A Combined Experimental and Theoretical Approach toward the Development of Optimized Luminescent Carbostyrils

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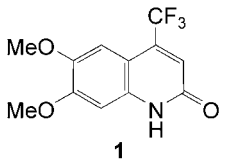
The synthesis and photophysical data of new carbostyrils (quinoline-2(1*H*)-ones) with the longest hitherto observed absorption- and emission wavelengths are described. Introduction of 6-amino, 7-MeO, and 4-(CF_3) substituents enabled us to rise the absorption and fluorescence maxima up to 414 and 557 nm, respectively. Supported by semi-empirical and *ab initio* calculations, the 6,7-(1,4-diazine)-fused carbostyril **23b** displayed absorption maxima at up to 440 nm, with quantum yields of up to 0.9 and large *Stokes* shifts (>100 nm), comparable to the best coumarin chromophores known. The new fluorophore is neither pH-sensitive between pH 6 and 10 nor susceptible to O_2 quenching. At pH 3, the emitted light appears greenish-white, which arises from three different stages of protonation.

Introduction. – In contrast to the coumarins ubiquitously used as fluorescent dyes [1], less attention has been paid to the aza-analogues quinolin-2(1*H*)-ones (carbostyrils), probably because of their lower extinction coefficients, hypsochromic absorption maxima, and more-cumbersome tuning of photophysical properties. However, carbostyrils are, in most cases, more resistant against pH changes (ring opening) and bleaching caused by chemical or thermal tackles. Nonetheless, 7-acetamido derivatives of *Carbostyril-124*, which absorb at *ca.* 335 nm and emit near 370 nm, have found applications in fluorescence analysis, as well as in 'antenna-sensitized' europium luminescence [2]. The preference of a 7-amino group as auxochrome has its origin in the corresponding highly esteemed coumarin analogues.

In earlier work [3], we have investigated substituent effects in all positions of the carbostyril system, which has provided fundamental data regarding their photophysical properties. Introduction of electron-donating and electron-accepting groups at certain positions does improve their spectral and luminescent characteristics. This converged to a so-called 'push-pull' model with two electron-donating substituents in positions 6 and 7, and a CF_3 group as the acceptor at C(4). As a result of these systematic investigations, we developed 6,7-dimethoxy-4-(trifluoromethyl)quinolin-2(1*H*)one (**1**), which has an absorption maximum at 370 nm, a quantum yield of *ca.* 0.5, and a *Stokes* shift of *ca.* 70 nm). Inspired by this promising result, we sought further improvements [4], especially to break through the visible barrier for the absorption wavelength of carbostyrils, thus opening the field for new applications, because adequately priced light-emitting diodes (LEDs) as new excitation sources at 370, 405, and 430 nm have become available [5].

Apart from the desired photophysical properties, our new fluorophores should also be readily accessible by simple chemical transformations. We envisaged to synthesize



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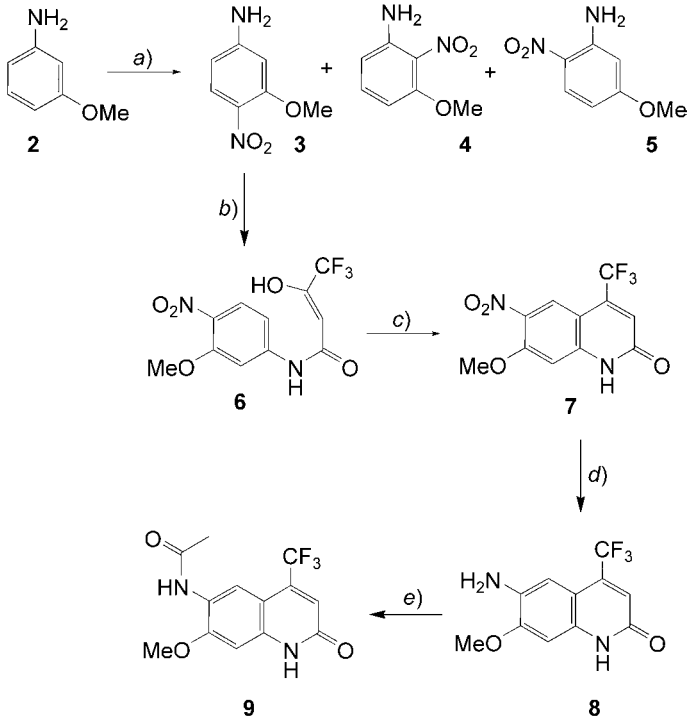
various derivatives of 6-amino-7-methoxy-4-(trifluoromethyl)quinolin-2(1*H*)-ones and to examine the influence of distinct donor substituents in position 6. Based on our previous results [3], we anticipated that the most-wavelength-sensitive position 6, occupied by a MeO group in **1**, had to be replaced by a stronger electron-donating amino group (see **8** below).

Our synthetic approach started with the preparation of suitable anilines that possess all the substituents in defined positions to access the desired carbostyrils after ring closure. Here, we describe the synthesis and spectral-luminescence characteristics of the new candidates complemented with semiempirical (AM1 [6], ZINDO [7]) and, in one case, *ab initio* (Hartree-Fock B3LYP [8]) molecular-orbital calculations.

Results and Discussion. – As depicted in *Scheme 1*, carbostyrils **7**–**9** are conveniently prepared from 3-methoxy-4-nitroaniline (**3**), which contains the NH_2 group for the ring closure and the 6-amino substituent masked as a NO_2 group. Compound **3** was obtained by nitration of 2-methoxyaniline (**2**) with urea nitrate in H_2SO_4 [9]. Notably, this method allows carrying out the nitration without protection of the NH_2 group. Separation of **3** from the isomeric by-products **4** and **5** could be accomplished by simple recrystallization from toluene. Surprisingly, compound **4** was greatly favored over the less-crowded **5**. Next, compound **3** was condensed with ethyl 4,4,4-trifluoro-3-oxobutanoate to the anilide **6**. The ring closure to the desired quinolinone **7** turned out to be difficult. Because the starting material **6** is electron deficient, it tends to undergo significant elimination back to the nitroaniline **3**. By switching from H_2SO_4 to H_3PO_4, we were able to prepare **7** in a reproducible yield of *ca.* 50% after recrystallization. Luckily, no significant amount of the 5-methoxy-6-nitro-4-(trifluoromethyl) isomer was found in the crude material. Having obtained the desired ring system, simple reduction of the NO_2 group under heterogeneous conditions afforded carbostyril **8**, which served as a first candidate for our spectroscopic investigations, and **9** was prepared to investigate the influence of *N*-acylation at the 6-position.

