ABSTRACT: Readily available phenylene-1,3-diamines can be converted into unprecedented analogues of rhodamine and malachite green possessing a central eight-membered ring in three steps. The overall process couples a cyanine chromophore with a urea bridge giving rise to new dyes possessing distinct spectral characteristics: absorption of orange light combined with a weak emission of red light both in solution and in the crystalline state. Their photophysics is governed by the twist of lateral phenyl rings and intramolecular and intermolecular CT transitions.

INTRODUCTION

The study of biological systems at the cellular and subcellular levels is greatly aided by small molecule fluorophores, of which members of the xanthene family, including fluorescein and rhodamine, have proved invaluable.1 Recently, there has been an increased focus on harnessing the photophysical properties of these ubiquitous dyes through structural modifications. In particular, π-expansion2−6 and replacement of the xanthene oxygen atom bridge with silicon,7−9 phosphorus,10 sulfur,11 or carbon12−14 in rhodamine,15−18 fluorescein,19,20 and rhodol21 scaffolds have proved to be popular and effective.

The dyes from this extended family, despite their structural and functional diversity, share the quintessential characteristics: (a) planar aromatic structures; (b) excellent spectroscopic properties including strong absorption and fluorescence; (c) relatively small Stokes shifts; and (d) biocompatibility. At the same time, nonplanar chromophores, however, feature a number of peculiar properties, making it possible to overcome the limitations of conventional chromophores such as: (a) increased possibility for intramolecular charge transfer (ICT) and (b) their tendency to be more soluble, less aggregating, and be able to form amorphous thin films. The latter makes nonplanar chromophores good candidates for potential use in optoelectronic devices.22,23

The replacement of the oxygen bridge in xanthene chromophores with a two- or three-atom unit, which has not been reported to date, would enable us to create rigid but nonplanar chromophores. The concept of this project was to address the above general idea by constructing an analogue of rhodamine in which the bridging oxygen atom is formally replaced with a urea moiety to create an eight-membered ring. This can also be thought of as an analogue of malachite green (MG) in which the diallylaminophenyl groups are tethered by urea. The inclusion of a ring of this size inside a chromophore is known to generate a distortion in planarity,24 resulting in an overall twisted geometry because of the strained central fragment.25−31 Through exploitation of this strategy, we demonstrate how this targeted introduction of structural diversity into well-known rhodamine chromophores can unlock solvent- and state-dependent photophysical properties.

RESULTS AND DISCUSSION

Scheme 1 details our proposed strategy to generate rhodamine analogues possessing a central urea-based eight-membered ring (8U-Rh) by taking advantage of the reactivity of electron-rich phenylene-1,3-diamines. In the first step, 1-dimethylamino-3-methylaminobenzene (1) smoothly reacts with 4-chlorobenzaldehyde in the presence of acetic acid as a catalyst to form a triarylmethane derivative 2a. Optimization of the subsequent cyclization step proved challenging because of the formation of a strained eight-membered ring system. Employment of phosgene solution led to a cyclized product 3a only in trace amounts as the high reactivity of phosgene results in low selectivity of this process. Indeed, mass spectrometry (MS) experiments suggest that the product of the addition to both secondary amino groups of a single triarylmethane forms even at −20 °C. The use of
triphosgene, a less reactive analogue, enables a more selective initial reaction with a secondary amino group. According to MS data, experiments with different substrate/triphosgene ratios showed the formation of intermediates bearing triphosgene residues with different degrees of decomposition. The cyclization step is a much slower process and requires 3−18 days at room temperature in order to obtain the cyclic product 3a bearing an eight-membered ring in 53% yield. The oxidation of compound 3a with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) leads to the formation of 8U-Rh 4a.

