharmaceutical compounds, and organic materials.^{4–6} Although several syntheses of this scaffold have been developed, there still remains a great need to find efficient methodologies for its construction. Traditional synthesis of isoquinolines include the Bischler–Napieralski,⁷ Pictet–Spengler,⁸ and Pomeranz–Fritsch reactions.⁹ Likewise, the transition metal-catalyzed C–H or C–halogen bond activation and electrophile-triggered annulation reaction have enabled an orthogonal access to isoquinolines.¹⁰ However, these methods

are often limited due to the use of special additives and/or expensive catalysts, which results in lower atom efficiency.¹¹ In this sense, Maulide’s group reported a metal-free selective cycloaddition between ynamides and nitriles that allowed efficient access to isoquinolines.¹² Another elegant approach is based on a metal-free annulation reaction between secondary enamides and arynes.¹³

Regarding the synthesis of fused isoquinolines, the pyrrolo-fused derivatives have remained almost unexplored, possibly due to the dearth of direct approaches to obtain these scaffolds.¹⁴ Specifically, pyrrolo[2,3-*c*]isoquinolines synthesis is

Scheme 1. (*E*)-Arylideneaminopyrroles 6a–c and Synthesis of Pyrrolo[2,3-*c*]isoquinolines 2 and 8a–c

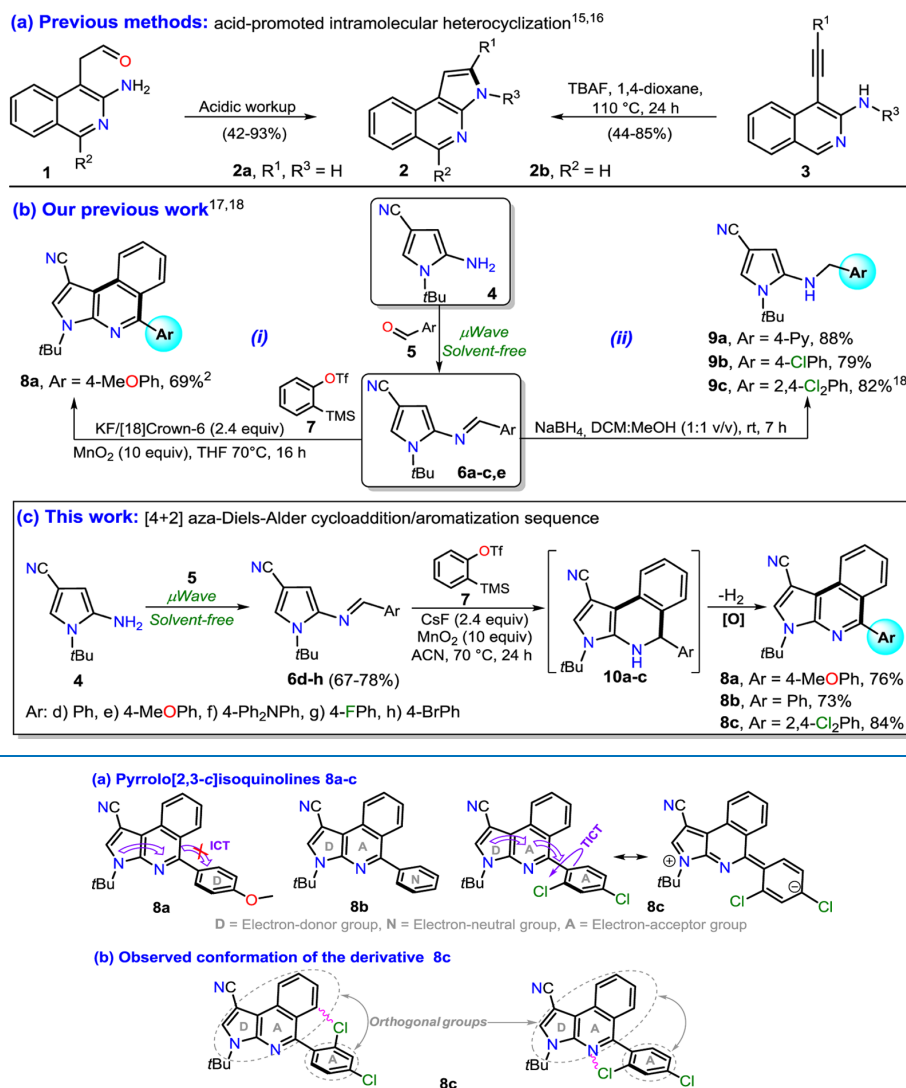


Figure 1. (a) Structure of pyrrolo[2,3-*c*]isoquinolines 8a–c. (b) Observed molecular conformation of 8c.

quite rare, but Biehl et al. reported the synthesis of derivative **2a** by an acid-promoted cyclization of 4-formylmethylisoquinolin-3-amines **1**.¹⁵ Likewise, Hajós developed a TBAF-promoted 5-endo-dig cyclization involving 4-ethynylisoquinoline-3-amines **3** as a viable route to derivative **2b** (Scheme 1a).¹⁶ A few years ago, we reported the synthesis of the pyrrolo[2,3-*c*]isoquinoline **8a** as a single example of cycloaddition between the (*E*)-arylideneaminopyrrole **6e** with the aryne derived from **7** (Scheme 1b,i).¹⁷ More recently, we reported an efficient synthesis and significant structural studies by X-ray of a series of (*E*)-arylideneaminopyrroles **6a–c** and their reduction products to secondary amines **9a–c** via a two-step synthesis sequence (solvent-free condensation and reduction) starting from 5-amino-1-*tert*-butyl-1H-pyrrole-3-carbonitrile (**4**) and arylaldehydes **5** (Scheme 1b,ii).¹⁸

Inspired by these earlier studies along with our interest in the development of efficient protocols for the synthesis of

fused *N*-heterocycles,^{2,19–23} we envisioned that using our established synthetic sequences^{17,18} might generate other (*E*)-arylideneaminopyrroles **6d–h**, which would be suitable heterodienes for normal electron-demand aza-Diels–Alder cycloaddition with benzyne in situ generated from **7**. Thus, reactions with three heterodienes substituted with different electron-acceptor (A) or electron-donor (D) groups led to the expected cycloadducts **10a–c** that, with later in situ aromatization, provided pyrrolo[2,3-*c*]isoquinolines **8a–c** in high atom economy and efficiency (Scheme 1c). We report herein a detailed study of the observed molecular conformations in the solid state of three (*E*)-arylideneaminopyrroles **6e–g** and two pyrrolo[2,3-*c*]isoquinolines **8b** and **8c** discussed in terms of their molecular and supramolecular structures, including the interpretation of their Hirshfeld surface maps and energy frameworks. Considering the lack of short contacts in the solid state, the term “weak interactions” presents, in this

work, a special meaning, leaving the interpretation of the intermolecular contacts necessarily in terms of energetic topology. In addition, a brief discussion about results of photophysical studies for compounds **8a–c** is presented, which was carried out due to their fused nature^{25–27} and our continued interest in this important property for *N*-heterocyclic derivatives.^{24–27}

It is important to note that, in the pyrroloisoquinoline moiety of **8a–c**, an intramolecular charge transfer (ICT) process occurs due to the π -excedent character of the pyrrole ring versus isoquinoline ring (Figure 1a). In addition, since compounds **8a–c** are substituted in position 5 with different aryl groups (A or D), there exist a direct influence over their molecular electronic distribution. Accordingly, photophysical properties of **8a–c** were explored in order to establish the scope of the pyrrolo[2,3-*c*]isoquinoline core as a new organic fluorophore. Additionally, since the structures of aza-diene intermediates **6** and products **8** were studied by X-ray diffraction, these analyses were conveniently related to both the synthetic and photophysical results. For example, the product **8c** (substituted with the 2,4-Cl₂Ph group) showed a fully perpendicular conformation due to the steric effect that can occur between the Cl atom at position 2 of the aryl group¹⁸ and the fused moiety (Figure 1b). In fact, only **8c** showed appreciable fluorescence intensity (FI) since, possibly, its aryl group favors a greater twisted intramolecular charge transfer (TICT) effect.^{3,27,28}

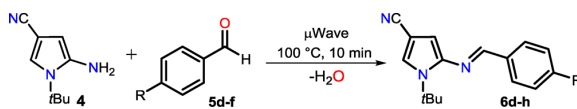
RESULTS AND DISCUSSION

Some information about the approach used for the formation of (*E*)-arylideneaminopyrroles **6d–h** and the synthesis of the pyrroloisoquinolines **8a–c** was described in our previous works (Scheme 1b).^{17,18} In this work, we decided to explore the scope and limits of the solvent-free microwave-assisted synthesis of **6** with diverse arylaldehydes **5d–h** and the 5-aminopyrrole **4** using our previously optimized conditions.¹⁸ Likewise, we carry out the synthesis of three pyrrolo[2,3-*c*]isoquinolines **8a–c** substituted with different A or D groups by the aza-Diels–Alder cycloaddition between **6** and 2-(trimethylsilyl)phenyl triflate (**7**).¹⁷ In addition, we report results about the photophysical properties of the final products and a wide analysis by X-ray of some pyrrolylimines and pyrroloisoquinolines. In summary, the discussion of this article includes synthetic results on nine compounds distributed as follows: six novel compounds (**6d**, **6f**, **6g**, **8b**, and **8c**), three previously reported compounds by us (**6b**, **6e**, and **8a**), the photophysical study of the three fused compounds **8a–c** and five novel crystal structures (**6e–g** and **8b** and **8c**) (Scheme 1c).

In this way, microwave-assisted reactions of **4** with **5d–h** at 100 °C for 10 min under solvent-free conditions enabled the time-efficient formation of the (*E*)-arylideneaminopyrroles **6d–h** in 67–78% yield (Table 1). This protocol was distinguished by its operational simplicity, broad substrate scope, and short reaction times, and no solvent, no transition metal catalyst, and no drying agent were used, rendering the experimental procedure user- and environment-friendly. The structures of pyrrolylimines **6d–h** were confirmed by ¹H NMR, ¹³C NMR, and HRMS measurements as well as by X-ray diffraction analysis (see Experimental Section and Figures S4–S19).

