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Ring Transformation of Unsaturated *N*-Bridgehead Fused Pyrimidin-4(3*H*)-ones: Role of Repulsive Electrostatic Nonbonded Interaction

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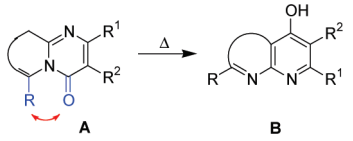
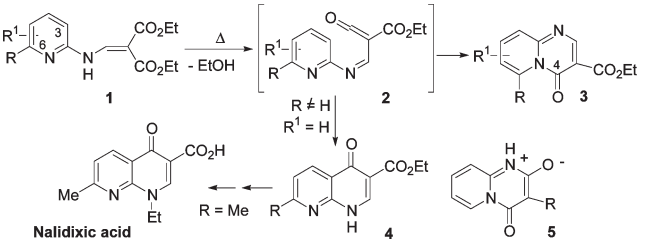


Thermal ring transformation ability of unsaturated *N*-bridgehead fused pyrimidin-4(3*H*)-ones **A** is governed by both the steric and the electrostatic interactions between the oxygen of the carbonyl group and the substituent in the peri position.

Intra- and intermolecular forces and nonbonded interactions[1] have been the subject of intense interest from both experimental and theoretical aspects in view of their fundamental roles in determining the three-dimensional structures and reactivities (e.g., ring transformations[2]) of molecules ranging from the simplest to highly complex. The thermal ring transformations[3] of unsaturated five- or six-membered bi- and polycyclic *N*-bridgehead ring systems **A** afford convenient and simple access to diverse scaffolds[4] with druglike properties for drug research, with valuable pharmacological potential within the chemical space.

SCHEME 1. Thermal Cyclization of Ethyl (2-Pyridylamino)-methylenemalonates



Recognition of this type of ring transformation led to the discovery of the prototype antibacterial agent, nalidixic acid (Scheme 1),[5] after which an enormous collaborative effort by the medicinal community resulted in the introduction of its third-generation blockbuster analogues ciprofloxacin[6] and levofloxacin[7] into everyday therapy to combat infections caused by Gram-negative and -positive bacteria.

Lappin showed that the thermal cyclization of **1** (R = H) yielded pyrido[1,2-*a*]pyrimidinones **3** (R = H), but the 6-Me derivative **1** (R = Me) gave 1,8-naphthyridine **4** (R = Me) (Scheme 1).[8] This surprising result was explained by the steric hindrance of the Me group on the neighboring ring N, with cyclization therefore occurring at the activated C3 position leading to formation of the naphthyridine skeleton. It was later pointed out that electrocyclization of the primarily formed iminoketene **2** occurs, under kinetic control, first on the ring N to yield **3**, which can undergo rearrangement to the thermodynamic product **4** under thermal conditions.[9] The presence of a 6-substituent on the pyrido[1,2-*a*]pyrimidinone skeleton enhances the ring transformation, as it generates tension through an unfavorable interaction between the 6 substituent and the O of the C4=O group. While the ring transformation of 2-(het)aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones can be achieved in low yields at around 350−400 °C,

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their 6-Me derivatives can be transformed in higher yields at lower temperature, 250−260 °C.[10]

X-ray diffraction studies on **5** led Wentrup et al. to draw attention to a weak attractive interaction between the C6-H and the O of the C4=O group, as the C4=O group tilted toward the ring N5 [O=C4−N5 angle: 115−118°, instead of 120°, and the "amide type" N5−C4 bonds are unusually long (144−149 pm), compared to a normal amide bond length (135 pm) showing no sign of amide-type conjugation.[11] Table S5 (Supporting Information) contains similar data determined by single-crystal diffraction studies on other 6-unsubstituted pyrido[1,2-*a*]pyrimidinones].