To showcase our system’s synthetic utility, this strategy was applied utilizing other aldehydes (Scheme 1). It was found that the efficacy of the cyclization reaction is dependent on both the steric hindrance (to a greater extent) and the electron-withdrawing properties of the aryl ring at the meso-position. Indeed, the reaction with 4-chlorobenzaldehyde was characterized by the shortest reaction time compared with that of 2-methylbenzaldehyde and mesitaldehyde; however, 2-trifluoromethylbenzaldehyde, which combined both these features, takes as long as 18 h to reach equilibrium. Further extension of the reaction time or variation of the temperature causes no improvement to the reaction yields. All in all, four additional 8U-Rh 4b−e were prepared in overall yields ranging from 1 to 21%.

In order to analyze the distorted nature of the synthesized dyes, the structures of chromophores 4b and 4c were determined by X-ray crystallography (Figures S1 and S2). In the crystal lattice, molecules 4b and 4c adopt a curved chromophore structure with unsymmetric geometry. The lateral benzene rings are positioned at different dihedral angles related to the central chromophore plane ranging from 27 to 43° for 4b and 29 to 32° for dye 4c. Moreover, the dihedral angle between lateral benzene rings reaches 68° for 4b and 60° for 4c, respectively (Figure S3). This angle controls the mutual orientation of the chromophore molecules in the crystal lattice resulting in the minimal distances of 4.480 Å for 4b and 3.591 Å for 4c, respectively (Figure S4), between π-systems of adjacent molecules.

The absorption spectra of the urea-bridged xanthenes 4a−e show intense maxima between 585 and 600 nm (Table 1, Figure 1). The influence of the electronic character of the central aryl group on the spectroscopic properties is clearly reflected in the spectrum of 4d, with π-π stacking of the chromophores resulting in a bathochromic shift and a large Stokes shift. Compounds 4a and 4d decomposed during the SOA experiment. Fluorescence maxima were not determined because of the extremely low emission response.

\[
\begin{array}{|c|c|c|c|c|c|c|}
\hline
\text{compd.} & \text{solvent} & \lambda_{\text{abs}} / \text{nm} & \varepsilon_{\text{max}} \times 10^{-3} / \text{M}^{-1} \text{cm}^{-1} & \lambda_{\text{em}} / \text{nm} & \Delta \lambda^\text{f} / \text{nm} & \Phi_{\text{f}} \\
\hline
4a & DCM & 595 & 71 & 635 & 1060 & 0.00068 \\
 & H\text{O} & 584 & 41 & 635 & 1230 & 0.00019 \\
4b & DCM & 589 & 71 & 635 & 1340 & 0.00044 \\
 & CH\text{3CN} & 580 & 50 & 635 & 1340 & 0.00014 \\
 & H\text{O} & 579 & 41 & 635 & 1340 & 0.00010 \\
 & SOA\text{b} & 586 & 637 & 1340 & 0.16 \\
4c & DCM & 587 & 68 & 637 & 1340 & 0.00148 \\
 & CH\text{3CN} & 579 & 48 & 637 & 1340 & 0.00035 \\
 & H\text{O} & 578 & 43 & 637 & 1340 & 0.00017 \\
 & SOA\text{b} & 583 & 638 & 1480 & 0.33 \\
4d & DCM & 600 & 58 & 656 & 1420 & 0.00058 \\
 & CH\text{3CN} & 590 & 41 & 656 & 1420 & 0.00019 \\
 & H\text{O} & 585 & 35 & 656 & 1420 & 0.00009 \\
4e & DCM & 598 & 72 & 639 & 1070 & 0.00059 \\
 & CH\text{3CN} & 590 & 52 & 639 & 1070 & 0.00050 \\
 & H\text{O} & 590 & 39 & 639 & 1070 & 0.00013 \\
 & SOA\text{b} & 596 & 646 & 1300 & 0.17 \\
\hline
\end{array}
\]

‒ Stokes shift. \(b\)Compounds 4a and 4d decomposed during the SOA experiment. Fluorescence maxima were not determined because of the extremely low emission response.
substituent is rather weak. The 8U-Rhs 4a and 4d possessing moderately electron-withdrawing 4-chloro- and 2-trifluoromethylphenyl substituents display somewhat red-shifted absorption maxima at 595 and 600 nm respectively, while urea-bridged rhodamines with electron-donating aryl moieties (4b,c) demonstrate absorption in the range 587−589 nm. The solvent polarity moderately affects the absorption properties of 8U-Rhs. The nonpolar dichloromethane (DCM) dyes 4a−e show more intense and more red-shifted absorption compared to acetonitrile and water solutions (Table 1).