Continuing our study, we anticipated that aza-dienes **6** would be suitable candidates for cycloadditions with the aryne

Table 1. Solvent-Free Microwave-Assisted Synthesis of (*E*)-Arylideneaminopyrroles **6d–h**^a



entry	R	product	yield (%)
1	H	6d	70
2	MeO	6e	67
3	Ph ₂ N	6f	68
4	F	6g	78
5	4-BrC ₆ H ₄	6h	76

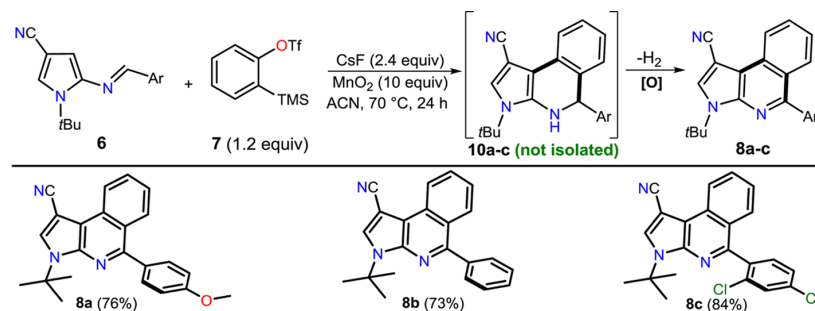
^aEquimolar quantities of reagents (2.0 mmol) under solvent-free conditions.

precursor **7**, affording 1,2-dihydropyrrolo[2,3-*c*]isoquinolines **10**, the oxidation of which would provide a direct route to the respective pyrroloisoquinolines **8**. As a test reaction, we submitted a mixture of the aza-heterodiene **6a**, the benzyne precursor **7**, and cesium fluoride in acetonitrile at 70 °C for 24 h under oxidative conditions. The excess of MnO₂ allowed an efficient in situ oxidation of the cycloadduct **10a** to afford the heteroaromatic product **8a** in 76% yield, though this cycloaddition was found to be unproductive at room temperature. Stimulated by this result, we investigated the scope of the reaction with other two aza-dienes under similar conditions (Scheme 2). In all cases, the reaction was found productive, affording compounds **8a–c** in good yields. This aza-Diels–Alder/aromatization reaction sequence between electron-rich heterodienes and an aryne provided a time-efficient entry to functionalized fused isoquinolines (see Experimental Section). It is important to mention that an attempt was made to obtain a 5-(4-diphenylamino)phenyl derivative in order to find the best optical properties in this product due to the strong electron-donor character of its 5-aryl group,^{3,29} but the reaction did not proceed when the heterodiene **6f** was used. Possibly, the stereoelectronic effects of the aryl group at the imine **6f** decrease its reactivity with respect to the aza-Diels–Alder cycloaddition with benzyne.

Structures of products **8a–c** were elucidated by ¹H NMR, ¹³C NMR, and mass spectroscopy and, gratifyingly, also solved by single-crystal X-ray diffraction analysis. From crystallographic results, it was possible to observe a significant dihedral angle between the 5-aryl group and the heterocyclic core of products, which apparently have an important correlation with the observed fluorescence intensity in **8a–c** (Figure 1 and Figure S19). The results and discussion of the photophysical studies are shown below and after X-ray diffraction studies are discussed.

Considering the molecular conformations observed and the special electronic properties of the fused products **8a–c**, the three compounds were selected in order to carry out photophysical studies and thus establish their scope as novel fluorophores for possible uses in chemosensors. This study was done since compounds **8a–c** have a fused structure substituted in position 5 with different electron-acceptor or electron-donor aryl groups (i.e., **8a** 4-MeOPh, **8b** Ph, and **8c** 2,4-Cl₂Ph), which is crucial in fluorescence phenomena that involve an intramolecular charge transfer (ICT) process, often observed in various *N*-heterocycles suitably substituted (see Figure 1). In addition, as it is observed from the crystallographic structures of **8b** and **8c** (perfectly extrapolated to **8a**

Scheme 2. Synthesis of Pyrrolo[2,3-*c*]isoquinolines **8a–c** via aza-Diels–Alder Reactions^a



^aAll reactions were performed with 1.0 equiv of heterodiene **6** and 1.2 equiv of the benzyne precursor **7** using CsF (2.4 equiv) and MnO₂ (10 equiv) at 70 °C in ACN for 24 h.

considering that no suitable crystals were obtained; Figure S19), the tendency in the orientation of aryl groups could favor a TICT phenomenon, presumably higher in **8c** considering that it has a more pronounced dihedral angle due to its aryl group. The UV–vis and fluorescence emission spectra of **8a–c** were achieved in cyclohexane (CH), tetrahydrofuran (THF), dichloromethane (DCM), *N,N*-dimethylformamide (DMF), and acetonitrile (ACN) (Figure 2 and Table 2).

In general, UV–vis spectra of **8a–c** show two bands around 255 and 345 nm with absorptivity coefficients ϵ ranging from 21,000 M^{−1} cm^{−1} (255 nm) to 8300 M^{−1} cm^{−1} (345 nm). When **8a–c** are excited at their λ_{ab} in an air-equilibrated solution at 298 K, they exhibit emission bands around 400 nm. The poor solvatochromic effect observed in both absorption and emission spectra and the short Stokes shift indicate that a small structural reorganization occur in these compounds when going from the ground to the excited state but without strong changes in the dipole moment. These properties indicate that there is no great ICT process in these compounds, which means that the absorption bands come essentially from $n \rightarrow \pi$ and $\pi \rightarrow \pi^*$ transitions.³⁰ As expected, the compound **8c** exhibit higher fluorescence quantum yield (ϕ_F) versus **8a** and **8b**, which reflect an important effect of the dihedral angle (°) between the 5-aryl and heterocyclic moieties on the photophysical properties; thus, the 2,4-Cl₂Ph group on **8c** would favor a greater TICT effect, which is very sensitive to D–A efficacy, strength, and steric hindrance caused by substituents near the D–A junction,^{27,28} such as the Cl atom at position 2 of the 5-aryl group (see Figure 1b).

On the other hand, an interesting behavior was observed when high polar and viscous solvents were used. In all cases, no matter the 5-aryl group, the fluorescence intensity decreases dramatically when DMF was used as a solvent (e.g., for **8c**, ϕ_F = 0.015 in CH, 0.010 in DCM, and 0.001 in DMF). This behavior reflects a high dependence of the FI with the dihedral angle between the 5-aryl group and the heterocyclic core. A possible explanation could be found in the relationship between the rotations of rotators in the molecule, which is gradually modified by changing the viscosity of the media, resulting in enhanced/decreased FI (i.e., increasing FI lifetime).³¹ Therefore, the λ_{em} has almost no change when the solvent polarity varies dramatically. Based on their structural and photophysical properties, the pyrrolo[2,3-*c*]isoquinolines **8** could be an interesting alternative for fluorescent molecular rotors (FMRs).³² Importantly, and due to the effect of the dihedral angle on the photophysical

properties, corroborated by the crystal structure resolution, and the possibility of change the substituents in the periphery, these properties could be enhanced by an appropriate substitution pattern of this heterocyclic core.

Regarding the crystallographic discussion, since the structures of **6e–g** and **8b** and **8c** were solved by single-crystal X-ray diffraction analysis,³³ the molecular and supramolecular details of these five compounds were studied. The absence of short contacts to describe correctly the crystals made necessary a deeper analysis using Hirshfeld surfaces and CE-B3LYP model energies. In addition, we found an important connection of these analyses with both the synthetic and photophysical results. Crystal data details are summarized in Table 3 (see also Table S1). In general, the crystal structures of pyrrolylimines **6e–g** show an interesting role of their aryl groups (4-MeOPh, 4-Ph₂NPh, or 4-FPh) in the molecular conformations, showing different electronic distributions in the imine group (blue boxes in Figure 3a–c). Likewise, the molecular conformation observed in pyrrolo[2,3-*c*]isoquinolines **8a–c** is a consequence of a stable orientation presented by the 5-aryl group, which is maintained once the compounds start the nucleation process in their trajectory to build the crystal (Figure 3d,e). As it is known, the molecular conformation plays an important role in features such as physical properties or biological activities.^{5,27}

In this sense, the aryl group effect in **6e–g** is noticed in the dihedral angles between the least-squares mean planes made by the pyrrole and benzene rings. In **6e**, the dihedral angle along the azomethine fragment (C–N=C–C, Figure 3a) is −179.92(14)°, and the bond distance between the C atom of the pyrrolic ring and the N atom of the imine group has a value of 1.386(2) Å. This evidences a greater resonance effect in **6e** as result of the electron-donor character of its MeO group, a structural property not seen in **6f** and **6g** (conformational effects) where the bond lengths are 1.398(3) and 1.395(3) Å, respectively. These findings suggest that groups of proper electronic nature could regulate the resonance properties in **6e–g**. Considering that the same interactions are detected in all the molecules (C–H⋯N between the *t*Bu group and the N atom of the azomethine group), the diverse conformations seem to be independent of other factors (i.e., intramolecular hydrogen bonds). Regarding **8a–c**, its 5-aryl group is connected to the pyrroloisoquinolinic core by sp² carbon atoms generating bond lengths of 1.487(5) and 1.492(3) Å for **8b** and **8c**, respectively, which suggests distances deviated from expected values for free rotational