To make use of the bathochromic effect of alkylamino groups relative to NH_2, we envisaged preparing selected examples of secondary- or tertiary-amino derivatives of **8**. Since direct alkylation of **8** is not a feasible strategy due to side reactions at N(1) or O(2), and as protection of N(1) seemed to be a circuitous route, we decided to start with a *de novo* preparation of appropriate anilines. 2-Methoxy-4-nitroaniline (**10**) served as the starting material for the desired derivatives **11**–**13** by straightforward alkylation (*Scheme 2*). It turned out that NaH and Me_2SO_4 were optimal for monomethylation, which can be run at moderate temperatures without occurrence of significant double alkylation (**11**). The *N*,*N*-dimethylaniline derivative **13** could be obtained with MeI and excess NaH. Next, compounds **11**–**13** were reduced to the

Scheme 1

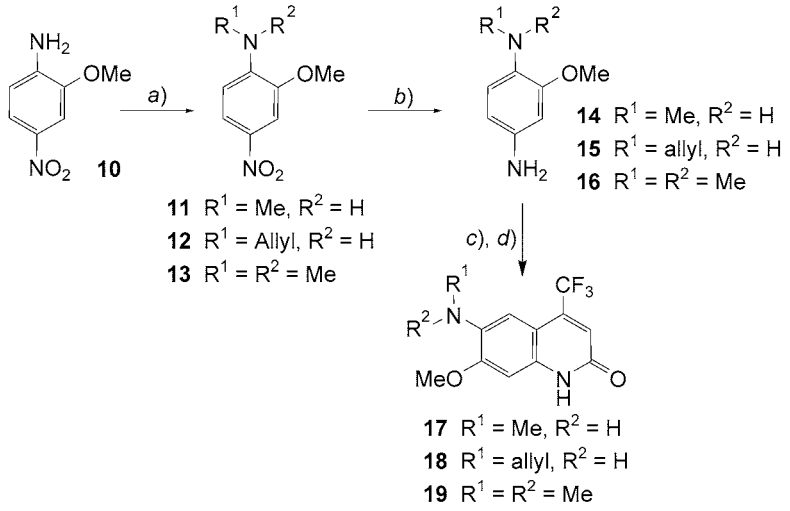


a) Urea nitrate, H_2SO_4, 4°, 1 h; 42% (**3**), 23% (**4**), <1% (**5**). *b*) $(CF_3)COCH_2CO_2Et$, 130°, 30 min; 94%. *c*) H_3PO_4, 110°, 1 h; 48%. *d*) H_2 (40 psi), PtO_2, EtOH, 40°, 20 h; 91%. *e*) Ac_2O, AcOH, 20°, 1 h; 95%.

benzenediamines **14**–**16**, which were then cyclized to **17**–**19** by *Knorr* reaction. Fortunately, as for the cyclization of **6** to **7**, no significant amounts of side products such as the 6-amino-5-methoxy-4-(trifluoromethyl) isomer were formed. In the case of **15**, the ring-closure had to be performed with H_3PO_4 instead of H_2SO_4 to avoid undesired additions to the allylic C=C bond. Although the procedures are not fully optimized yet, they allow for the preparation of diverse *N*-alkylated 6-amino-7-methoxy-4-(trifluoromethyl)quinolin-2(1*H*)-ones in overall yields of 33–58%.

To our delight, compound **8** exhibited an absorption maximum at 403 nm, and the 6-*N*-Me analogue **17** a maximum at 414 nm (*Table 1*). In comparison with the hitherto most-bathochromically absorbing carbostyril **1** (368 nm), this constitutes a shift of the absorption maximum by 33 and 46 nm, respectively. The fluorescence maximum went up to *ca.* 530 nm, with quantum yields of *ca.* 0.5. Remarkably, although fitted with the strongest electron donor, the *N*,*N*-dimethylamino analogue **19** exhibited only a very moderate increase in absorption wavelength compared with **1**, but displayed the highest fluorescence wavelength ever measured for carbostyrils (557 nm), leading to a *Stokes* shift of 173 nm. However, compared with **17** and **8**, the fluorescence quantum yield was lower (0.28). Based on calculated (AM1) structures, we assume that this drawback of **19** mainly results from the increased steric hindrance of the Me_2N group, resulting in a

Scheme 2



a) Me_2SO_4, allyl bromide or MeI, NaH, THF, reflux, 8–20 h; 48–93%. *b*) Sn^0, HCl, MeOH, 60°, 30–60 min; 73–89%. *c*) $(CF_3)COCH_2CO_2Et$, xylene, 130°, 30 min. *d*) H_2SO_4 or H_3PO_4, 80–100°, 60–90 min; 33–58% (2 steps).

Table 1. *Experimental* (exp) vs. *Calculated* (calc) *Photophysical Data* for the *Electronic Absorption* (abs) *and Fluorescence* (flu) *of Different Carbostyrils.* In DMSO at 25°; λ in nm.

Compound	λ_{abs} (exp)	ε (exp)	λ_{abs} (calc)	f	λ_{flu} (exp.)	$\Delta\lambda$	Φ
1	368	10400	367	0.36	444	76	0.45
7	358	10520			[a])		
8	403	7350	372	0.13	533	130	0.38
9	368	7330	353	0.28	448	80	0.28
17	414	7950	376	0.31	532	118	0.48
18	409	7000	–	–	526	117	0.47
19	384	8470	351	0.33	557	173	0.28

[a]) Not fluorescent

significant out-of-plane rotation of the C(7)–N bond and, thus, loss of electron-donating power.