The chromophore structure of 8U-Rhs resembles two known functional organic dyes, namely, rhodamine B (RB), possessing a rigid planar structure, and MG, which belongs to the triphenylmethane dye family. A comparison of spectral properties of 8U-Rhs 4a−e with RB shows that insertion of the “urea bridge” into the xanthene chromophore gives rise to a 35 nm bathochromic shift of the absorption maximum, while for MG, the absorption is blue-shifted by 20 nm.

The fluorescence maxima of 8U-Rhs 4a−e are typically around 635−640 nm, that is, they are ~60 nm bathochromically shifted compared to RB. Regardless of the substitution pattern, 8U-Rhs 4a−e are very weakly emissive, reminiscent of the picosecond fluorescence of MG. Non-negligible Stokes shifts (Table 1, Figure 1) suggest certain geometrical differences between the molecules in their ground and excited states.

The hypothesis that the rotational motion of molecular fragments, in a similar manner to MG, is the reason why 8U-Rhs show weak emission prompted us to study the dependence of fluorescence efficiency on the solution viscosity. In methanol/glycerol mixtures, an increase in fluorescence efficiency was observed upon increasing the glycerol ratio (Figure 2, Table 2).

Likewise, stiffening of the environment by dissolution in highly viscous sucrose octaacetate (SOA) limits the twisting of the 8U-Rhs’ structure in the excited state, which results in a significant increase in the fluorescence efficiency. In SOA solutions, compounds 4b, 4c, and 4e exhibit a 500−1000 fold increase in the fluorescence quantum yield with emission in a similar spectral region compared to traditional low viscous solvents (Figure 3, Table 1). This experiment unambiguously proves that rotations within the chromophore are responsible for the weak fluorescence of the “urea-bridged” rhodamines in regular solvents. The fact that the electron-donating effect of the urea fragment is much weaker than that of nitrogen and comparable with the oxygen atom reinforces a conclusion that the bent geometry rather than the presence of the nitrogen atom causes fluorescence quenching.

Fluorescence spectra were also recorded for 8U-Rhs in the polycrystalline state. Low fluorescence responses with peak wavelengths at 715 nm for 4a (Φ = 0.22%), 740 nm for 4b (Φ = 0.04%), 728 nm for 4c (Φ = 0.15%), and 740 nm for 4e (Φ =

Table 2. Fluorescence Quantum Yields of 8U-Rh Solutions under Different Viscosity Environments

| glycerol/MeOH volume ratio | η/cP   | 4a | 4b | 4c | 4e |
|----------------------------|--------|----|----|----|----|
| 100:0                      | 521.03 | 4.06 | 3.60 | 6.05 | 3.55 |
| 80:20                      | 132.33 | 2.02 | 0.81 | 1.55 | 1.07 |
| 60:40                      | 58.01  | 0.34 | 0.18 | 0.37 | 0.26 |
| 0:100                      | 0.52   | 0.03 | 0.02 | 0.04 | 0.03 |

Figure 3. Absorption (solid) and fluorescence (dashed) spectra in SOA and fluorescence spectra in the polycrystalline state (dotted) for compounds 4b, 4c, and 4e.
0.05%) were observed (Figure 3). The weak quantum yields lead us to suspect the self-quenching effect in the crystalline solid states, which may be associated with the size of the crystals. In this study, however, we found that there is no obvious difference in quantum yields between the polycrystalline and ground powder, as shown in Table S12. In comparison to the emission in solution, a >90 nm bathochromic shift is observed for the polycrystalline state, indicating that there is a strong influence of crystal packing on the emission properties, which causes the red shift and significant quenching of fluorescence.