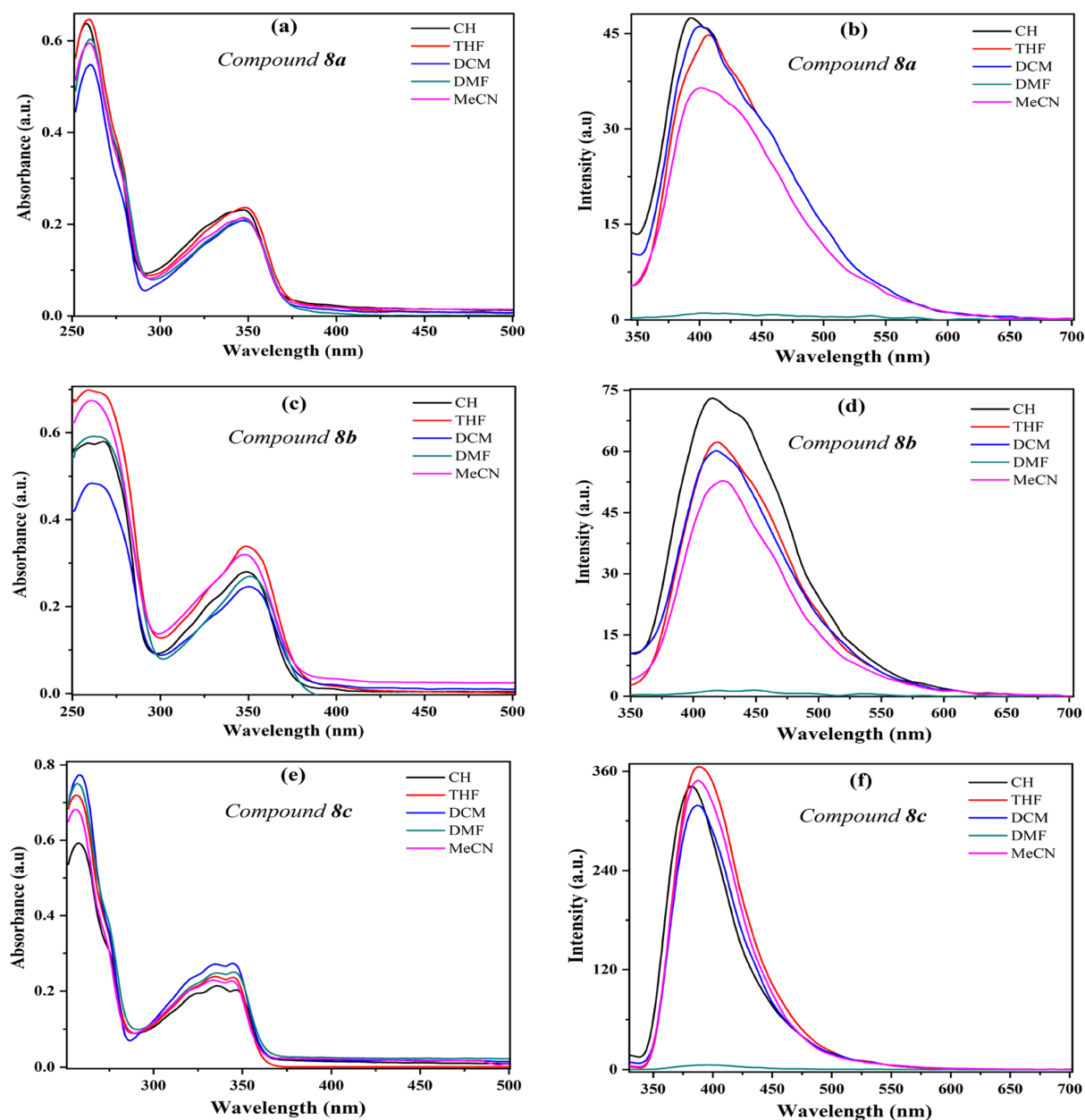


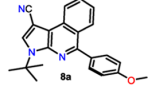
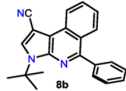
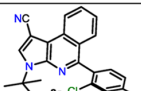
Figure 2. Absorption and emission spectra of compounds **8a–c** in different solvents at 30 μ M. (a, b) Compound **8a**. (c, d) Compound **8b**. (e, f) Compound **8c**.

bonds as a consequence of hybridization effects (Figure 3d,e; see also Scheme 2). The two conformations for these compounds are characterized by dihedral angles observed in Figure 3d,e.

In the supramolecular assembly of **6e–g**, no classic hydrogen bonds were found, and only weak hydrogen interactions were detected based on the intermolecular H \cdots (O, N) lengths. In **6e**, pairs of inversion-related molecules are connected by two equivalent weak C–H \cdots Oⁱ (2.65 Å; (i) 1 – x, 1 – y, 1 – z) hydrogen interactions, involving one methyl in the *t*Bu group (Figure 4a). These pairs are the slabs of infinite chains running along the [–111] direction and connected by

weaker C–H \cdots Nⁱⁱ (2.78 Å; (ii) 1 – x, 2 – y, 2 – z) interactions, involving the CN and MeO groups. The three-dimensional (3D) assembly is completed by C–H \cdots Oⁱⁱⁱ (2.76 Å; (iii) 2 – x, 2 – y, 1 – z) hydrogen interactions, joining molecules by the connection between *t*Bu and MeO groups in adjacent molecules along the *a* axis (Figure 4a). In **6f**, the formation of weak C–H \cdots Nⁱⁱⁱ interactions involving the *t*Bu (2.71 Å; (i) x, 3/2 – y, –1/2 + z) and triphenylamine (TPA) (2.72 Å; (ii) 1 – x, –1/2 + y, 3/2 – z) groups builds the solid forming chains running along the [010] direction. These chains are further connected in the three dimensions by the same sort of C–H \cdots N contacts forming a framework that

Table 2. Photophysical Properties of Compound 8a–c in Different Solvents^a

Compound	Solvent ^a	λ_{ab} (nm) (ϵ , M ⁻¹ cm ⁻¹)	λ_{em} (nm) (ϕ_F) ^b	Stokes Shift (cm ⁻¹)
	CH	258 (21233), 347 (7700)	393 (0.006)	3373
	THF	260 (21333), 348 (7866)	407 (0.001)	4166
	DCM	260 (18266), 347 (6933)	400 (0.004)	3818
	DMF	260 (20133), 346 (7100)	403 (0.0004)	4088
	MeCN	260 (19867), 347 (7167)	401 (0.003)	3881
	CH	267 (19333), 349 (9333)	414 (0.005)	4499
	THF	259 (23266), 349 (11267)	419 (0.002)	4787
	DCM	261 (16100), 350 (8200)	418 (0.005)	4648
	DMF	261 (19700), 351 (8967)	418 (0.0003)	4567
	MeCN	261 (21566), 348 (10667)	423 (0.002)	5095
	CH	258 (19733), 335 (7133), 344 (6767)	382 (0.015)	3673
	THF	256 (24967), 334 (7933), 345 (7866)	388 (0.011)	4167
	DCM	258 (25733), 344 (9033), 344 (9100)	387 (0.010)	3230
	DMF	257 (24967), 337 (8266), 345 (8333)	395 (0.001)	3669
	MeCN	255 (21600), 333 (7600), 344 (7633)	387 (0.012)	3230

^a30 μ M. ^bRelative quantum yields were obtained with anthracene ($\phi_F = 0.28$ in ethanol) as the reference.

Table 3. Crystallographic Data of the Pyrrolylimines 6e–g and Pyrrolo[2,3-*c*]Isoquinolines 8b and 8c

compound	6e	6f	6g	8b	8c
chemical formula	C ₁₇ H ₁₉ N ₃ O	C ₂₈ H ₂₆ N ₄	C ₁₆ H ₁₆ FN ₃	C ₂₂ H ₁₉ N ₃	C ₂₂ H ₁₇ Cl ₂ N ₃
M_r	281.35	418.53	269.32	325.40	394.28
crystal system/space group	triclinic/ $P\bar{1}$	monoclinic/ $P2_1/c$	monoclinic/ $P2_1/c$	orthorhombic/ $Pna2_1$	triclinic/ $P\bar{1}$
a, b, c (Å)	6.5117(9), 10.8618(15), 12.3586(14)	9.813(2), 25.305(4), 9.7316(11)	8.8167(10), 17.559(2), 9.4619(9)	8.8186(12), 10.9933(15), 18.078(2)	8.4643(7), 9.8411(8), 12.2281(6)
α, β, γ (°)	107.350(11), 96.512(11), 106.366(13)	90.0, 101.981(14), 90.0	90.0, 90.43(1), 90.0	90.0, 90.0, 90.0	97.028(6), 98.958(6), 96.320(7)
V (Å ³)	781.70(19)	2363.9(7)	1464.8(3)	1752.6(4)	989.90(13)
Z	2	4	4	4	2
μ (mm ⁻¹)	0.08	0.07	0.08	0.07	0.34
crystal size (mm)	0.31 \times 0.25 \times 0.19	0.23 \times 0.17 \times 0.14	0.21 \times 0.15 \times 0.15	0.21 \times 0.16 \times 0.15	0.25 \times 0.20 \times 0.19

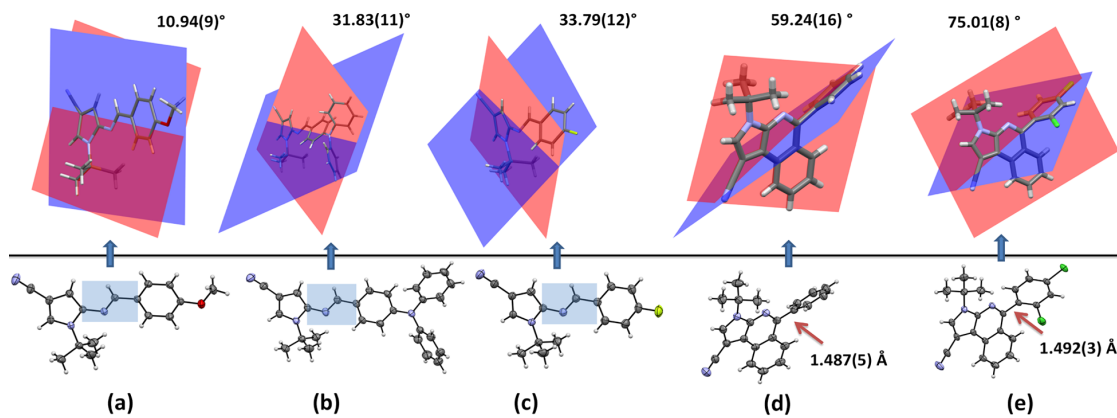


Figure 3. (Bottom) Structures of (a) 6e, (b) 6f, (c) 6g, (d) 8b, and (e) 8c showing anisotropic displacement ellipsoids at the 30% probability level and highlighting the azomethine fragment in blue (6e–g) and the C–C bond length distance (8b and 8c). (Top) Dihedral angles between the least-squares mean planes made by the pyrrolic (red plane) and aryl (blue plane) rings (6e–g) and the pyrroloisoquinolinic core (red plane) and aryl ring (blue plane) (8b and 8c).

seems solely dependent on these connections (Figure 4b). In 6g, the presence of a F atom over the aryl group allows the connection of pairs of inversion-related molecules (by C–H \cdots Fⁱ; 2.72 Å; (i) 1 + x , y , 1 + z) connected by two equivalent C–H \cdots Nⁱⁱ (2.68 Å; (ii) 1 – x , 1 – y , 2 – z) hydrogen interactions. As it was observed in 6e and 6f, the CN group interacts with the azomethine (in C–H \cdots Nⁱⁱ) and *t*Bu groups, C–H \cdots Nⁱⁱⁱ (2.72 Å; (iii) 2 – x , 1 – y , 2 – z), forming bifurcated hydrogen interactions building (010) sheets, which are further connected in the [010] direction by van der Waals forces (Figure 4c).