Compound **9** was prepared to study the influence of *N*-acylation, which is a common linking method, *e.g.*, to join metal-ion-complexing side chains. As expected, according to the decrease in donor strength at position 6, both absorption and emission wavelengths were shifted hypsochromically. By comparing the data of **9** with those of the model compound **1**, one can conclude that an acylated 6-NH_2 group has about the same effect on the fluorescence properties as a MeO group at the same position. The large shift of absorption and emission wavelengths upon acylation can be used to monitor the enzymatic cleavage of, *e.g.*, peptide bonds by observation of the fluorescence signal appearing at 531 nm (compound **8**) [10].

From previous experiments [3], we expected quite good agreement between calculated and experimental absorption maxima. There is, however, one notable exception: the donor properties of amino groups, and, hence, the bathochromic shift induced (**8**, **17**–**19**), are greatly underestimated by the ZINDO procedure [11]. Apart from these limitations in terms of accuracy, one should see a general trend for the calculated absorption data and fairly good agreement with experimentally determined values.

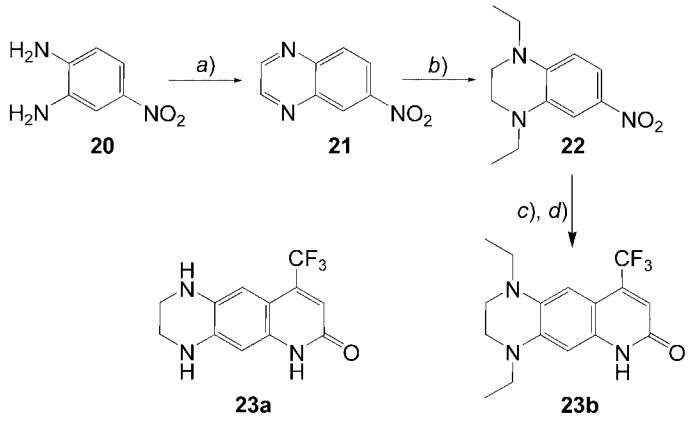
As stated above (*Table 1*), although fitted with the strongest donor, **19** exhibited a less-bathochromic absorption, as well as a rather low quantum yield. This drawback seemed to result from increased steric hindrance of the bulkier Me_2N group. To increase both the extinction coefficient and the quantum yield, it was essential to replace the 7-MeO group by an amino functionality. To combine low steric demands with strong electron-donating properties, we envisaged to incorporate the 6- and the 7-amino groups into a cyclic system, which would also prevent their twisting and, consequently, lead to longer wavelength absorption and emission. Indeed, *ab initio* calculations of the transition energies for the model compound **23a** by time-dependent density-functional theory (TD-B3LYP/6-31 + G** with AM1-optimized S_0 and S_1 geometries) indicated a calculated wavelength absorption of 402 nm, much higher than the calculated values for the compounds given in *Table 1*, and a fluorescence maximum of 473 nm. According to these calculations, a nearly planar arrangement of the amino groups with a concomitant increase of the substituent's donor properties is enforced. Most notably, similar tetrahydroquinoxaline structures have been patented as androgen receptor ligands recently, but no electronic spectra have been reported [12].

A convenient synthetic strategy for the preparation of **23b** was found in the literature [13]. In our hands, the described precursor synthesis *via* quinoxaline **21** has been improved, as outlined in the *Exper. Part*. Compound **21** was converted to **22** by reductive alkylation with $NaBH_4$ and AcOH. Reduction to the corresponding air-sensitive aniline (1,4-diethyl-1,2,3,4-tetrahydroquinoxalin-6-amine) under heterogeneous conditions (Pd/C) followed by *in situ* ring closure with isopropyl 4,4,4-trifluoro-3-oxobutanoate provided **23b** in 73% yield (*Scheme 3*).

As anticipated, the electronic spectra of **23b** showed absorption maxima between *ca.* 416 (H_2O, heptane) and 430 nm (DMSO, EtOH), and emission maxima between 502 (heptane) and 556 nm (H_2O), respectively. Quantum yields in organic solvents were up to 0.9, and, in H_2O, they reached values between 0.26 and 0.41, depending on the pH (*Table 2*). The calculated values for the transition energies (absorption and emission) agreed well with the experimental data for heptane. No quenching by O_2 was observed. In H_2O, the absorption maxima in the pH range 6–10 and emission maxima between pH 6 and 12 were constant, which indicated that the emission arises from the neutral form, even at high pH. In contrast, the spectra of **23b** in acidic solution underwent changes due to single and double protonation (*Figure*).

Isosbestic points (see arrows in the *Figure*) at 395 (excitation) and 550 nm (emission) allowed for the observation of absorption-independent titration curves in both the excitation and emission spectra. The complete disappearance of the neutral-form with an excitation maximum at 420 nm was accompanied by the successive formation of two very close new maxima at 385 (monocation) and 380 nm (dication). The emission of the singly-protonated form (pK_a *ca.* 3.1) gave rise to an intermediate maximum at 475 nm (*Figure*).

Scheme 3



a) Oxalaldehyde, MeCN, 50°, 15 h; 90%. *b*) $NaBH_4$, AcOH, dioxane, 90°, 15 h; 83%. *c*) H_2 (40 psi), 10% Pd/C, EtOH, 20 h. *d*) $(CF_3)COCH_2CO_2{}^i$Pr, $ZnCl_2$, anh. EtOH, 180°, 10 min; 73% (2 steps).