To rationalize the photophysical processes, density functional theory (DFT) and time-dependent (TD) DFT/B3LYP/6-31G(d,p) and CAM-B3LYP/6-31G(d,p) calculations were performed for the geometry optimization of 8U-Rh cations in the ground and excited states. Also, to evaluate the solvent effect, the polarizable continuum model was adopted. The Supporting Information file includes additional calculation details and an overview of the calculation results.

Based on the data presented in Supporting Information (optimized structures, shapes of the corresponding molecular orbitals, energies, and oscillator strengths of electronic transitions for 8U-Rh, RB, and MG), it can be seen that the calculations reproduce the similarity of the structures in addition to the mutual location of experimental absorption spectra of 8U-Rhs, RB, and MG (Tables S1 and 3), as well as the weak dependence of these spectra on solvent polarity (Table S2).

Table 3. \(S_0 \rightarrow S_1\) and \(S_1 \rightarrow S_0\) Transition Data for 4a–4d Cations and Ion Pairs in CH\(_3\)CN (TD B3LYP/6-31G(d,p))

| Cations | Ion pairs | \(S_0 \rightarrow S_1\) | \(S_1 \rightarrow S_0\) | \(S_0 \rightarrow S_1\) (A) | \(S_0 \rightarrow S_1\) (B) |
|---------|-----------|----------------|----------------|----------------|----------------|
| 4a      | 2.245 eV  | 0.954 eV       | 2.395 eV       | 0.3201 eV      | 1.466 eV       |
|         | 552.18 nm | 1300 nm        | 517.7 nm       | 3873 nm        | 845.6 nm       |
|         | 1.3751    | 0.0003         | 0.693          | 0.0000         | 0.109          |
| 4b      | 2.276 eV  | 0.863 eV       | 2.243 eV       | 0.894 eV       | 1.524 eV       |
|         | 544.8 nm  | 1436 nm        | 552.7 nm       | 1386 nm        | 813.5 nm       |
|         | 1.300     | 0.001          | 1.1672         | 0.0001         | 0.0124         |
| 4c      | 2.285 eV  | 0.797 eV       | 2.459 eV       | 0.746 eV       | 1.577 eV       |
|         | 542.50 nm | 1556 nm        | 504.1 nm       | 1663 nm        | 786.4 nm       |
|         | 1.3452    | 0.0015         | 0.909          | 0.0001         | 0.0148         |
| 4d      | 2.241 eV  | 0.771 eV       | 2.372 eV       | 0.679 eV       | 1.440 eV       |
|         | 553.15 nm | 1608 nm        | 522.6 nm       | 1825 nm        | 861.1 nm       |
|         | 1.2159    | 0.0020         | 0.6892         | 0.0020         | 0.091          |

However, the minimum energy of the excited 8U-Rhs, like in the case of MG,\(^\text{35}\) (but different from planar RB), corresponds to the structure with rotated lateral rings. This structure is characterized by low energy transitions to the ground state with extremely low oscillator strengths (Tables 3 and S1). Such type of structure is created in the evolution of the system after electronic excitation, during which the rotation of phenyl rings is accompanied by intramolecular CT. A similar mechanism has been proposed for MG.\(^\text{39}\) To gain further insights, we have extended our calculations to include R′Cl⁻ ion pairs. The reason for this lies in that the calculation results of RB\(^\text{22}\) show that the three orbitals of Cl⁻ are energetically neighbor to the HOMO orbital located on R′. This also applies for the urea-bridged rhodamines in solvents of medium polarity (Figure S5). With such an energy arrangement of R′Cl⁻ system orbitals, the appearance of intramolecular CT states (HOMO(Cl⁻) \(- \text{LUMO}(R'')) located near states localized on 8U-Rhs can be expected.