Hirshfeld (HF) surface analysis mapped over d_{norm} (analysis of the contact distances d_i and d_e from the HF surface to the nearest atom inside and outside, respectively) was performed in order to investigate these contacts further. In 6e, the bright red spots over d_{norm} corresponds exclusively to the C–H \cdots O (2.65 Å; 1 – x , 1 – y , 1 – z) hydrogen interactions showing that C–H \cdots N interactions are not relevant (Figure S20a). On the other hand, C–H \cdots N interactions are clearly, but weakly, observed in the HF surface for 6f, showing that, in this crystal, they are “close contacts” compared with the remaining

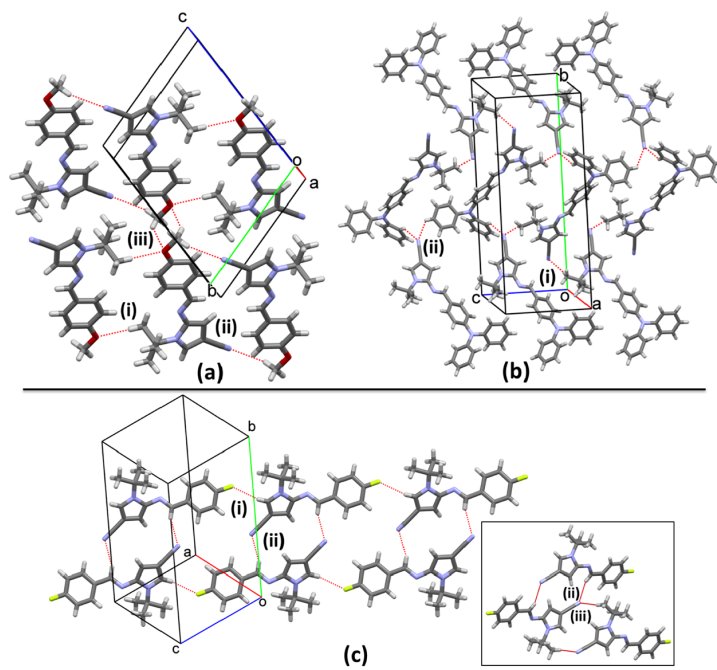


Figure 4. Crystal structures of (a) **6e**, (b) **6f**, and (c) **6g** showing the C–H···O, C–H···N, and C–H···F hydrogen-bond interactions. The (i), (ii), and (iii) codes serve as a reference with the description in the text.

interactions. Additional C–H··· π interactions (3.38 Å) were detected between the *t*Bu group and one Ph group of **6f** (Figure S20b). In **6g**, the red spots are showing mainly the C–H···N contacts, leaving other contacts with nearly non-observable spots; including C–H···F (Figure S20c). In the 2D fingerprint plots, H···N/N···H contacts comprise 12–17% of the total HF surface in **6e–g**, which is not the highest effect to the crystal structure. In all compounds, no close (<2.6 Å) contacts are observed, showing the absence of strong hydrogen bonds in the blue/white regions on the HF surfaces. The nonbonded H···H (40–57%) contacts suggest a principal role of long-range hydrophobic interaction in the formation of the crystals.

Energy framework representations of the intermolecular interactions were computed using the CE-B3LYP model, which serves to interpret the topological architecture of the supramolecular features from an energetic perspective, considering the difficulty to interpret the formation of the crystal based on long hydrogen contacts (Figure 5). The strongest interaction in **6e** is not related to the closest C–H···O (2.65 Å; $1-x, 1-y, 1-z$) hydrogen contact as expected from the atom–atom analysis. Instead, the strongest contacts form chains of molecules connected by total interaction energies of $-36.6 \text{ kJ mol}^{-1}$ along the [100] direction connected between them by interaction energies of -37.9 and $-32.1 \text{ kJ mol}^{-1}$ along the [011] direction with contributions from electrostatic and dispersion energies in similar magnitudes (Figure 5a and Table S2). The energy framework describes an anisotropic topology, showing that the crystal is formed mainly by dispersion forces along the *a* axis. These chains of molecules are connected between them by a combination of electrostatic (only important in the connection of the chains along [011] by the azomethine fragments, red framework) and dispersion contributions forming the 3D

structure (Figure 5a). The topology is characterized by the formation of layers stacked along the [01-1] direction.

The interaction energies for selected molecular pairs in the first coordination sphere around the asymmetric unit for **6e–g** are summarized in Table S2. As it is observed, the dispersion terms contribute in high proportion to the formation of the crystals, explaining the absence of short hydrogen contacts due to the electronic distributions that do not allow a great nucleophilicity over O and N atoms and the absence of acidic hydrogen atoms. Additionally, the highest total energies are observed in **6f**, which is related to the highest thermal stability compared with **6e** and **6g**, considering that their melting points are 142–143, 181–182, and 138–139 °C for **6e–g**, respectively. As it was observed previously, these framework energies are comparable with the experimental sublimation enthalpies.³⁴

As observed in **6e–g**, the hydrogen C–H···N interactions involving the nitrile group are weak, with distances greater than 2.6 Å rather difficult to detect without using Hirshfeld surfaces. In **8b**, one possibility for such contacts is observed in Figure 6a. However, this weak C–H···Nⁱ contact has a length of 2.92 Å ((i) $1/2 + x, 3/2 - y, z$), leaving this interaction as not relevant. The planar conformation on the pyrroloisoquinolinic core allows the formation of $\pi\cdots\pi^{\text{ii}}$ (3.740(2) Å; (ii) $1/2 + x, 3/2 - y, z$) stacking contacts (Figure 6a). These interactions form chains of molecules along the [100] direction. Hirshfeld surface shows a complete lack of short contacts, leaving the map without red spots and only blue regions, suggesting that the crystal is formed only by long-distance hydrophobic interactions despite the presence of potential donor/acceptor regions in the molecule as it is observed in the electrostatic potential map in Figure S21a.

In **8c**, the nitrile group has bifurcated weak C–H···N contacts with the pyrrolicⁱ and 2,4-dichlorophenyl^l rings (2.74

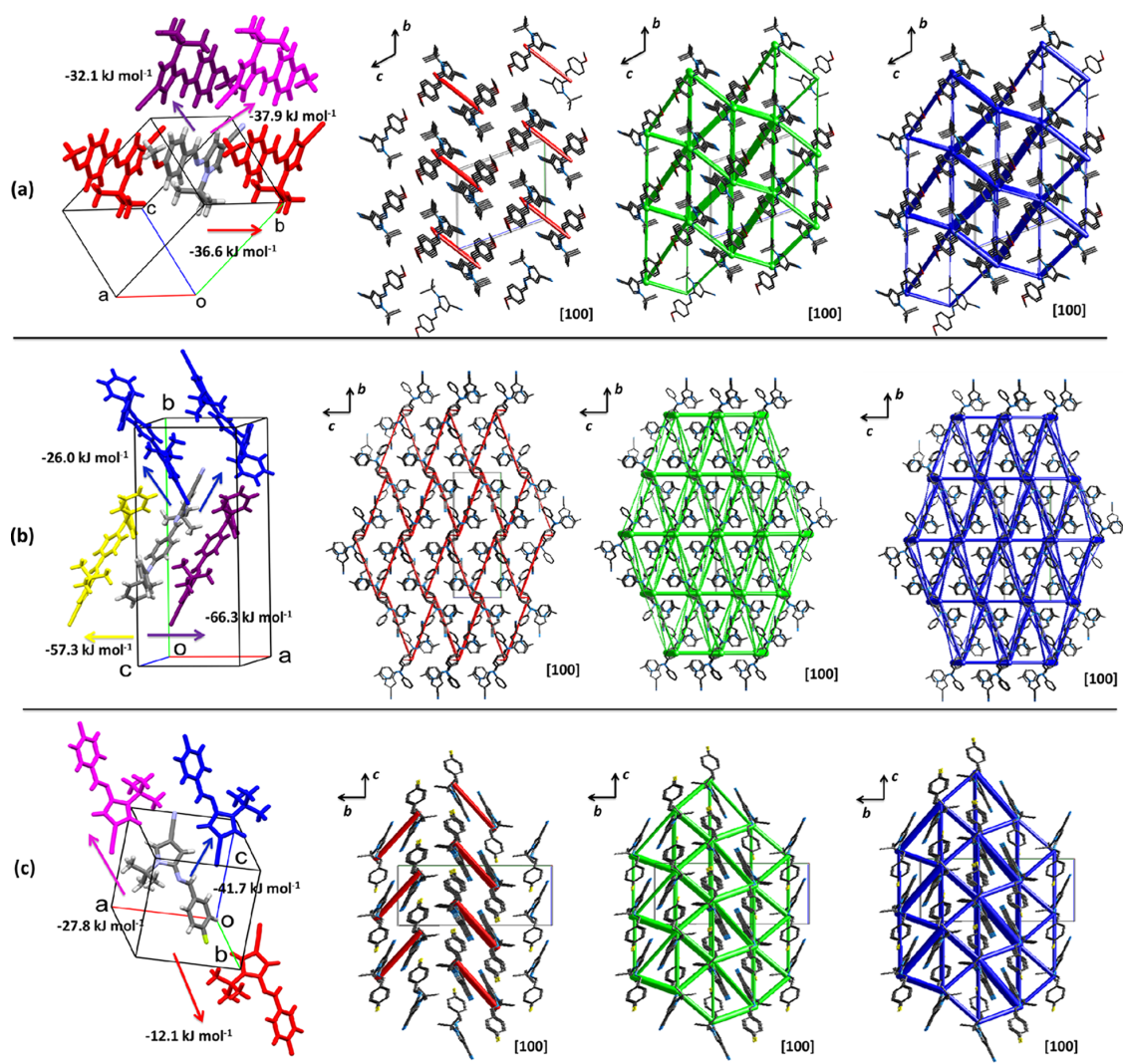


Figure 5. Description of molecular close contacts and energy framework diagrams for electrostatic (red) and dispersion (green) contributions to the total interaction energies (blue) in compounds (a) 6e, (b) 6f, and (c) 6g.

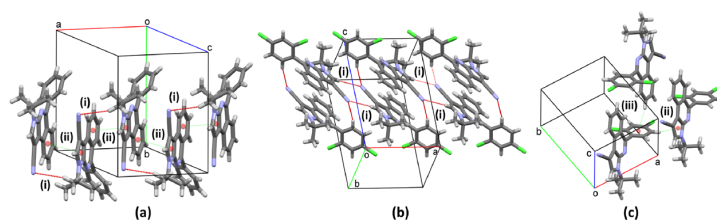


Figure 6. Crystal structures of (a) 8b and (b, c) 8c showing the C-H...N and C-H... π hydrogen-bond interactions and π ... π stacking contacts. The (i), (ii) and (iii) codes serve as reference with the description in the text.

Å, (i) $-x, -y, 1-z$, forming chains of molecules along [100] (Figure 6b). C-H... π interactions play an important role in the crystal with contacts involving also the pyrrolicⁱⁱ and 2,4-dichlorophenylⁱⁱⁱ rings as hydrogen acceptors (2.73 Å, (ii) $1+x, y, z$; 2.91 Å, (iii) $2-x, 1-y, 1-z$) (Figure 6c). Hirshfeld surface analysis shows that the C-H... π interaction involving the pyrrolicⁱⁱ ring also has another connotation. The H...N

distance has a value 2.75 Å, and the C-H...N angle is 159° , indicating an interaction between the H atom and the nonhybridized 2p atomic orbital in the pyrrolic N atom that in fact is perpendicular to the plane of the ring and is part of the π cloud. This bifurcated interaction, C-H... π and C-H...N, is observed as a doublet spot over the HF surface (Figure S21b).