Table 2. *Experimentally Determined Absorption* (λ_{abs}), *Excitation* (λ_{ext}), *and Emission* (λ_{em}) *Wavelengths, Extinction Coefficients* (ε), *and Quantum Yields* (Φ) *of Fluorescence of* **23b**

Medium	λ_{abs}	ε	λ_{ext}	λ_{em}	$\Delta\lambda$	Φ
Gas phase [a])	402		402	473	71	
Heptane	416	15900	420	502	82	0.93
$CDCl_3$	424	17700	434	513	79	0.60
$CDCl_3$ (+ 0.4% TFA)	451	17000	460	517	57	0.92
DMSO	432	16100	440	543	103	0.66
EtOH	430	15600	440	526	86	0.92
EtOH (+ 0.4% $MeSO_3H$)	470		470	550	80	0.90
EtOH (+ 1.2% $MeSO_3H$)	375		375	453	78	0.15
H_2O (pH 12)	395		397	556	159	0.26
H_2O (pH 7)	420	17300	424	556	132	0.26
H_2O (pH 2.8)	375		380	475	95	0.41
H_2O (pH 0.5)	372	18000	370	528	158	0.26

[a]) Calculated by density-functional method (TD-B3LYP/6-31 + G**).

Multiple-fluorescence phenomena caused by protonation of coumarins and carbostyrils are well known [14]. Changes in **23b** are particularly interesting. Since molar absorption coefficients for all three forms are in a similar range, the formation of nearly isosbestic triple points allows for significantly simplified measurements. A comparison of UV- and excitation spectra indicated that the degree of protonation is unchanged upon excitation. Only at pH 12, where N(1) is deprotonated in the ground state, does the excited form have a different pK_a, and fluorescence arises from the neutral form. These findings are in strong contrast to the behavior of, *e.g.*, 7-(dimethylamino)-4-methylquinolin-2(1*H*)-one ($\lambda_{abs} = 320$ and 310 nm in acidic solution; $\Delta pK_a - 2.37$) [14]. In the case of **23b**, the quantum yields of the neutral form and the mono- and dication were all in a similar range. The mixed emission spectra at

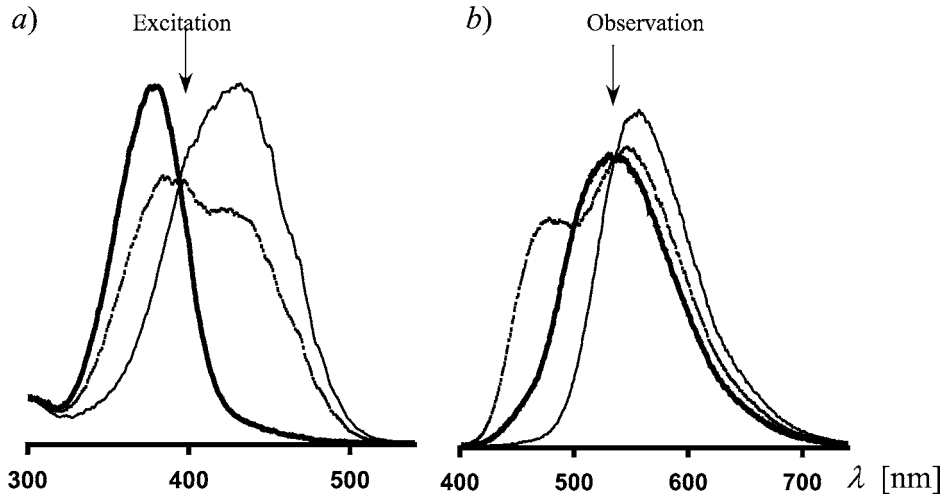


Figure. a) *Absorption and* b) *Emission Spectra of* **23** *in H_2O at pH 7* (unprotonated), *pH 3.35* (monoprotonated; dotted line), *and pH 1.0* (diprotonated; bold line). Nearly isosbestic points are marked with arrows.

pH 2.5–3.5 (half-width up to 162 nm) covered most of the visible range, and this fluorescence light appeared greenish-white. In contrast to acidic H_2O, the excitation maxima of the monoprotonated form of **23b** in EtOH were red-shifted ($\Delta\lambda_{max} = 90$ nm in H_2O). Upon further protonation with more acid, the absorption maximum in EtOH underwent a blue-shift, which resulted in similar wavelengths as in H_2O at pH 1 (see below). The *Stokes* shift in EtOH was found to be rather independent of the degree of protonation.

To investigate this unusual red-shift in EtOH, ^{1}H-NMR measurements were performed based on HMBC-type correlations of the free and the monoprotonated forms in $CHCl_3$. In this solvent, which strongly promotes ion pairing, the electron-spectral data are similar to those for the first protonation step in EtOH, and a second protonation requires much stronger acids. Addition of 0.4% trifluoroacetic acid (TFA) to a $CDCl_3$ solution of **23b** resulted in a deshielding of all H-atoms close to C(5), indicating local distortion of the electronic structure. Therefore, we can assume that the first protonation step takes place at N(6) under ion-pair formation. In line with these experimental results, calculated (B3LYP/6-311G(d,p)//B3LYP/6-311G(d,p) + ZPE) protonation energies indicated that protonation at N(6) should be favored over that at N(7) by 20 kJ mol^{-1}. Protonation at N(6) is also indicated by the equal pK_a values of the ground and excited states of **23b**, in contrast to the 7-(dimethylamino)-4-methylquinolin-2(1*H*)-one [14].

Conclusions. – We have shown that by appropriate selection of the position and type of substituents, carbostyrils with the longest so-far observed absorption and emission wavelengths can be accessed. The introduction of amino groups in position 6 in combination with 7-MeO and 4-(CF_3) substituents gave rise to absorption maxima of up to 414 nm (**17**), and fluorescence maxima of up to 557 nm (**19**). Supported by theoretical calculations and our large data set, the lead structure **23** for luminescence-

optimized carbostyrils was disclosed. Thereby, **23b** was readily obtained in an overall yield of 55% over four steps. It exhibited high quantum yields (up to 0.9), two-fold increased extinction coefficients (ε up to 18000), and bathochromically shifted absorption maxima (λ_{max} 440 nm). Thus, the carbostyril dye **23b** has properties comparable to the best known coumarins in terms of *Stokes* shift, fluorescence maximum, and quantum yield. The fluorophore is fully stable against both acids and bases, and is not sensitive towards O_2. In acidic medium, **23b** emits white light and, therefore, might find application in electroluminescent devices [15].