In the ground state, the steric strain caused by a C6-R substituent can be relieved in several ways: extended N5−C4 (mainly) and C6−N5 (to a lesser degree) bond lengths; widened N5−C4=O and N5−C6−R bond angles, or a widened R-C6···C4=O dihedral angle. If the C4−N5 bond is longer, the dihedral angle is usually smaller (Table S7, Supporting Information). The driving force of the ring transformation is to release the strain accumulated in the ground-state between the C4=O group and the C6 substituent.

We recently reported[12] the thermal cyclization of the halo derivatives of **6**. We usually obtained **8**, but in contrast with the 6-methyl derivative,[13,14] the 6-Cl derivative **6d** unexpectedly gave **9d**, in spite of the Cl atom being similar in size to the Me group[15] (Scheme 2, Table 1). Naphthyridinone **9d** was accompanied by a dimer **10d** formed from iminoketene **7d** in a stepwise "head-to-tail" [4 + 2] cycloaddition. 6-Br derivative **6e** gave a similar result. The aforementioned results led us to extend our investigations to the cyclization of 6-F and 6-I derivatives **6c**,**f**, in the hope that **6c**, containing an F atom (roughly half the size of a Cl atom[15]), would give **8c** or at least a mixture of **8c** and **9c**, while **6f** has a sterically more demanding atom at position 6 (see Table 1) and might well provide **9f**. For characterization of the size of the substituent, we selected Charton's υ values,[15] which were derived from the van der Waals radii (Table 1).

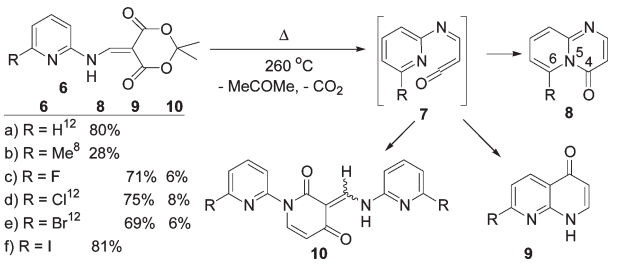
Below, we present our results, together with some theoretical considerations, to provide a better understanding of the role of the C6 substituent in the ring transformations of these types of molecules.

The starting **6c**,**f** were prepared in a one-pot reaction of Meldrum's acid, $HC(OMe)_3$, and the appropriate 2-aminopyridine. Thermal cyclization was carried out in preheated Ph_2O at 260 °C for a few minutes. Surprisingly, while **6c** gave a mixture of **9c** and **10c**, similarly to the 6-Cl and 6-Br derivatives,[12] **6f** afforded pyridopyrimidinone **8f**, which could be synthesized by an independent route, too.

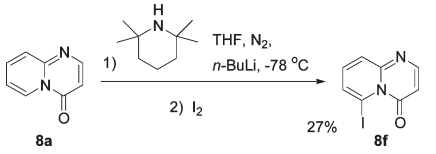
TABLE 1. Charton's υ Steric Parameters of the Investigated 6-R Substituents[15]

	H	Me	F	Cl	Br	I
Charlton's υ value	0	0.52	0.27	0.55	0.65	0.78

SCHEME 2. Thermal Cyclization of Isopropylidene (2-Pyridylamino)methylenemalonates



SCHEME 3. Lithiation of 4*H*-Pyrido[1,2-*a*]pyrimindin-4-one 8a



Lithiation of **8a** with a 1:1.1 mixture of *n*-BuLi and 2,2,5,5-tetramethylpiperidine, followed by treatment with I_2, yielded **8f** (Scheme 3). As far as we are aware, this is the first example of the functionalization of the pyrido[1,2-*a*]pyrimidinone skeleton at position C6.

As these surprising results could not be explained merely in terms of steric interactions between the 6 substituent and the O of the C4=O group, we carried out DFT calculations to determine the potential ground-state geometric data on **8**. The ground-state structure of **8b** could also be determined by means of single-crystal X-ray analysis (Supporting Information). Fair agreement was achieved between the calculated and experimental data on **8b** (Table 2, rows 2 and 3), considering that the theoretical calculations gave data relating to vacuum, while in the solid state the crystal packaging exerts some influence on the geometrical parameters. While all the non-hydrogen atoms are situated in a plane in **8a**, in the presence of a 6-Me group the Me group and the O of the C4=O group are situated in opposite directions outside this plane, creating a dihedral angle of 11.9° (measured)/15.2° (calculated).