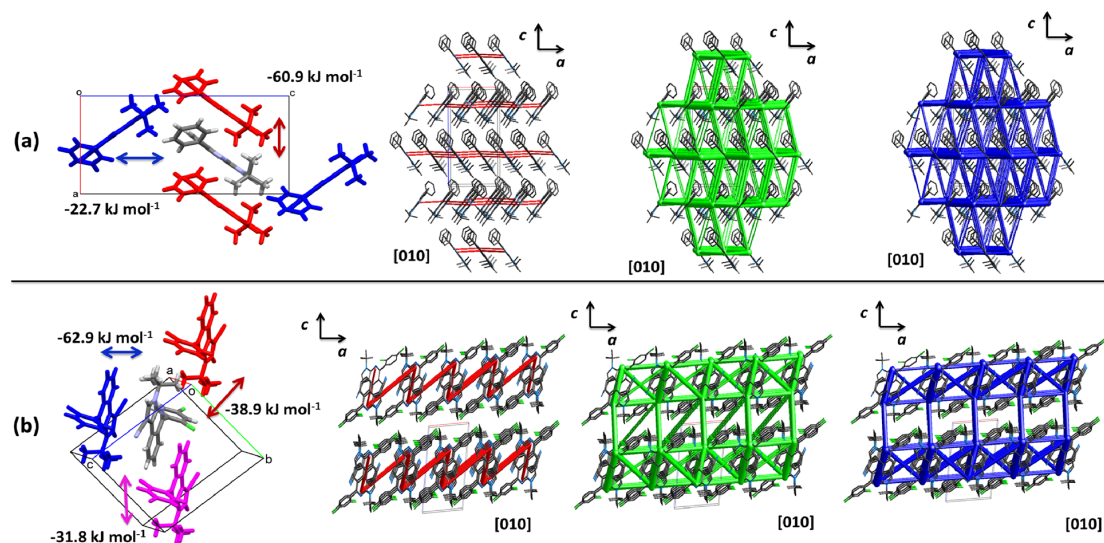


Figure 7. Description of molecular close contacts and energy framework diagrams for electrostatic (red) and dispersion (green) contributions to the total interaction energies (blue) in compounds (a) **8b** and (b) **8c**.

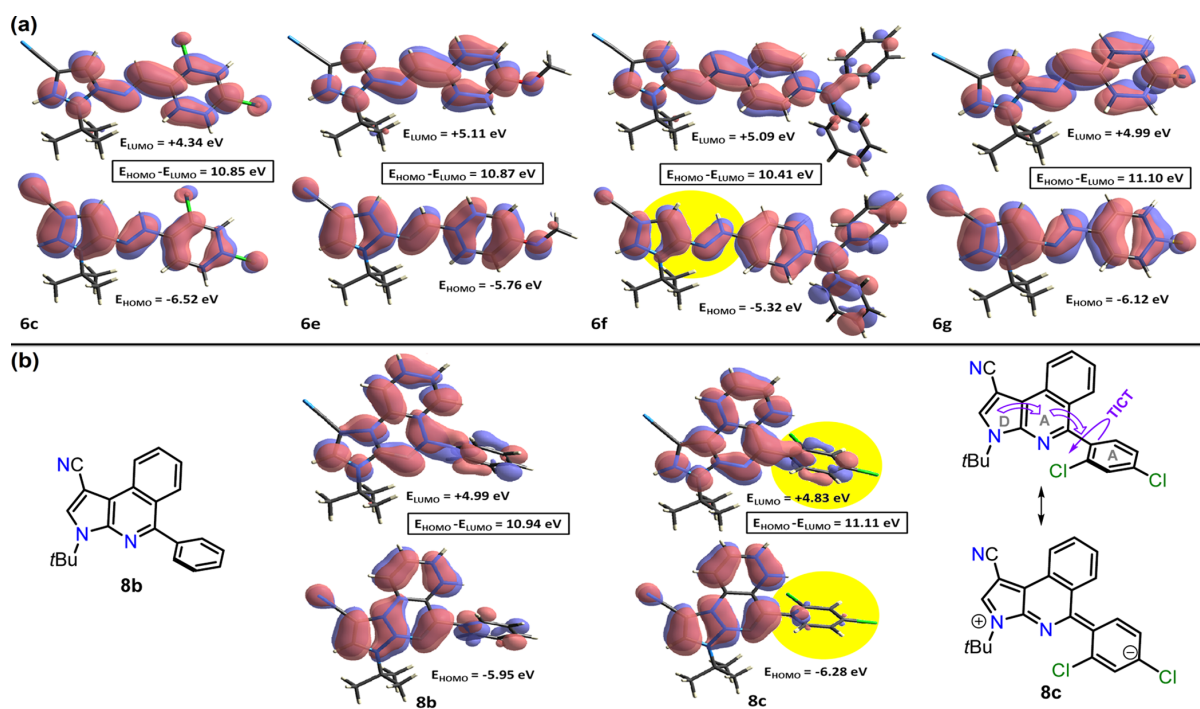


Figure 8. Computed energy levels HOMO and LUMO for aza-dienes (a) **6c** and **6e-g** and (b) products **8b** and **8c** using the crystallographic information files (.cif) by the STO-3G basis set at the Hartree-Fock level of theory.

Another interesting interaction is detected in the HF surface involving a Me group from the *t*Bu group and the C atom placed between the substituent halogens in the aryl group of **8c**. Due to the geometry (H...C distance of 2.81 Å and C-H...C angle of 156°), this contact could be understood as a C-H...C interaction, which is not frequently reported (Figure S21b). The contact is possible due to the sp^2 hybridization of the C atom that allows the interaction of the H atom with the

perpendicular pure 2p orbital overlapped in the π cloud. The 2D fingerprints show that, essentially, the crystal in **8b** is mainly built by hydrophobic interactions with H...H contacts comprising 56% of the total HF surface (Figure S21a). Despite the suggestion of other interactions, such as H...N, they showed to be very large in **8b** and thus irrelevant in the supramolecular assembly. In **8c**, the 2D fingerprint plot shows that H...N interactions comprise 13% of the HF surface

(Figure S21b). In this case, the H···H contacts are less relevant (35%) compared with **8b**, suggesting a less hydrophobic character.

In order to obtain a better understanding of the crystal packing, the CE-B3LYP model was used to investigate the supramolecular assembly in terms of energy frameworks (Table S3). In **8b**, the strongest pairwise interactions have a total energy value $-60.9 \text{ kJ mol}^{-1}$, forming chains of molecules along the [100] direction interacting by the fused heterocyclic moiety in a $\pi\cdots\pi$ stacking disposition (Figure 7a). Considering the high stabilization in this direction, it is possible to assume that the short distance among adjacent centroids (5.72 \AA) is due to dispersion forces. In fact, this term contributes mainly to this interaction, showing that these forces are responsible for assembling along the *a* axis instead of particular atom–atom contacts. The second strongest interactions connect these chains along the [001] direction with $-22.7 \text{ kJ mol}^{-1}$ as the total energy, which is also represented in higher proportion by the dispersion term. The energy frameworks show a curious topology. Electrostatic forces act to keep the molecules assembled along the *a* axis (Figure 7a). Observing the closeness of neighboring molecules due to dispersion forces along this [100] direction, the electrostatic term rises due to the short distance between heterocyclic-fused rings where some degree of electronic polarization exists. However, the dispersion forces are the most important interactions in the crystal, forming (001) sheets stacked along the *c* axis and building a 3D structure by less energetic interactions giving an anisotropic tendency.

In **8c**, the strongest pairwise interactions occur between the nearest (7.39 \AA) molecules involving the pyrroloisoquinolinic moieties oriented in a parallel form, allowing a total energy value of $-62.9 \text{ kJ mol}^{-1}$ (Figure 7b and Table S3). Similar to **8b**, the dispersion term contributes in higher proportion to the interaction, showing the importance of the π cloud in the pyrroloisoquinolinic core to build “strong” dispersion attractions in this sort of structures. Other molecules are connected by total energies such as -38.9 and $-31.8 \text{ kJ mol}^{-1}$ in which the dispersion term always represents the most important interaction. The energy frameworks show similar electrostatic interactions as observed in **8b**, forming chains along the [100] direction with a curious zigzag topology joining the fused heterocyclic rings. The dispersion-cylinder magnitudes show an isotropic structure built by the strongest interactions forming a sort of compacted scaffolding structure. Between the strong pillars, other diagonal cylinders of low magnitude are present acting between halogen atoms, which does not mean an actual absence but a low energetic contact by a possible repulsion between close electron shells (Figure 7b) compared with **8b**, suggesting a less hydrophobic character.

In order to have a deeper insight into the electronic properties for the studied compounds and achieve a better connection of the experimental results, the energy levels of the electron-donor HOMO (highest occupied molecular orbital) and electron-acceptor LUMO (lowest unoccupied molecular orbital) for aza-dienes **6c**,¹⁸ **6e–g**, and products **8b** and **8c** were computed (Figure 8). These calculations were carried out through the STO-3G basis set at the Hartree–Fock level of theory implemented in CrystalExplorer³⁵ using the crystallographic information files (.cif) obtained from the X-ray diffraction measurements. In the analyzed aza-dienes, the electron densities in the frontier molecular orbitals (FMO) are

mostly localized over the whole of the molecules (except the *t*Bu group), especially over the pyrrolylimine and aryl fragments (Figure 8a).

The HOMO–LUMO energy gaps suggest that **6g** and **6f** are the less and more reactive molecules toward electrophilic reagents, respectively. These results are consistent with the strong electron-donor character of the 5-aryl group in **6f**,^{3,28} though FMO can be affected by the solvent, which could shift the electron density in the FMO from one fragment to another.³⁶ Remarkably, the HOMO in **6f** has a poor contribution (low electronic density) in the aza-dienic moiety versus the other imines analyzed (**6c**, **6e**, and **6g**), which could explain the poor reactivity of **6f** (mentioned above) with respect to the aza-Diels–Alder reaction with benzyne (yellow circle in Figure 8a). In **8b** and **8c**, the electron densities are mostly localized over the pyrroloisoquinolinic fragment; however, the HOMO in **8c** present lower electronic density over the 2,4-dichlorophenyl group as a consequence of the marked dihedral angle ($75.01(8)^\circ$) between this aryl group with the pyrroloisoquinolinic fragment, as mentioned earlier in the crystallographic results. Consequently, the charge transfer from the pyrroloisoquinolinic core to 2,4-dichlorophenyl group could be better observed upon photoexcitation of **8c** (yellow circle in Figure 8b).³⁷ These findings confirm that the fluorescence phenomenon of **8c** is governed by a TICT mechanism.^{3,27,28}

■ CONCLUSIONS

In summary, we have established a general synthetic access to various (*E*)-2-arylideneaminopyrroles **6**, which served as key intermediates of some pyrrolo[2,3-*c*]isoquinolines **8a–c** through the aryne aza-Diels–Alder cycloaddition. Both intermediates and final products were obtained in good yields (up to 78 and 84%, respectively), their structures were determined on the basis of NMR measurements and HRMS analysis, and pleasantly, the structures were confirmed by single-crystal X-ray diffraction analyses. The fused *N*-heterocycles **8a–c** are substituted in position 5 with aryl groups of different electronic nature; thus, their photophysical properties were investigated, finding absorption bands with a non-ICT character and a fluorescence intensity sensible to the dihedral angle between the 5-aryl group and the heterocyclic core. Interestingly, we find a relationship between viscosity and the solvent with the fluorescence intensity of these kinds of compounds, this property could be very useful for fluorescence molecular rotor (FMR) applications. On the other hand, the crystallographic results show that all the interactions found in **6e–g** and **8b** and **8c** are weak, and van der Waals forces seem to be the main responsible for the solid formation. The analysis of individual interatomic interactions and the difficult search for hydrogen bonds did not allow a rational description of the crystal formation. However, using the CE-B3LYP model, in addition to studying the energetic topology and understanding the crystal architecture of compounds, we managed to find an important connection with both the synthetic and photophysical results.

■ EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial sources and used without further purification, unless otherwise noted. All starting materials were weighed and handled in air at room temperature. The reactions were

monitored by TLC and visualized by UV (254 nm). Column and flash chromatography was performed on silica gel (230–400 mesh or 70–230 mesh, respectively). All reactions under microwave irradiation were performed using a sealed reaction vessel (10 mL, max pressure = 300 psi) containing a Teflon-coated stirring bar (obtained from CEM). Microwave-assisted reactions were performed in a CEM Discover focused microwave ($\nu = 2.45$ GHz) reactor equipped with a built-in pressure measurement sensor and a vertically focused IR temperature sensor; controlled temperature, power, and time settings were used for all reactions. NMR spectra were recorded at 400 MHz (^1H) and 100 MHz (^{13}C) at 298 K. NMR spectroscopic data were recorded in CDCl_3 and $\text{DMSO}-d_6$ using, as internal standards, the residual nondeuterated signal for ^1H NMR and the deuterated solvent signal for ^{13}C NMR spectroscopy. DEPT spectra were used for the assignment of carbon signals. Chemical shifts (δ) are given in ppm and coupling constants (J) are given in Hz. The following abbreviations are used for multiplicities: s = singlet, d = doublet, t = triplet, and m = multiplet. Melting points were collected using a Stuart SMP10 melting point apparatus, and the acquired data are uncorrected. High-resolution mass spectra (HRMS) were recorded using an Agilent Technologies Q-TOF 6520 spectrometer by electrospray ionization (ESI). 5-Amino-1-(*tert*-butyl)-1*H*-pyrrole-3-carbonitrile **4** was prepared using a known procedure.³⁸ The electronic absorption and fluorescence emission spectra were recorded in quartz cuvettes having a path length of 1 cm. UV–vis and emission measurements were achieved at room temperature (20 °C). For fluorescence measurements, both the excitation and the emission slit widths were 5 nm.

Synthesis and Characterization. General Procedure for the Synthesis of (E)-5-(Arylideneamino)-1-*tert*-butyl-1*H*-pyrrole-3-carbonitriles **6d–h (Scheme 1b).** A 10.0 mL sealable oven-dried tubular reaction vessel was charged with 5-amino-1-(*tert*-butyl)-1*H*-pyrrole-3-carbonitrile (**4**; 327 mg, 2.0 mmol) and arylaldehydes **5d–h** (2.0 mmol). The resulting mixture was subjected to microwave under solvent-free conditions at 100 °C and maintained this temperature for 40 min, after which the reaction mixture was cooled to 50 °C by airflow. The resulting crude product was purified by flash chromatography on silica gel using a mixture of *n*-pentane/ CH_2Cl_2 (1:1, v/v) as an eluent to give the expected *N*-pyrrolylimines **6d–h** in good yields. Crystals suitable for X-ray structure analysis were obtained from methanol by slow evaporation of the solution at room temperature.

(E)-5-(Benzylideneamino)-1-(*tert*-butyl)-1*H*-pyrrole-3-carbonitrile (6d**).** Following the general procedure in the reaction with benzaldehyde (**5d**; 205 μL , 2.0 mmol), the imine **6d** was obtained as a yellow solid (352 mg, 70%). mp 86–87 °C. Recrystallization of **6d** from methanol afforded crystalline yellow prisms suitable for X-ray diffraction analysis. ^1H NMR (CDCl_3 , 400 MHz): δ 1.72 (s, 9H), 6.42 (d, $J = 1.9$ Hz, 1H), 7.27 (d, $J = 1.9$ Hz, 1H), 7.46–7.49 (m, 3H), 7.83–7.86 (m, 2H), 8.46 (s, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 101 MHz): δ 30.1 (CH_3), 58.4 (C), 90.2 (C), 98.2 (CH), 117.0 (C), 124.9 (CH), 128.4 (CH), 128.8 (CH), 131.2 (CH), 136.2 (C), 143.0 (C), 155.1 (CH) ppm. HRMS (ESI⁺): calcd for $\text{C}_{16}\text{H}_{18}\text{N}_3^+$ 252.1495 [$\text{M} + \text{H}$]⁺; found, 252.1494.

(E)-1-(*tert*-Butyl)-5-((4-methoxybenzylidene)amino)-1*H*-pyrrole-3-carbonitrile (6e**).** Following the general procedure in the reaction with 4-methoxybenzaldehyde (**5e**; 250 μL , 2.1 mmol), the imine **6e** was obtained as a yellow solid (377 mg,

67%). mp 142–143 °C (lit.¹⁷ mp 143–144 °C). Recrystallization of **6e** from methanol afforded crystalline yellow prisms suitable for X-ray diffraction analysis. ^1H NMR (CDCl_3 , 400 MHz): δ 1.71 (s, 9H), 3.88 (s, 3H), 6.34 (d, $J = 1.8$ Hz, 1H), 6.98 (d, $J = 8.8$ Hz, 2H), 7.24 (d, $J = 1.8$ Hz, 1H), 7.79 (d, $J = 8.8$ Hz, 2H), 8.38 (s, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 101 MHz): δ 30.0 (CH_3), 55.4 (CH_3), 58.2 (C), 89.9 (C), 97.6 (CH), 114.3 (CH), 117.2 (C), 124.5 (CH), 129.2 (C), 130.2 (CH), 143.5 (C), 154.8 (CH), 162.2 (C) ppm. These NMR data matched the previously reported data.¹⁷

(E)-1-(*tert*-Butyl)-5-((4-(diphenylamino)benzylidene)amino)-1*H*-pyrrole-3-carbonitrile (6f**).** Following the general procedure in the reaction with 4-(diphenylamino)benzaldehyde (**5f**; 303 mg, 1.1 mmol), the imine **6f** was obtained as a yellow solid (570 mg, 68%). mp 181–182 °C. Recrystallization of **6f** from methanol afforded crystalline yellow prisms suitable for X-ray diffraction analysis. ^1H NMR (CDCl_3 , 400 MHz): δ 1.70 (s, 9H), 6.33 (d, $J = 1.8$ Hz, 1H), 7.06 (d, $J = 8.7$ Hz, 2H), 7.11 (t, $J = 7.5$ Hz, 2H), 7.15 (d, $J = 7.8$ Hz, 4H), 7.24 (d, $J = 1.8$ Hz, 1H), 7.31 (t, $J = 7.8$ Hz, 4H), 7.67 (d, $J = 8.7$ Hz, 2H), 8.35 (s, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 101 MHz): δ 30.0 (CH_3), 58.2 (C), 89.9 (C), 97.5 (CH), 117.3 (C), 121.2 (CH), 124.1 (CH), 124.4 (CH), 125.5 (CH), 129.3 (C), 129.5 (CH), 129.5 (CH), 143.6 (C), 146.8 (C), 150.7 (C), 154.5 (CH) ppm. HRMS (ESI⁺): calcd for $\text{C}_{28}\text{H}_{27}\text{N}_4^+$ 419.2230 [$\text{M} + \text{H}$]⁺; found, 419.2226.

(E)-1-(*tert*-Butyl)-5-((4-fluorobenzylidene)amino)-1*H*-pyrrole-3-carbonitrile (6g**).** Following the general procedure in the reaction with 4-fluorobenzaldehyde (**5g**; 204 μL , 1.9 mmol), the imine **6g** was obtained as a yellow solid (400 mg, 78%). mp 138–139 °C. Recrystallization of **6g** from methanol afforded crystalline yellow prisms suitable for X-ray diffraction analysis. ^1H NMR (CDCl_3 , 400 MHz): δ 1.71 (s, 9H), 6.40 (d, $J = 2.0$ Hz, 1H), 7.15 (t, $J = 8.7$ Hz, 2H), 7.27 (d, $J = 2.0$ Hz, 1H), 7.82–7.85 (m, 2H), 8.42 (s, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 101 MHz): δ 30.1 (CH_3), 58.3 (C), 90.2 (C), 98.2 (CH), 116.0 (CH, d, $J_{\text{C-F}} = 22.1$ Hz), 117.0 (C), 124.9 (CH), 130.3 (CH, d, $J_{\text{C-F}} = 8.8$ Hz), 132.6 (C), 142.8 (C), 153.7 (CH), 164.6 (C, d, $J_{\text{C-F}} = 252.4$ Hz) ppm. HRMS (ESI⁺): calcd for $\text{C}_{16}\text{H}_{17}\text{FN}_3^+$ 270.1401 [$\text{M} + \text{H}$]⁺; found, 270.1400.

(E)-5-((4-Bromobenzylidene)amino)-1-(*tert*-butyl)-1*H*-pyrrole-3-carbonitrile (6h**).** Following the general procedure in the reaction with 4-bromobenzaldehyde (**5h**; 352 mg, 1.90 mmol), the imine **6h** was obtained as a yellow solid (477 mg, 76%). mp 156–157 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 1.71 (s, 9H), 6.43 (d, $J = 1.8$ Hz, 1H), 7.28 (d, $J = 1.8$ Hz, 1H), 7.60 (d, $J = 8.6$ Hz, 2H), 7.70 (d, $J = 8.6$ Hz, 2H), 8.40 (s, 1H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 101 MHz): δ 30.1 (CH_3), 58.4 (C), 90.4 (C), 98.5 (CH), 116.9 (C), 125.2 (CH), 125.7 (C), 129.7 (CH), 132.1 (CH), 135.1 (C), 142.6 (C), 153.6 (CH) ppm. HRMS (ESI⁺): calcd for $\text{C}_{16}\text{H}_{17}^{79}\text{BrN}_3^+$ 330.0600 [$\text{M} + \text{H}$]⁺; found, 330.0599.