Experimental Part

General. Chemicals and reagents were purchased from *Aldrich* or *Fluka*, and were used without further purification. M.p.: *Gallenkamp MPD-350* melting-point apparatus, in open capillary tubes. IR Spectra: *Perkin-Elmer 298* spectrophotometer, KBr pellets; in cm^{-1}. ^{1}H-NMR Spectra: *Varian XL-200* at 200 MHz, or *Bruker AMX-360* at 360 MHz, chemical shifts (δ) in ppm rel. to internal $SiMe_4$ ($\delta = 0$ ppm). Microanalyses were performed on a *Fisons EA-1108* elemental analyzer.

Absorption and Fluorescence Spectra. Solvents for ultraviolet (UV) and fluorescence spectra were purified by distillation. UV/VIS Spectra were recorded on a *Shimadzu UV-2101PC* spectrophotometer. Excitation and emission spectra were obtained on a *Shimadzu RF-5001PC* spectrofluorophotometer fitted with a 150-W Xe lamp (operated as a continuous wave source), slits selectable in six steps to produce spectral bandwidths of 1.5, 3, 5, 10, 15, and 20 nm, resp., and an *R452-01* photomultiplier. Excitation and emission monochromators: ion-blazed holographic concave grating *F/2.5*. UV Spectra were recorded at a conc. of 40 μM, excitation and emission spectra at 4 μM. Quantum yields (Φ) were calculated rel. to quinine sulfate in 0.1M aq. $HClO_4$ soln. ($\Phi = 0.546$) [16].

Computational Procedures. Starting structures of the compounds investigated were created with the aid of the SYBYL molecular-modeling package [17a]. Semi-empirical molecular-orbital calculations were done by the AMPAC [17b] program packages. Geometries for ground states were completely optimized (keyword PRECISE) by the semi-empirical AM1 [6] Hamiltonian, with the eigenvector following the routine in [18]. Based on the AM1-optimized structures, electronic transition energies were calculated by the ZINDO method [7]. Solvent effects (DMSO, $n = 1.479$, $D = 45.0$) were treated with the self-consistent reaction-field approximation [19]. For the model compound **23a**, time-dependent density-functional calculations were performed [20] based on *Becke*'s three-parameter hybrid *Hartree-Fock* density functional and the *Lee-Yang-Parr* correlation functional [8], using the 6-31 + G** basis set (*Gaussian 98* program suite [21]).

3-Methoxy-4-nitroaniline (**3**) *and 3-Methoxy-2-nitroaniline* (**4**). *3-Methoxyaniline* (**2**; 5.0 g, 40.6 mmol) was slowly added to cold 96% H_2SO_4 (20 ml). To this soln. was added urea nitrate (5.0 g, 40.6 mmol) in small portions under stirring at 0–4°. The mixture was stirred for 1 h at this temp. and then poured over crushed ice. Insoluble products were filtered off. The filtrate was neutralized with aq. NH_3 soln., and the resulting precipitate (6.30 g of a crude mixture of **3**–**5**) was collected, washed with H_2O, and dried. *3-Methoxy-4-nitroaniline* (**3**) was separated by recrystallization from toluene: 2.87 g (42%). The mother liquor was evaporated, and the residue was subjected to dry-column flash chromatography (FC) on SiO_2 (*LiChroprep Si60*, *Merck*; toluene/acetone 9:2) to afford a mixture of **4** (R_f 0.66) and **5** (R_f 0.61; toluene/acetone 3:1). *3-Methoxy-2-nitroaniline* (**4**) was purified by recrystallization from toluene: 1.56 g (23%). The minor isomer **5** (*5-methoxy-2-nitroaniline*) was discarded.

Data of **3**: M.p. 154° (toluene; lit. 155–156° [22]). R_f 0.28 (toluene/acetone 3:1). IR: 3470, 3360, 1635, 1595, 1560, 1480, 1440, 1350, 1280. ^{1}H-NMR ($CDCl_3$): 3.90 (*s*, MeO); 4.30 (*s*, NH_2); 6.20 (*d*, H–C(2)); 6.22 (*dd*, H–C(6)); 7.95 (*d*, H–C(5)). Anal. calc. for $C_7H_8N_2O_3$: C 50.00, H 4.80, N 16.66; found: C 50.05, H 4.77, N 16.70.

Data of **4**: M.p. 114° (toluene; lit. 117–120° [23]). R_f 0.66 (toluene/acetone 3:1). IR: 3420, 3340, 1640, 1600, 1570, 1510, 1445, 1355, 1330. ^{1}H-NMR ($CDCl_3$): 3.86 (*s*, MeO); 4.95 (*s*, NH_2); 6.28 (*d*, H–C(6)); 6.35 (*d*, H–C(4)), 7.15 (*t*, H–C(5)). Anal. calc. for $C_7H_8N_2O_3$: C 50.00, H 4.80, N 16.66; found: C 50.04, H 4.56, N 16.29.