The simulation of absorption spectra of the ion pair R′Cl⁻ of 4b (Table S3) illustrates that in low- and medium-polarity solvents, weak intensity CT transitions are present, but they are hidden under the large intensity band for the \(S_0 \rightarrow S_1\) transition localized on \(8U-Rh'\). This leads to subtle changes in the absorption spectrum, including peak broadening and a small shift of the main absorption band. Such effects disappear in polar solvents.

Optimization of the R′Cl⁻ pair in the excited state showed that, in addition to the previously described structure with rotated lateral rings (A-case, similar to MG), a minimum of another type appears (B-case) (Table S4). This corresponds to a molecule with less twisted rings and is described by an intramolecular CT configuration because the HOMO orbital is predominately located on Cl⁻ (Table S4). The energies and oscillator strengths of the \(S_1 \rightarrow S_0\) transition corresponding to the B-structure are greater in comparison to the A-structure (Table 3). Comparing three optimized ion pair structures, it can be stated that the B-structure is characterized by the smallest distance between R′ and Cl⁻ (Table S4, Figure 4), allowing for more efficient mixing of electronic configurations. In other cases, that is, forms of Sₙ and A, the presence of Cl⁻ in solution plays a smaller role, and their properties are described well enough by analyzing their cations.

However, it should be noted that with such complex systems as 8U-Rhs, full mapping of the potential energy surface in the excited state is a very difficult task. In Table S4, we indicate this problem by providing two sets of values for each of the optimized structures obtained using different starting points in space. It can be assumed that there are even more possible positions, and the experimental results are because of an average of the ensemble.

Figure 4 presents a diagram of electronic states for compound 4b as a R′Cl⁻ pair in acetonitrile solution (data in Table 3).
Upon excitation, the 8U-Rhs can relax from the S\textsubscript{1} state into a practically dark form A with a very low energy gap to the ground state (0.7–1.1 eV with B3LYP calculations and larger by about 0.4 eV with the CAM-B3LYP method) and with the oscillator strength value close to zero (Tables 3 and S4). This is the pathway of nonradiative decay that has been analyzed in detail for MG.\textsuperscript{37–39} In this form of excited state, the lateral ring planes of the 8U-Rhs are significantly twisted with respect to each other, which is possible because of the flexibility of the eight-membered ring.

### CONCLUSIONS

In summary, we have designed and synthesized a series of rhodamine analogues bearing a central eight-membered ring. These new dyes adopt a curved geometry in the crystal lattice because of the highly strained central ring. In terms of electronic absorption behavior, 8U-Rhs resemble both rhodamines and triphenylmethane dyes. The 8U-Rhs exhibit strong absorption, which is red-shifted with respect to conventional rhodamine dyes and blue-shifted compared to MG that lacks a central electron-donating group and has free rotation for all phenyl groups. The presence of the central eight-membered ring in the 8U-Rhs causes quenching of fluorescence in all nonviscous solvents because of nonradiative deactivation pathways, in a similar manner to MG. Weak 8U-Rhs’ fluorescence can be attributed to the CT transition with small oscillator strength in the R’Cl\textsuperscript{−} ion pair. In such a pair (contact in solution), there is a relatively short distance between Cl and R, and intermolecular CT interactions are factors that compete with the tendency to rotate the lateral rings. Although in this work this intermolecular CT mechanism is considered as a source of observed weak fluorescence, it can also be seen as a mechanism that quenches the fluorescence of the chromophore that is excited as a high-oscillator system. In this context, it can be thought that the concentration quenching of RB fluorescence,\textsuperscript{5,8} which is discussed in terms of dimer formation, may also be associated with the formation of CT contact pairs.