As the calculated dihedral angle (12.6°) in **8c** is similar to that in **8b** (Table 2), and the size of the F atom is only half that of the Me group,[15] it is postulated that, besides a steric interaction, there is also an unfavorable electrostatic interaction between the valence shell electrons of the F and O atoms. (The influence of the electron pair repulsion of heteroatoms on a strong conformation preference was recently reported.[16]) This results in a longer (149.4 pm) and, therefore, a weaker N5−C4 bond relative to that in the 6-Me derivative **8b**. Furthermore, in spite of the similar sizes of the

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(14) da Silva et al. reported that thermal cyclization of the 4,6-dimethyl derivative of **6** in boiling Ph_2O for 5 min gave 80% of 5,7-dimethyl-1,8-naphthyridin-4-one. When we repeated the experiment 6,8-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was the main product, in agreement with the result of Lesher.[13] After a reaction of time 5 h, the amounts of pyridopyrimidinone and 1,8-naphthyridinone were nearly equal. Da Silva, L. E.; Joussef, A. C.; Nunes, R. J.; de Oliveira, K. N. *Synth. Commun.* **2008**, *38*, 15.

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TABLE 2. Ground-State Geometry of 4*H*-Pyrido[1,2-*a*]pyirimidin-4-ones 8 Calculated by DFT at the B3LYP/6-311++G(2d,2p) Level

	R	bond length N5−C4 (pm)	bond length C6−R (pm)	angle N5−C6−R (deg)	angle C4−N5−C6 (deg)	distance[a] between O and R (pm)	dihedral angle O=C4··C6-R (deg)
8a	H	146.5	107.8	113.8	116.9	222.4	0.01
8b	Me	147.2	150.5	122.2	120.8	263.6	15.2
	Me[b]	*145.0(3)*	*150.4(3)*	*121.7(2)*	*121.1(2)*	*262.2*	*11.9*
8c	F	149.4	132.1	117.3	121.5	251.8	12.6
8d	Cl	148.4	173.4	120.3	122.0	278.6	30.0
8e	Br	148.2	190.2	121.4	121.9	287.1	30.8
8f	I[c]	147.7−150.1	212.2−215.1	122.3−123.9	121.1−122.0	296.9−308.6	27.5−33.8

[a]Distance between the geometric centers of the substituents on C4 and C6. [b]Italics indicate experimental data determined by single-crystal X-ray diffraction study. [c]Calculations were carried out at the B3LYP/LANL2DZ, B3LYP/DGDZVP, B3LYP/CEP31G, B3LYP/CEP121G and MP2/LANL2DZ, and MP2/DGDZVP levels, and the ranges are given.

Cl atom and the Me group (see Table 1), the dihedral angle (R−C6···C4=O) in **8d** is twice as large as that in **8b** (Table 2), which is probably also a consequence of the repulsion of the electron pairs of the neighboring halo and O atoms.

The electrostatic interaction between the halo and O atoms gradually decreases in the sequence F, Cl, Br, and I derivatives as the distance between the halo atom and O becomes longer (Table 2), and the electrostatic interaction falls off exponentially with the distance. For the Cl and Br derivatives **8d**,**e**, containing sterically more demanding halo atoms, the steric effect plays a greater role than for the F derivative **8c**, while the dihedral angles are bigger, and the C4−N5 bonds are somewhat shorter.