4,4,4-Trifluoro-3-hydroxy-N-*(3-methoxy-4-nitrophenyl)but-2-enamide* (**6**). Ethyl 4,4,4-trifluoro-2-oxobutanoate (4.0 g, 21.7 mmol) was heated in an open flask to 130°. Then, **3** (1.5 g, 8.92 mmol) was slowly added, and heating was continued for 30 min. The product precipitated from the cooled soln. and was filtered off, washed with a small amount of cyclohexane, and dried: 2.57 g (94%) of **6**. M.p. 185° (toluene). R_f 0.36 (toluene/MeOH/

acetone/AcOH 70:20:5:5). IR: 3320, 1675, 1620, 1565, 1500, 1395, 1280, 1265, 1205, 1140, 1095, 1005, 855, 840, 805. ^{1}H-NMR ($CDCl_3$): 3.90 (*s*, MeO); 5.80 (*s*, HO); 6.15 (*d*, H–C(2)); 6.98 (*dd*, H–C(6′)); 7.75 (*d*, H–C(2′)); 7.85 (*d*, H–C(5′)); 10.26 (*s*, NH). Anal. calc. for $C_9H_{11}F_3N_2O_5$: C 43.15, H 2.96, N 9.15; found: C 43.25, H 3.11, N 9.02.

*7-Methoxy-6-nitro-4-(trifluoromethyl)quinolin-2(1*H*)-one* (**7**). Compound **6** (830 mg, 2.71 mmol) was added to hot (110°) polyphosphoric acid (H_3PO_4) under stirring, and heating was continued for 1 h. After cooling and diluting with H_2O (100 ml), the resulting precipitate was filtered off, washed with H_2O, and dried. The crude product (580 mg) was recrystallized from EtOH: 375 mg (48%) of **7**. M.p. 308° (dec.; EtOH). R_f 0.33 (toluene/acetone 1:1). IR: 3290, 1660, 1630, 1560, 1540, 1420, 1380, 1320, 1265, 1250, 1185, 1165, 1125, 1080, 1000. ^{1}H-NMR ($CDCl_3$): 4.00 (*s*, MeO); 7.00 (*s*, H–C(3)); 7.15 (*s*, H–C(8)); 8.22 (*s*, H–C(5)); 12.50 (*s*, NH). Anal. calc. for $C_{11}H_7F_3N_2O_4$: C 45.85, H 2.45, N 9.72; found: C 45.97, H 2.31, N 9.60.

*6-Amino-7-methoxy-4-(trifluoromethyl)quinolin-2(1*H*)-one* (**8**). A suspension of **7** (220 mg, 0.763 mmol) in anh. EtOH (40 ml) was reduced by shaking with H_2 (40 psi) at 40° for 20 h in the presence of PtO_2. After removing the solvent and the catalyst, the product was purified by recrystallization from toluene: 190 mg (91%) of **8**. M.p. 304° (dec.; toluene). R_f 0.30 (toluene/acetone 1:1). IR: 3420, 3300, 2880, 1660, 1520, 1440, 1320, 1280, 1265, 1210, 1160, 1125, 1010, 910. ^{1}H-NMR ((D_6)DMSO): 3.85 (*s*, MeO); 5.04 (*s*, H–N(6)); 6.68 (*s*, H–C(3)); 6.86 (*s*, H–C(8)); 6.93 (*s*, H–C(5)); 11.96 (*s*, H–N(1)). Anal. calc. for $C_{11}H_9F_3N_2O_2$: C 51.17, H 3.51, N 10.85; found: C 50.89, H 3.32, N 10.41.

N-*[1,2-Dihydro-7-methoxy-2-oxo-4-(trifluoromethyl)quinolin-6-yl]acetamide* (**9**). To a soln. of **8** (27.85 mg, 0.108 mmol) in glacial AcOH (0.5 ml) was added Ac_2O (150 µl). After stirring at r.t. for 1 h, the solvent was removed under reduced pressure, and the residue was purified by dry-column FC (*LiChroprep Si60*, *Merck*; toluene/acetone 1:1): 30.77 mg (95%) of **9**. M.p. 295° (dec.; toluene). R_f 0.48 (acetone). IR: 3360, 2920, 1680, 1670, 1625, 1550, 1480, 1450, 1370, 1325, 1290, 1270, 1230, 1165, 1125. ^{1}H-NMR ($CDCl_3$): 2.10 (*s*, Ac); 3.90 (*s*, MeO); 6.78 (*s*, H–C(3′)); 7.00 (*s*, H–C(8′)); 8.50 (*s*, H–C(5′)); 9.35 (s, H–N(1)). Anal. calc. for $C_{13}H_{11}F_3N_2O_3$: C 52.01, H 3.69, N 9.33; found: C 52.26, H 3.75, N 9.33.

2-Methoxy-N-*methyl-4-nitroaniline* (**11**). NaH (1.34 g, 44.7 mmol; contains 20% of heavy oil) was added to a soln. of **10** (3.0 g, 17.8 mmol) in anh. THF (25 ml). While heating under reflux, dimethyl sulfate (6.45 g, 51 mmol) was added dropwise, and the soln. was refluxed for 8 h. Then, MeOH (5 ml) and NaOH (5 g) in H_2O (10 ml) were added, and heating was continued for 1 h. After cooling, the soln. was extracted with CH_2Cl_2 (3 × 70 ml). Then, Ac_2O was added, and the soln. was kept for 1 h at r.t. and evaporated. The residue was purified by dry-column FC (*J. T. Baker* SiO_2 (40 µm); toluene/acetone 7:1): 1.56 g (48%) of **11**. M.p. 103° (toluene; lit. 101–102° [24]). R_f 0.77 (toluene/acetone 3:1). IR: 3430, 1600, 1540, 1490, 1380, 1340, 1290. ^{1}H-NMR ((D_6)DMSO): 2.85 (*d*, MeN); 3.93 (*s*, MeO); 6.55 (*d*, H–C(6)); 6.72 (*q*, NH); 7.55 (*d*, H–C(3)); 7.87 (*dd*, H–C(5)). Anal. calc. for $C_8H_{10}N_2O_3$: C 52.74, H 5.53, N 15.38; found: C 52.98, H 5.50, N 15.38.