General Procedure for the Synthesis of 3-(*tert*-Butyl)-5-aryl-3*H*-pyrrolo[2,3-*c*]isoquinoline-1-carbonitriles **8a–c (Scheme 1b).** A sealable (Teflon screw cap) oven-dried tubular reaction vessel was charged with the appropriate arylideneaminopyrrole **6** (0.30 mmol), CsF (109 mg, 0.72 mmol), and manganese dioxide (263 mg, 3.0) and subjected to high vacuum for 20 min. The mixture was placed under an argon atmosphere, and anhydrous acetonitrile (2.0 mL) was added. To this stirred solution kept at room temperature was added 2-(trimethylsilyl)phenyl triflate (**7**; 87 μL , 0.36 mmol) in one portion, the reaction vessel was sealed, and the resulting

reaction mixture was stirred at 70 °C for 24 h. The product reaction mixture was diluted with EtOAc and water. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give the crude product. The resulting crude product was purified by flash chromatography on silica gel using a mixture of *n*-pentane/EtOAc (50:1, v/v) as an eluent to give the pyrrolo[2,3-*c*]isoquinolines **8a–c**. Crystals suitable for X-ray structural analyses were obtained from methanol by slow evaporation of the solution at room temperature.

3-(tert-Butyl)-5-(4-methoxyphenyl)-3H-pyrrolo[2,3-*c*]isoquinoline-1-carbonitrile (8a**).** Following the general procedure in the reaction with the imine **6e** (87 mg, 0.31 mmol), the compound **8a** was obtained as a white solid (80 mg, 73%). mp 190–191 °C (lit.¹⁷ 190–191 °C). ¹H NMR (CDCl₃, 400 MHz): δ 1.89 (s, 9H), 3.93 (s, 3H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.79 (dd, *J* = 7.2 Hz, 1H), 7.85 (s, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 8.78 (d, *J* = 8.3 Hz, 1H) ppm. ¹³C{¹H} NMR (CDCl₃, 101 MHz): δ 29.5 (CH₃), 55.4 (CH₃), 55.7 (C), 82.8 (C), 113.3 (C), 113.7 (CH), 117.7 (C), 122.4 (CH), 123.2 (C), 125.2 (CH), 128.7 (CH), 130.2 (CH), 130.3 (CH), 131.6 (CH), 131.7 (C), 132.6 (C), 142.1 (C), 155.4 (C), 159.9 (C) ppm. HRMS (ESI+): calcd for C₂₃H₂₂N₃O⁺ 356.1757 [M + H]⁺; found, 356.1759. These NMR data matched the previously reported data.¹⁷

3-(tert-Butyl)-5-phenyl-3H-pyrrolo[2,3-*c*]isoquinoline-1-carbonitrile (8b**).** Following the general procedure in the reaction with the imine **6d** (73 mg, 0.29 mmol), the compound **8b** was obtained as a white solid (72 mg, 76%). mp 186–187 °C. Recrystallization of **8b** from methanol afforded crystalline yellow prisms suitable for X-ray diffraction analysis. ¹H NMR (CDCl₃, 400 MHz): δ 1.89 (s, 9H), 7.49–7.58 (m, 4H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.79 (dd, *J* = 7.1 Hz, 1H), 7.87 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.79 (d, *J* = 8.2 Hz, 1H) ppm. ¹³C{¹H} NMR (CDCl₃, 101 MHz): δ 29.5 (CH₃), 58.8 (C), 82.9 (C), 113.6 (C), 117.6 (C), 122.4 (CH), 123.2 (C), 125.3 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 130.3 (CH), 130.3 (CH), 130.5 (CH), 131.6 (C), 140.1 (C), 142.0 (C), 155.7 (C) ppm. HRMS (ESI+): calcd for C₂₂H₂₀N₃⁺ 326.1652 [M + H]⁺; found, 326.1656.

3-(tert-Butyl)-5-(2,4-dichlorophenyl)-3H-pyrrolo[2,3-*c*]isoquinoline-1-carbonitrile (8c**).** Following the general procedure in the reaction with the imine **6c** (89 mg, 0.28 mmol), the compound **8c** was obtained as a white solid (93 mg, 84%). mp 176–174 °C. Recrystallization of **8c** from methanol afforded crystalline yellow prisms suitable for X-ray diffraction analysis. ¹H NMR (CDCl₃, 400 MHz): δ 1.86 (s, 9H), 7.41–7.44 (m, 2H), 7.50 (t, *J* = 7.0 Hz, 1H), 7.61 (s, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.81 (t, *J* = 7.0 Hz, 1H), 7.90 (s, 1H), 8.80 (d, *J* = 8.3 Hz, 1H) ppm. ¹³C{¹H} NMR (CDCl₃, 101 MHz): δ 29.5 (CH₃), 59.0 (C), 82.2 (C), 114.4 (C), 117.3 (C), 122.5 (CH), 123.5 (C), 125.7 (CH), 127.0 (CH), 127.9 (CH), 129.8 (CH), 130.6 (CH), 130.8 (CH), 131.2 (C), 132.5 (CH), 134.7 (C), 135.0 (C), 137.2 (C), 141.6 (C), 152.2 (C) ppm. HRMS (ESI+): calcd for C₂₂H₁₈³⁵Cl₂N₃⁺ 394.0872 [M + H]⁺; found, 394.0869.

Photophysical Properties. UV–Vis Absorption and Fluorescence Studies. The solvatochromic studies of the compounds **8a–c** were carried out from 50 μM stock solutions in cyclohexane (CH), tetrahydrofuran (THF), dichloro-

methane (DCM), dimethylformamide (DMF), and acetonitrile (ACN). The relative quantum yields were obtained using anthracene ($\phi_F = 0.28$ in ethanol at 340 nm) as the reference and calculated according to the following equation^{24–27}

$$\phi_{f,x} = \phi_{f,st} \cdot \frac{F_x}{F_{st}} \cdot \frac{1 - 10^{-A_{st}}}{1 - 10^{-A_x}} \cdot \frac{\eta_x^2}{\eta_{st}^2}$$

where *x* and *st* indicate the sample and standard solution, respectively, ϕ_F is the quantum yield, *F* is the integrated area of the emission, *A* is the absorbance at the excitation wavelength, and η is the index of refraction of the solvents.

Refinement. Crystal data, data collection, and structure refinement details are summarized in Table S1. Single crystals of the compounds were obtained by recrystallization from methanol and mounted in oil. The X-ray diffraction intensity data were measured at room temperature (298(2) K) with an Agilent SuperNova, Dual, Cu at zero, Atlas four-circle diffractometer equipped with a CCD plate detector. In the data acquisition, a Mo microfocus sealed tube was used ($\lambda = 0.71073$ Å). The collected frames were integrated with the CrysAlisPro software package (Agilent Technologies, version 1.171.37.35). Data were corrected for the absorption effect using the same CrysAlisPro software package by the empirical absorption correction using spherical harmonics implemented in the SCALE3 ABSPACK scaling algorithm. The structure was solved using an iterative algorithm³⁹ and subsequently completed by a difference Fourier map. All the hydrogen atoms, with H-atom parameters constrained during refinements, were placed in calculated positions (C–H = 0.93–0.96 Å) and included as riding contributions with isotropic displacement parameters set at 1.2–1.5 times the *U*_{eq} value of the parent atom. The crystal structures were refined using the program SHELXL2014.⁴⁰ The graphic material was prepared using the software Mercury 3.8.⁴¹ In the structural calculations, the software PLATON was used.⁴²

Computational Methods. Hirshfeld (HF) surface analysis⁴³ mapped over *d*_{norm} (analysis of the contact distances *d*_i and *d*_e from the HF surface to the nearest atom inside and outside, respectively) was calculated in order to investigate the close contacts further which are observed as bright red spots over *d*_{norm}. Electrostatic potentials were calculated using TONTO, a Fortran-based object-oriented system for quantum chemistry and crystallography,^{44,45} and subsequently mapped over the HF surface using the STO-3G basis set at the Hartree–Fock level of theory over the range of ±0.14 a.u. Energy frameworks describing the intermolecular interaction energies were computed based on CE-B3LYP interaction energies (kJ mol^{−1}), which use B3LYP/6-31G(d,p) molecular wave functions calculated applying the crystal symmetry obtained from X-ray results, which include electrostatic (*E*_{ele}), polarization (*E*_{pol}), dispersion (*E*_{dis}), and exchange-repulsion (*E*_{rep}) terms.⁴⁶ Computed energies between molecular pairs are represented using cylinders joining the centroids (centers of mass) of the molecules with a radius proportional to the magnitude of the interaction. The calculations were performed using the models implemented in CrystalExplorer.³⁵

Copies of NMR spectra (^1H and $^{13}\text{C}\{^1\text{H}\}$) for imines **6d–h** and products **8a–c** and details of X-ray crystallography (tables and graphic material) (PDF)

Accession Codes

CCDC 1959987 (**6e**), 1959991 (**6f**), 1959989 (**6g**), 1959988 (**8b**), and 1959990 (**8c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk or contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The authors declare no competing financial interest.

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REFERENCES

- (1) Eftekhari-Sis, B.; Zarak, M. Chemistry of α -Oxoesters: A Powerful Tool for the Synthesis of Heterocycles. *Chem. Rev.* **2015**, *115*, 151–264.
- (2) Castillo, J.-C.; Portilla, J. Recent advances in the synthesis of new pyrazole derivatives. *Targets Heterocycl. Syst.* **2018**, *22*, 194–223.
- (3) Mako, T. L.; Racicot, J. M.; Levine, M. Supramolecular Luminescent Sensors. *Chem. Rev.* **2019**, *119*, 322–477.
- (4) Chrzanowska, M.; Grajewska, A.; Rozwadowska, M. D Asymmetric Synthesis of Isoquinoline Alkaloids: 2004–2015. *Chem. Rev.* **2016**, *116*, 12369–12465.
- (5) Buskes, M. J.; Harvey, K. L.; Prinz, B.; Crabb, B. S.; Gilson, P. R.; Wilson, D. J. D.; Abbott, B. M. Exploration of 3-Methylisoquinoline-4-carbonitriles as Protein Kinase A Inhibitors of Plasmodium falciparum. *Bioorg. Med. Chem.* **2016**, *24*, 2389–2396.
- (6) Guo, T.; Yu, L.; Zhao, B.; Li, Y.; Tao, Y.; Yang, W.; Hou, Q.; Wu, H.; Cao, Y. Highly Efficient, Red-Emitting Hyperbranched Polymers Utilizing a Phenyl-Isoquinoline Iridium Complex as the Core. *Macromol. Chem. Phys.* **2012**, *213*, 820–828.
- (7) Awuah, E.; Capretta, A. Strategies and Synthetic Methods Directed Toward the Preparation of Libraries of Substituted Isoquinolines. *J. Org. Chem.* **2010**, *75*, 5627–5634.
- (8) Seayad, J.; Seayad, A. M.; List, B. Catalytic Asymmetric Pictet–Spengler Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 1086–1087.
- (9) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. A New Modification of the Pomeranz–Fritsch Isoquinoline Synthesis. *J. Chem. Soc., Perkin Trans. 1* **1974**, *0*, 2185–2190.
- (10) Zhao, D.; Lied, F.; Glorius, F. Rh(III)-Catalyzed C–H Functionalization/Aromatization Cascade with 1,3-Dienes: A

Redox-Neutral and Regioselective Access to Isoquinolines. *Chem. Sci.* **2014**, *5*, 2869–2873.