### EXPERIMENTAL SECTION

All chemicals were used as received unless otherwise noted. All reported \textsuperscript{1}H NMR spectra were collected using 500 and 600 MHz spectrometers. Chemical shifts (\textdelta ppm) were determined with TMS as the internal reference; \textit{J} values are given in Hz. Chromatography was performed on silica gel (230–400 mesh). The mass spectra were obtained by electron ionization (EI-MS) or electrospray ionization (ESI-MS). All photo-physical studies were performed with freshly-prepared air-equilibrated solutions at room temperature (298 K).

A PerkinElmer Lambda 25 UV/Vis spectrophotometer and a Hitachi F7000 fluorescence spectrometer were used to acquire the absorption and emission spectra. Spectroscopic grade solvents were used without further purification. Fluorescence quantum yields were determined in CH\textsubscript{3}Cl\textsubscript{2}, acetonitrile, and water using sulforhodamine 101 in ethanol as the standard. The solid-state fluorescence measurements were conducted using a 405 nm diode laser coupled with a 540 nm longpass filter.

Preparation of SOA Solutions for Measurements. Concentrated dye solutions in dichloroethane were added to a homogenous mixture of SOA and dichloroethane in a 9:1 ratio (small amount of dichloroethane makes the mixture less viscous). A homogenous dye solution is concentrated at reduced pressures and viscous foam-like dye mixture of SOA and dichloroethane in a 9:1 ratio (small amount of treated dye solutions in dichloroethane are added to a homogeneous state (0.7 eV with the CAM-B3LYP method) and with the oscillator system. In this context, it can be thought that the ionization (EI-MS) or electrospray ionization (ESI-MS). All photo-physical studies were performed with freshly-prepared air-equilibrated solutions at room temperature (298 K).

Fluorescence of the chromophore that is excited as a high-oscillator system. In this context, it can be thought that the solid-state fluorescence was measured using an Edinburgh FLS980 fluorimeter equipped with an integrating sphere assembly F-M01.

### General Procedure for the Preparation of Compounds 2

An ethanol solution (20 mL) of 6 mmol N,N,N-trimethyl-p-phenylenediamine 1 (or N-methyl-3-(pyrrolidin-1-yl)aniline \textit{S}) and an aromatic aldehyde (3 mmol) containing two drops of acetic acid was stirred for 48 h at rt. The product was filtered, washed with ethanol, and dried in vacuo to give a pure product.
The Journal of Organic Chemistry

4.1 mmol, diisopropylethylamine (6 mmol) and diisopropylcarbodiimide were dissolved in 12 mL of dry DCM. The resulting solution was stirred for 30 min at room temperature under an argon atmosphere. The reaction mixture was then evaporated and the residue was purified by column chromatography (SiO₂) using a solvent system of 9:1 CH₂Cl₂/MeOH with the addition of 1.2 g of 4 Å molecular sieves. Upon evaporation of the solvents, hexane was added to the mixture. The product was filtered off, washed with fresh hexane, and dried at 80 °C for 4 h (4 Å at 40 °C). In some cases, when the crystalline product was contaminated with the residue of Alqaft 336, the product was dissolved with a small amount of DCM and crystallized by the addition of diethyl ether and a few drops of methanol to give a pure reaction product.

(Z)-N-(12-(4-Chlorophenyl)-9-(dimethylamino)-5,7-dimethyl-6-oxo-6,7-dihydroidibenzo[d,g][1,3]diazocin-3(5H)-ylidene)-N-methylmethanaminium Chloride 4b. Dark glossy crystalline solid. Column chromatography (SiO₂) was performed using a solvent system of 9:1 CH₂Cl₂/MeOH with the addition of 1.2 g of Alqaft 336. Yield 5% (26 mg). 1H NMR (500 MHz, CDCl₃): δ 6.92 (s, 1H), 6.65 (d, 2H, J = 9.6 Hz), 6.65 (d, 2H, J = 2.5 Hz), 6.48 (d, 2H, J = 2.5 Hz), 6.37 (s, 1H), 3.60 (s, 6H), 3.27 (s, 3H), 3.21 (s, 3H), 1.87 (s, 3H). 13C NMR (126 MHz, CDCl₃): δ 160.4, 159.1, 158.8, 158.5, 155.2, 151.1, 142.0, 140.2, 137.7, 137.0, 131.8, 130.9, 130.3, 125.7, 125.7, 124.4, 112.8, 112.1, 103.7, 106.2, 41.9, 39.7, 37.25, 37.25, 19.7. HRMS (ESI-TOF): m/z: [M⁺] calcd for C₂₃H₂₆N₅O₂, 427.2498; found, 427.2499.