2-Methoxy-4-nitro-N-*(prop-2-enyl)aniline* (**12**). NaH (0.40 g, 13.4 mmol; contains 20% of heavy oil) was added to a soln. of **10** (3.0 g, 17.8 mmol) in anh. THF (25 ml). While heating under reflux, allyl bromide (2.4 g, 17.8 mmol) was added dropwise, and the soln. was refluxed for 20 h. After cooling, the NaBr salt was filtered off. The soln. was evaporated, and the residue was purified by dry-column FC (*J. T. Baker* SiO_2 (40 µm); toluene): 3.44 g (93%) of **12**. M.p. 60° (toluene). R_f 0.47 (toluene). IR: 3430, 1590, 1535, 1490, 1465, 1440, 1320, 1285. ^{1}H-NMR ((D_6)DMSO): 3.90 (*t*, CH_2N); 3.92 (*s*, MeO); 5.20 (*t*, H–N(1)); 5.22 (*d*, H–C(3′)); 5.90 (*m*, H–C(2′)); 6.50 (*d*, H–C(6)); 7.63 (*d*, H–C(3)); 7.89 (*dd*, H–C(5)). Anal. calc. for $C_{10}H_{12}N_2O_3$: C 57.69, H 5.81, N 13.45; found: C 58.09, H 5.97, N 13.25.

2-Methoxy-N,N-*dimethyl-4-nitroaniline* (**13**). NaH (0.80 g, 26.7 mmol; contains 20% of heavy oil) was added to a soln. of **10** (1.5 g, 8.92 mmol) in anh. THF (20 ml). While heating under reflux, MeI (4.0 g, 51 mmol) was added dropwise, and the soln. was refluxed for 8 h. The mixture was evaporated, the resulting residue was washed with H_2O, dissolved in Ac_2O (10 ml), and refluxed for 2 h. Excess Ac_2O was removed, and the product was purified by dry-column FC (*J. T. Baker* SiO_2 (40 µm); toluene): 1.05 g (60%) of **13**. M.p. 97° (toluene; lit. 99–100° [25]). R_f 0.84 (toluene/acetone 3:1). IR: 2900, 2800, 1590, 1490, 1330, 1275, 1240. ^{1}H-NMR ((D_6)DMSO): 2.95 (*d*, Me_2N); 3.93 (*s*, MeO); 6.90 (*d*, H–C(6)); 7.67 (*d*, H–C(3)); 7.83 (*dd*, H–C(5)). Anal. calc. for $C_9H_{12}N_2O_3$: C 55.09, H 6.16, N 14.28; found: C 56.60, H 6.44, N 14.05.

2-Methoxy-N^1-*methylbenzene-1,4-diamine* (**14**). A soln. of **11** (0.40 g, 2.20 mmol) and Sn^0 (0.60 g, 5.06 mmol; granulate form) in MeOH (10 ml) was heated under reflux. Then, conc. HCl (5 ml) was added dropwise, whereupon a vigorous reaction set in. After 1 h, the cooled soln. was neutralized with aq. NaOH soln. (12 ml) and separated from the precipitated $Sn(OH)_2$. The soln. was extracted with Et_2O (3 × 50 ml), the ether layer was dried ($MgSO_4$), filtered, and evaporated: 0.29 g (87%) of **14**. M.p. 69° (MeOH/H_2O; lit. 67–69° [26]). R_f 0.27 (toluene/acetone 3:1). IR: 3360, 3240, 2870, 2810, 1590, 1510, 1450, 1410, 1350, 1300, 1275, 1235, 1200,

1155, 1030, 945, 840, 800. ^{1}H-NMR ($CDCl_3$): 2.80 (*s*, MeN); 3.43 (*s*, H–N(1), 2 H–N(4)); 3.80 (*s*, MeO); 6.27 (*d*, H–C(3)); 6.30 (*d*, H–C(5)); 6.48 (*dd*, H–C(6)). Anal. calc. for $C_8H_{12}N_2O$: C 63.13, H 7.95, N 18.41; found: C 60.17, H 7.84, N 17.35.

*2-Methoxy-*N^1*-(prop-2-enyl)benzene-1,4-diamine* (**15**). A soln. of **12** (1.44 g, 6.92 mmol) and Sn^0 (2.20 g, 18.5 mmol; granulate form) in MeOH (15 ml) was heated under reflux. Then, conc. HCl (10 ml) was added dropwise, whereupon a vigorous reaction set in. After 30 min, the soln. was coolded, neutralized with aq. NaOH soln. (25 ml), separated from the precipitated $Sn(OH)_2$, and extracted with Et_2O (3 × 50 ml). The ether phase was dried ($MgSO_4$), filtered, and evaporated: 1.10 g (89%) of **15**. Oil. R_f 0.37 (toluene/acetone 3 : 1). IR: 3400, 3330, 2930, 2830, 1595, 1510, 1455, 1420, 1305, 1280, 1230, 1200, 1165, 1140, 1030, 995, 945, 920, 830. ^{1}H-NMR ($CDCl_3$): 3.50 (*s*, H–N(1), 2 H–N(4)); 3.70 (*t*, CH_2N); 3.75 (*s*, MeO); 5.20 (*dq*, H–C(3′)); 5.95 (*m*, H–C(2′)); 6.22 (*d*, H–C(5)); 6.25 (*d*, H–C(3)); 6.45 (*d*, H–C(6)). Anal. calc. for $C_{10}H_{14}N_2O$: C 67.39, H 7.92, N 15.72; found: C 66.88, H 8.11, N 15.70.