- (11) Qi, L.; Hu, K.; Yu, S.; Zhu, J.; Cheng, T.; Wang, X.; Chen, J.; Wu, H. Tandem Addition/Cyclization for Access to Isoquinolines and Isoquinolones via Catalytic Carbopalladation of Nitriles. *Org. Lett.* **2017**, *19*, 218–221.
- (12) Xie, L.-G.; Niyomchon, S.; Mota, A. J.; González, L.; Maulide, N. Metal-Free Intermolecular Formal Cycloadditions Enable an Orthogonal Access to Nitrogen Heterocycles. *Nat. Commun.* **2016**, *7*, 10914.
- (13) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. Orthogonal Synthesis of Indolines and Isoquinolines via Aryne Annulation. *J. Am. Chem. Soc.* **2008**, *130*, 1558–1559.
- (14) Sun, L.-L.; Liao, Z.-Y.; Tang, R.-Y.; Deng, C.-L.; Zhang, X.-G. Palladium and Copper Cocatalyzed Tandem N–H/C–H Bond Functionalization: Synthesis of CF_3 -Containing Indolo- and Pyrrolo-[2,1-*a*]isoquinolines. *J. Org. Chem.* **2012**, *77*, 2850–2856.
- (15) Rao, U. N.; Han, X.; Biehl, E. R. Preparation of 3*H*-pyrrolo[2,3-*c*]isoquinolines and 3*H*-pyrrolo[2,3-*c*][2,6]- and 3*H*-pyrrolo[2,3-*c*][1,7]naphthyridines. *ARKIVOC* **2002**, *x*, 61–66.
- (16) Dixit, B.; Balog, J.; Riedl, Z.; Drahos, L.; Hajós, G. New Approach for the Synthesis of 3*H*-pyrrolo[2,3-*c*]isoquinoline Derivatives. *Tetrahedron* **2012**, *68*, 3560–3565.
- (17) Castillo, J.-C.; Quiroga, J.; Abonia, R.; Rodríguez, J.; Coquerel, Y. The Aryne aza-Diels–Alder Reaction: Flexible Syntheses of Isoquinolines. *Org. Lett.* **2015**, *17*, 3374–3377.
- (18) Macías, M. A.; Castillo, J.-C.; Portilla, J. A Series of (*E*)-5-(Arylideneamino)-1-*tert*-Butyl-1*H*-pyrrole-3-carbonitriles and Their Reduction Products to Secondary Amines: Syntheses and X-Ray Structural Studies. *Acta Cryst.* **2018**, *C74*, 82–93.
- (19) Portilla, J.; Quiroga, J.; Abonia, R.; Insuasty, B.; Nogueras, M.; Cobo, J.; Mata, E. Solution-phase and solid-phase synthesis of 1-pyrazol-3-ylbenzimidazoles. *Synthesis* **2008**, *2008*, 387–394.
- (20) Castillo, J.-C.; Quiroga, J.; Abonia, R.; Rodríguez, J.; Coquerel, Y. Pseudo-Multicomponent Reactions of Arynes with *N*-Aryl Imines. *J. Org. Chem.* **2015**, *80*, 9767–9773.
- (21) Castillo, J.-C.; Rosero, H.-A.; Portilla, J. Simple Access Toward 3-Halo- and 3-Nitro-pyrazolo[1,5-*a*]pyrimidines Through a One-Pot Sequence. *RSC Adv.* **2017**, *7*, 28483–28488.
- (22) Charris-Molina, A.; Castillo, J.-C.; Macías, M.; Portilla, J. One-Step Synthesis of Fully Functionalized Pyrazolo[3,4-*b*]pyridines via Isobenzofuranone Ring Opening. *J. Org. Chem.* **2017**, *82*, 12674–12681.
- (23) Orrego-Hernández, J.; Lizarazo, C.; Cobo, J.; Portilla, J. Pyrazolo-fused 4-azafluorenones as key reagents for the synthesis of fluorescent dicyanovinylidene-substituted derivatives. *RSC Adv* **2019**, *9*, 27318–27323.
- (24) Orrego-Hernández, J.; Portilla, J. Synthesis of Dicyanovinyl-Substituted 1-(2-Pyridyl)pyrazoles: Design of a Fluorescent Chemosensor for Selective Recognition of Cyanide. *J. Org. Chem.* **2017**, *82*, 13376–13385.
- (25) Castillo, J.-C.; Tigreros, A.; Portilla, J. 3-Formylpyrazolo[1,5-*a*]pyrimidines as Key Intermediates for the Preparation of Functional Fluorophores. *J. Org. Chem.* **2018**, *83*, 10887–10897.
- (26) Tigreros, A.; Rosero, H.-A.; Castillo, J.-C.; Portilla, J. Integrated Pyrazolo[1,5-*a*]pyrimidine-Hemicyanine System as a Colorimetric and Fluorometric Chemosensor for Cyanide Recognition in Water. *Talanta* **2019**, *196*, 395–401.
- (27) García, M.; Romero, I.; Portilla, J. Synthesis of Fluorescent 1,7-Dipyrrolyl-bis-pyrazolo[3,4-*b*:4',3'-*e*]pyridines: Design of Reversible Chemosensors for Nanomolar Detection of Cu^{2+} . *ACS Omega* **2019**, *4*, 6757–6768.
- (28) Wu, J.; Liu, W.; Ge, J.; Zhang, H.; Wang, P. New Sensing Mechanisms for Design of Fluorescent Chemosensors Emerging in Recent Years. *Chem. Soc. Rev.* **2011**, *40*, 3483–3495.
- (29) Peckus, D.; Matulaitis, T.; Franckevičius, M.; Mimaitė, V.; Tamulevičius, T.; Simokaitienė, J.; Volyniuk, D.; Gulbinas, V.; Tamulevičius, S.; Gražulevičius, J. V. Twisted Intramolecular Charge

Transfer States in Trinary Star-Shaped Triphenylamine-Based Compounds. *J. Phys. Chem. A* **2018**, *122*, 3218–3226.

(30) Tigreros, A.; Ortiz, A.; Insuasty, B. Effect of π -conjugated linkage on photophysical properties: Acetylene linker as the better connection group for highly solvatochromic probes. *Dyes Pigm.* **2014**, *111*, 45–51.

(31) Yang, Z.; Cao, J.; He, Y.; Yang, J. H.; Kim, T.; Peng, X.; Kim, J. S. Macro-/micro-environment-sensitive chemosensing and biological imaging. *Chem. Soc. Rev.* **2014**, *43*, 4563–4601.

(32) Lee, S.-C.; Heo, J.; Woo, H. C.; Lee, J.-A.; Seo, Y. H.; Lee, C.-L.; Kim, S.; Kwon, O.-P. Fluorescent Molecular Rotors for Viscosity Sensors. *Chem. – Eur. J.* **2018**, *24*, 13706–13718.

(33) CCDC 1817750 (**6e**), 1817752 (**6f**), 1899534 (**6g**), 1817752 (**8b**), and 1899534 (**8c**) contain the supplementary crystallographic data for this paper.

(34) Thomas, S. P.; Spackman, P. R.; Jayatilaka, D.; Spackman, M. A. Accurate Lattice Energies for Molecular Crystals from Experimental Crystal Structures. *J. Chem. Theory Comput.* **2018**, *14*, 1614–1623.

(35) Turner, M. J.; McKinnon, J. J.; Wolff, S. K.; Grimwood, D. J.; Spackman, P. R.; Jayatilaka, D.; Spackman, M. A. (2017). *CrystalExplorer17*. University of Western Australia. <http://hirshfeldsurface.net/>.

(36) Saha, S.; Quiney, H. M. Solvent effects on the excited state characteristics of adenine–thymine base pairs. *RSC Adv* **2017**, *7*, 33426–33440.

(37) Misra, R.; Bhattacharyya, S. P. *Intramolecular Charge Transfer: Theory and Applications*. 2018. First Ed. Wiley-VCH Verlag GmbH & Co. KGaA. p: 16–17.

(38) Allegretti, M.; Anacardio, R.; Cesta, M. C.; Curti, R.; Mantovanini, M.; Nano, G.; Topai, A.; Zampella, G. A Practical Synthesis of 7-Azaindolylcarboxy-endo-tropanamide (DF 1012). *Org. Process Res. Dev.* **2003**, *7*, 209–213.

(39) Palatinus, L.; Chapuis, G. SUPERFLIP - a computer program for the solution of crystal structures by charge flipping in arbitrary dimensions. *J. Appl. Crystallogr.* **2007**, *40*, 786–790.

(40) Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, *71*, 3–8.

(41) Macrae, C. F.; Bruno, I. J.; Chisholm, J. A.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.; Taylor, R.; van de Streek, J.; Wood, P. A. Mercury CSD 2.0 - new features for the visualization and investigation of crystal structures. *J. Appl. Crystallogr.* **2008**, *41*, 466–470.

(42) Spek, A. L. PLATON SQUEEZE: a tool for the calculation of the disordered solvent contribution to the calculated structure factors. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, *71*, 9–18.

(43) Spackman, M. A.; Jayatilaka, D. Hirshfeld surface analysis. *CrystEngComm* **2009**, *11*, 19–32.

(44) Jayatilaka, D.; Grimwood, D. J.; Lee, A.; Lemay, A.; Russel, A. J.; Taylor, C.; Wolff, S. K.; Cassam-Chenai, P.; Whitton, A. (2005). TONTO. <http://hirshfeldsurface.net/>.

(45) Spackman, M. A.; McKinnon, J. J.; Jayatilaka, D. Electrostatic potentials mapped on Hirshfeld surfaces provide direct insight into intermolecular interactions in crystals. *CrystEngComm* **2008**, *10*, 377–388.

(46) Mackenzie, C. F.; Spackman, P. R.; Jayatilaka, D.; Spackman, M. A. CrystalExplorer model energies and energy frameworks: extension to metal coordination compounds, organic salts, solvates and open-shell systems. *IUCrJ*. **2017**, *4*, 575–587.