The decreased stability of F, Cl, and Br derivatives **8c**−**e** is in harmony with the observation of Ferrarini et al. that the 6- F, 6-Cl, and 6-Br derivatives of 2-phenyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one could be transformed into 1,8-naphthyridin-4-ones only at 220 °C within 10 min.[17]

The 6-I derivative **8f** is more stable than the other halo derivatives, even at the reaction temperature, as the electrostatic interaction is minimized in **8f** by the longer distance between the O and I atoms, the C6−I derivative containing the longest 6-Hlg bond (Table 2). The ready polarizability of the electron cloud of the I atom also decreases the repulsive interaction (if it exists at all in this case) between the neighboring I and O atoms. Furthermore, 6-I derivative **8f** may be stabilized by a weak intramolecular halogen bonding.[18]

In **8b**, only the size of the Me group influences the adopted conformation and its ring transformation capability, while for the F derivative **8c**, mainly the electrostatic repulsion predominates. In **8d**, **e**, both factors may play roles. At 260 °C, **8b**,**f** are sufficiently stable during the short reaction period, but the F, Cl, and Br derivatives **8c**−**e** are easily transformed to **9c**−**e** via iminoketenes **7c**−**e**.

The electrostatic potential surfaces for pyridopyrimidinones **8a**−**f** support the above interpretation (Figure 1). For the F derivative **8c**, electrostatic repulsion was indicated by the red areas on the F and O atoms. This gradually became smaller and smaller from the Cl to the I derivative.

In conclusion, we have demonstrated that for nitrogen bridgehead ring systems **A**, where substituent R has a lone pair(s) on the atom connected to the ring, not only the steric demand but also the valence-shell electron repulsion of substituent R and the O of the C4=O group can play a role in the ring transformation. In the ring transformation of 6-fluoropyridopyrimidinone, the electrostatic interaction is the main factor, while in the case of the 6-Me derivative it is the steric size, and for the 6-Cl and 6-Br derivatives both interactions should be considered. In the latter derivatives, the longer life span of the iminoketene intermediate further gives a chance for a "head-to-tail" [4 + 2] cycloaddition of the iminoketene intermediate.

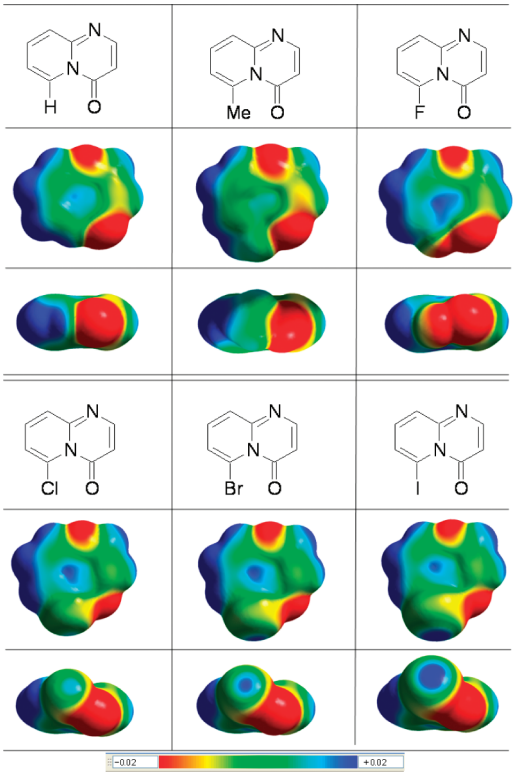

FIGURE 1. Electrostatic potential surfaces for pyridopyrimidinones **8** at the 0.02 electron/au^3 density isocotour level computed at the B3LYP6-311++G(2d,2p) level of theory. Blue is positive potential (attractive for the negative charge), red is negative potential (repulsive for the negative charge), and green represents near zero potential. In the 3rd and 6th rows, the main plane of the molecule is perpendicular to the plane of the paper.

Experimental Section

General Procedures. Melting points are uncorrected, and yields were not maximized. ^{1}H and ^{13}C NMR spectra were

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recorded in DMSO-d_6. Coupling constants are reported in hertz and chemical shifts in ppm (δ, ppm) downfield from TMS, which was used as internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), broad (br). LC−MS investigations were carried out on equipment with a quaternary pump, an autosampler, a detector, and a single quadruple mass spectrometer with ESCi source.