(Z)-N-(9-(Dimethylamino)-5,7-dimethyl-6-oxo-12-(2,4,6-trimethylphenyl)-6,7-dihydroidibenzo[d,g][1,3]diazocin-3(5H)-ylidene)-N-methylmethanaminium Chloride 4c. Dark glossy crystalline solid. Column chromatography (SiO₂) was performed using a solvent system of 9:1 CH₂Cl₂/MeOH with the addition of 1.2 g of Alqaft 336. Yield 20% (104 mg). 1H NMR (500 MHz, CDCl₃): δ 6.65 (d, 2H, J = 9.6 Hz), 6.65 (d, 2H, J = 2.5 Hz), 6.48 (d, 2H, J = 2.5 Hz), 6.37 (s, 1H), 3.60 (s, 6H), 3.27 (s, 3H), 3.21 (s, 3H), 1.87 (s, 3H). 13C NMR (126 MHz, CDCl₃): δ 160.4, 159.1, 158.8, 158.5, 155.2, 151.1, 142.0, 140.2, 137.7, 137.0, 131.8, 130.9, 130.3, 125.7, 125.7, 124.4, 112.8, 112.1, 103.7, 106.2, 41.9, 39.7, 37.25, 37.25, 19.7. HRMS (ESI-TOF): m/z: [M⁺] calcd for C₂₃H₂₆N₅O₂, 427.2498; found, 427.2499.

(Z)-N-(9-(Dimethylamino)-5,7-dimethyl-6-oxo-12-(2,4,6-trimethylphenyl)-6,7-dihydroidibenzo[d,g][1,3]diazocin-3(5H)-ylidene)-N-methylmethanaminium Chloride 4d. Dark glossy crystalline solid. Column chromatography (SiO₂) was performed using a solvent system of 9:1 CH₂Cl₂/MeOH with the addition of 1.2 g of Alqaft 336. Yield 20% (104 mg). 1H NMR (500 MHz, CDCl₃): δ 6.65 (d, 2H, J = 9.6 Hz), 6.65 (d, 2H, J = 2.5 Hz), 6.48 (d, 2H, J = 2.5 Hz), 6.37 (s, 1H), 3.60 (s, 6H), 3.27 (s, 3H), 3.21 (s, 3H), 1.87 (s, 3H). 13C NMR (126 MHz, CDCl₃): δ 160.4, 159.1, 158.8, 158.5, 155.2, 151.1, 142.0, 140.2, 137.7, 137.0, 131.8, 130.9, 130.3, 125.7, 125.7, 124.4, 112.8, 112.1, 103.7, 106.2, 41.9, 39.7, 37.25, 37.25, 19.7. HRMS (ESI-TOF): m/z: [M⁺] calcd for C₂₃H₂₆N₅O₂, 427.2498; found, 427.2499.
Preparation of Single Crystals. Monocrystalline samples were obtained by the vapor diffusion method using acetonitrile (solvent) and diethyl ether (precipitant) for compound 4b and acetonitrile (solvent) and THF (precipitant) for 4c.

## ASSOCIATED CONTENT
4 Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00414.

Experimental details, spectral data for all products, and X-ray structure (PDF) (CIF)

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The manuscript was written with contributions from all authors.

### Notes
The authors declare no competing financial interest.

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