Isopropylidene [(6-Iodopyridin-2-yl)amino]methylenemalonate (6f). A 1:2 mixture of Meldrum's acid (1.76 g, 12 mmol) and trimethyl orthoformate (3 mL, 25 mmol) was heated under reflux for 4 h, and the reaction mixture was then evaporated to dryness. The residue was dissolved in EtOH (20 mL), 2-amino-6-iodopyridine (2.20 g, 10 mmol) was added, and the reaction mixture was stirred at ambient temperature overnight. The precipitate was filtered off, washed with EtOH, and used in the cyclization reaction without further purification: yellow crystals (3.70 g, 99%); mp 219 °C; ^{1}H NMR (200 MHz, DMSO-d_6, 27 °C) δ = 11.32 (d, $^3J_{H,H}$ = 13.8 Hz, 1 H, NH), 9.04 (d, $^3J_{H,H}$ = 13.8 Hz, 1 H, CH), 7.70 (5′-H) and 7.63 (ovl.m., 2 H, 3′-H), 7.56 (dd, $^3J_{H,H}$ = 6.8 Hz, $^3J_{H,H}$ = 7.2 Hz, 1 H, 4′-H), 1.68 (s, 6 H, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6, 27 °C) δ = 163.6 (2-C or 4-C), 163.3 (2-C or 4-C), 150.64 (CH or 2′-C), 150.60 (2′-C or CH), 141.4 (4′-C), 132.4 (5′-CH), 116.9 (6′-C), 113.8 (3′-C), 104.9 (6-C), 89.3 (3-C), 27.0 (2 C, CH_3). Anal. Calcd for $C_{12}H_{10}IN_2O_4$: C, 38.52; H, 2.96; N, 7.49. Found: C 38.34; H 2.63; N 7.68.

6-Iodopyrido[1,2-*a*]pyrimidin-4-one (8f). Method A. Isopropylidene [(6-iodopyridin-2-yl)amino]methylenemalonate (**6f**) (2.00 g, 5.3 mmol) was added to Ph_2O (40 g) preheated to 260 °C. The reaction mixture was heated at 260 °C for 10 min and then quickly cooled to room temperature and diluted with *n*-hexane (80 mL). The precipitated crystals of **8f** were filtered off, washed with *n*-hexane and then with EtOAc, and recrystallized from THF: yellow crystals (1.18 g, 81%; mp 167 °C).

Method B. A solution of anhydrous TMP (1.27 mL, 7.54 mmol) in anhydrous THF (25 mL) was cooled to −78 °C, and a solution of butyllithium in hexane (4.3 mL, 6.85 mmol) was introduced dropwise under an atmosphere of dry nitrogen. The mixture was stirred for 10 min, after which time 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **8a** (1.0 g, 6.85 mmol) was added to the solution. After 1 h of stirring, solid I_2 (1.71 g, 6.85 mmol) was introduced. After 1 h, the mixture was allowed to warm to rt, hydrolysis was carried out with water, and the organic layer was removed under reduced pressure. The aqueous phase was extracted with DCM (3 × 20 mL), and the combined organic extracts were dried over $MgSO_4$ and evaporated. The crude product of **8f** was purified by column chromatography on silica gel (Kieselgel 60 F_{254}, toluene/methanol = 4:1) and was recrystallized from THF: yellow crystals (0.51 g, 27%); mp 166−167 °C; ^{1}H NMR (200 MHz, DMSO-d_6, 27 °C): δ = 8.21 (d, $^3J_{H,H}$ = 6.3 Hz, 1 H, 2-H), 7.82 (dd, $^3J_{H,H}$ = 6.9 Hz, $^4J_{H,H}$ = 1.2 Hz, 1 H, 7-H), 7.54 (dd, $^3J_{H,H}$ = 8.9 Hz, $^4J_{H,H}$ = 1.2 Hz, 1 H, 9-H), 7.38 (dd, $^3J_{H,H}$ = 8.9 Hz, $^3J_{H,H}$ = 6.9 Hz, 1 H, 8-H), 6.37 (d, $^3J_{H,H}$ = 6.3 Hz, 1 H, 3-H); ^{13}C NMR (50 MHz, DMSO-d_6, 27 °C) δ = 159.3 (4-C), 153.4 (9*a*-C), 152.9 (2-C), 136.8 (8-C), 133.8 (7-C), 127.2 (9-C), 105.2 (3-C), 88.4 (6-C); MS(EI+) m/z = 272 $[M]^+$, 244, 204, 146, 127, 117, 90, 78, 64, 53, 40; HRMS(ES+) m/z = 272.9530 $[MH]^+$, calcd for $C_8H_6IN_2O^+$ 272.9525.

Isopropylidene [(6-Fluoropyridin-2-yl)amino]methylenemalonate (6c). A 1:2 mixture of Meldrum's acid (1.76 g, 12 mmol) and trimethyl orthoformate (3 mL, 25 mmol) was heated under reflux for 4 h, and the reaction mixture was then evaporated to dryness. The residue was dissolved in EtOH (20 mL), 2-amino-6-fluoropyridine (1.12 g, 10 mmol) was added, and the reaction mixture was stirred at ambient temperature overnight. The precipitate of **6c** was filtered off, washed with EtOH and used in cyclization reaction without further purification: yellow crystals (2.63 g, 99%); mp 189−190 °C; ^{1}H NMR (200 MHz, DMSO-d_6, 27 °C) δ = 11.42 (d, $^3J_{H,H}$ = 13.8 Hz, 1 H, NH), 8.99 (d, $^3J_{H,H}$ = 13.8 Hz, 1 H, CH), 8.05 (q, $^3J_{H,H}$ = 8.0 Hz, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,F}$ = 8.2 Hz, 1 H, 4′-H), 7.60 (dd, $^3J_{H,H}$ = 7.8 Hz, $^5J_{H,F}$ = 1.9 Hz, 1 H, 3′-H), 7.02 (dd, $^3J_{H,H}$ = 8.0 Hz, $^3J_{H,F}$ = 2.2 Hz, 1 H, 5′-H), 1.68 (s, 6 H, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6, 27 °C) δ = 163.5 (2-C or 4-C), 163.2 (2-C or 4-C), 162.3 (d, $^1J_{C,F}$ = 240.5 Hz, 6′-C), 150.7 (CH), 149.0 (d, $^3J_{C,F}$ = 13.5 Hz, 2′-C), 145.3 (d, $^3J_{C,F}$ = 8.3 Hz, 4′-C), 111.6 (d, $^4J_{C,F}$ = 4.0 Hz, 3′-C), 106.3 (d, $^2J_{C,F}$ = 35.2 Hz, 5′-C), 104.9 (6-C), 89.4 (3-C), 27.0 (2 C, CH_3); ^{19}F NMR (376.5 MHz, DMSO-d_6, 27 °C) δ = −68.2 (d, $^3J_{F,H}$ = 2.2 Hz, $^4J_{F,H}$ = 8.2 Hz, $^5J_{F,H}$ = 1.9 Hz). Anal. Calcd for $C_{12}H_{11}FN_2O_4$: C, 54.14; H, 4.16; N, 10.52. Found: C 54.34; H 4.03; N 10.60.

Thermal Cyclization of Isopropylidene [(6-Fluoropyridin-2-yl)-amino]methylenemalonate (6c). Isopropylidene [(6-fluoropyridin-2-yl)amino]methylenemalonate (**6c**) (2.00 g, 7.5 mmol) was added to Ph_2O (40 g) preheated to 260 °C. The reaction mixture was heated at 260 °C for 10 min and then quickly cooled to room temperature and diluted with *n*-hexane (80 mL). The precipitated crystals were filtered off and washed with *n*-hexane, and **9c** and **10c** were separated by fractional crystallization from EtOH.

7-Fluoro-1,4-dihydro-1,8-naphthyridin-4-one (9c): yellow crystals (0.87 g, 71%); mp 241 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 27 °C) δ = 12.27 (br, 1 H, NH), 8.58 (t, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,F}$ = 8.2 Hz, 1 H, 6-H), 7.91 (dd, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 5.9 Hz, 1 H, 2-H), 7.12 (dd, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,F}$ = 2.1 Hz, 1 H, 5-H), 6.13 (dd, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,H}$ = 0.9 Hz, 1 H, 3-H); ^{13}C NMR (100 MHz, DMSO-d_6, 27 °C) δ = 176.8 (4-C), 163.5 (d, $^1J_{C,F}$ = 242.0 Hz, 7-C), 149.4 (d, $^3J_{C,F}$ = 19.0 Hz, 8*a*-C), 141.8 (d, $^3J_{C,F}$ = 11.0 Hz, 5-C), 140.4 (2-C), 119.0 (d, $^4J_{C,F}$ = 3.0 Hz, 4*a*-C), 111.0 (3-C), 106.3 (d, $^2J_{C,F}$ = 38.0 Hz, 6-C); ^{19}F NMR (376.5 MHz, DMSO-d_6, 27 °C) δ = −61.1 (dd, $^3J_{F,H}$ = 8.2 Hz, $^4J_{F,H}$ = 2.1 Hz); MS(EI+) m/z = 164 $[M]^+$, 136, 116, 109, 96, 82, 68, 53, 38; HRMS(ES+) m/z = 165.0438 $[MH]^+$, calcd for $C_8H_6FN_2O^+$ 165.0464.

1-(6-Fluoro-2-pyridyl)-3-[(6-chloro-2-pyridylamino)methylene]-1,2,3,4-tetrahydropyridin-2,4-dione (10c): yellow crystals (71 mg, 6%); HPLC purity 83%; mp > 300 °C; isomer ratio based on ^{1}H NMR measurements Z/E = 64:36; ^{1}H NMR (400 MHz, DMSO-d_6, 27 °C) δ = 13.55 (d, $^3J_{13\text{-}H,14\text{-}H}$ = 12.5 Hz, 0.64 H) and 12.30 (d, $^3J_{13\text{-}H,14\text{-}H}$ = 12.5 Hz, 0.36 H, 14-H), 9.19 (d, $^3J_{13\text{-}H,14\text{-}H}$ = 12.5 Hz, 1 H, 13-H), 8.18 (m) and 8.09 (m, 2 H, 4-H and 19-H), 7.96 (d, $^3J_{11\text{-}H,12\text{-}H}$ = 8.5 Hz, 0.64 H) and 7.91 (d, $^3J_{11\text{-}H,12\text{-}H}$ = 8.5 Hz, 0.36 H, 12-H), 7.73 (m, 1 H) and 7.58 (m, 1 H, 5-H and 20-H), 7.26 (m, 1 H) and 7.08 (m, 1 H, 3-H and 18-H), 5.88 (d, $^3J_{11\text{-}H,12\text{-}H}$ = 8.5 Hz, 0.64 H) and 5.86 (d, $^3J_{11\text{-}H,12\text{-}H}$ = 8.5 Hz, 0.36 H, 11-H); ^{13}C NMR (100 MHz, DMSO-d_6, 27 °C) δ = 184.0 (M) and 180.9 (m, 10-C)* (*M: major set of signals; m: minor set of signals), 163.4 (M) and 163.1 (m, 8-C), 161.0 (2 C, 2-C and 17-C), 151.8 (M) and 151.0 (m, 13-C), 148.9 and 148.5 (2 C, 6-C and 15-C), 145.3 and 143.9 (2 C, 4-C and 19-C), 142.2 (M) and 141.4 (m, 12-C), 119.2 and 111.7 (2 C, 5-C and 20-C), 109.5 (m) and 108.4 (M, 11-C), 108.5 and 106.7 (2 C, 3-C and 18-C), 105.6 (M) and 105.4 (m, 9-C); HRMS(ES+) m/z = 329.0847, calcd for $C_{16}H_{11}F_2N_4O_2$.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **6c**,**f**, **8f**, **9c**, and **10c**, X-ray data for compound **8b** (CIF), with computational details including geometries and electrostatic potential surface for compounds **8** at all levels of theory, and additional tables. This material is available free of charge via the Internet at http://pubs.acs.org.