*2-Methoxy-*N^1,N^1*-dimethylbenzene-1,4-diamine* (**16**). A soln. of **13** (0.63 g, 3.21 mmol) and Sn^0 (0.80 g, 6.75 mmol; granulate form) in MeOH (10 ml) was heated under reflux. Then, conc. HCl (8 ml) was added dropwise, whereupon a vigorous reaction set in. After 1 h, the soln. was cooled and neutralized with aq. NaOH soln. (20 ml). The precipitated $Sn(OH)_2$ was separated, the soln. was extracted with Et_2O (3 × 50 ml), the ether phase was dried ($MgSO_4$), and evaporated: 0.39 g (73%) of **16**. M.p. 88° (MeOH/H_2O). R_f 0.19 (toluene/acetone 3 : 1). IR: 3400, 3300, 3200, 2930, 2670, 1610, 1510, 1440, 1325, 1300, 1270, 1205, 1180, 1035, 935, 835, 810, 730. ^{1}H-NMR ($CDCl_3$): 2.68 (*s*, Me_2N); 3.50 (*s*, 2 H–N(4)); 3.80 (*s*, MeO); 6.23 (*dd*, H–C(5)); 6.25 (*d*, H–C(3)); 6.78 (*dd*, H–C(6)). Anal. calc. for $C_9H_{14}N_2O$: C 65.03, H 8.49, N 16.85; found: C 64.39, H 8.77, N 16.26.

*7-Methoxy-6-(methylamino)-4-(trifluoromethyl)quinolin-2(1*H*)-one* (**17**). Ethyl 4,4,4-trifluoro-2-oxobutanoate (500 mg, 2.71 mmol) and xylene (3 ml) were heated in an open flask to 130°. Then, **14** (220 mg, 1.45 mmol) was added slowly, and heating was continued for 30 min. After evaporation under reduced pressure, conc. H_2SO_4 (2 ml) was added, and the mixture was heated to 90° for 1 h. Then, the mixture was cooled, diluted with H_2O (5 ml), and neutralized with aq. NH_3 soln. The resulting yellow precipitate was recrystallized from toluene: 160 mg (41%) of **17**. M.p. 255° (dec.; toluene). R_f 0.23 (toluene/acetone 1 : 1). IR: 3460, 2920, 2820, 1660, 1625, 1530, 1475, 1455, 1425, 1360, 1320, 1290, 1275, 1210, 1160, 1145, 1120, 1015, 910, 875. ^{1}H-NMR ($CDCl_3$): 2.85 (*d*, MeN); 3.94 (*s*, MeO); 4.75 (*d*, H–N(6)); 6.63 (*s*, H–C(5)); 6.72 (*s*, H–C(3)); 6.89 (*s*, H–C(8)); 11.90 (*s*, H–N(1)). Anal. calc. for $C_{12}H_{11}F_3N_2O_2$: C 52.95, H 4.07, N 10.29; found: C 52.78, H 4.14, N 10.13.

*7-Methoxy-6-[(prop-2-enyl)amino]-4-(trifluoromethyl)quinolin-2(1*H*)-one* (**18**). Isopropyl 4,4,4-trifluoro-2-oxobutanoate (1.2 g, 6.06 mmol) and xylene (4 ml) were heated in an open flask to 130°. Then, **15** (0.61 g, 3.45 mmol) was added slowly, and heating was continued for 30 min. The solvent was removed under reduced pressure, polyphosphoric acid (H_3PO_4, 10 g) was added, and the mixtrue was heated to 100° for 90 min. Then, the mixture was cooled, diluted with H_2O (30 ml), and neutralized with aq. NH_3 soln. The resulting yellow precipitate was filtered off, washed with H_2O, and dried (450 mg crude product). Recrystallization from toluene afforded 340 mg (33%) of **18**. M.p. 270° (toluene). R_f 0.32 (toluene/acetone 1 : 1). IR: 3440, 2920, 2830, 1670, 1625, 1530, 1450, 1440, 1365, 1325, 1270, 1240, 1210, 1165, 1145, 1125, 1015, 925, 875. ^{1}H-NMR ($CDCl_3$): 3.83 (*d*, CH_2N); 4.02 (*s*, MeO); 4.52 (*s*, H–N(6)); 5.28 (*dd*, 2 H–C(3′)); 5.95 (*m*, H–C(2′)); 6.83 (*s*, H–C(5)); 6.86 (*s*, H–C(8)); 6.93 (*s*, H–C(8)); 13.40 (*s*, H–N(1)). Anal. calc. for $C_{14}H_{13}F_3N_2O_2$: C 56.38, H 4.39, N 9.39; found: C 56.32, H 4.24, N 9.23.

*6-(Dimethylamino)-7-methoxy-4-(trifluoromethyl)quinolin-2(1*H*)-one* (**19**).

Ethyl 4,4,4-trifluoro-2-oxobutanoate (500 mg, 2.71 mmol) and xylene (3 ml) were heated in an open flask to 130°. Then, **16** (260 mg, 1.56 mmol) was added slowly, and heating was continued for 30 min. The solvent was removed under reduced pressure, conc. H_2SO_4 (2 ml) was added, and the mixture was heated to 80–85° for 1 h. Then, the mixture was cooled down, diluted with H_2O (5 ml), and neutralized with aq. NH_3 soln. The resulting yellow precipitate was recrystallized from toluene: 260 mg (58%) of **19**. M.p. 238° (dec.; toluene). R_f 0.37 (toluene/acetone 1 : 1). IR: 2950, 2830, 2780, 1680, 1620, 1560, 1515, 1475, 1445, 1430, 1400, 1360, 1330, 1315, 1275, 1220, 1175, 1160, 1110, 1010, 950. ^{1}H-NMR ($CDCl_3$): 2.82 (*s*, Me_2N); 4.04 (*s*, MeO); 6.88 (s, H–C(8)); 6.93 (*s*, H–C(3)); 7.25 (*s*, H–C(5)); 12.95 (*s*, H–N(1)). Anal. calc. for $C_{13}H_{13}F_3N_2O_2$: C 54.55, H 4.58, N 9.79; found: C 53.81, H 4.45, N 9.73.

6-Nitroquinoxaline (**21**). To a mixture of 40% oxalaldehyde (5 ml, 43.6 mmol) in MeCN (50 ml) was added *4-nitrobenzene-1,2-diamine* (**20**; 4.0 g, 26.1 mmol) at 50° over a period of 1 h. Stirring was continued at this temp. for 15 h. Then, the mixture was cooled down and diluted with H_2O (150 ml), affording crude **21** (4.11 g, 90%) as a brown precipitate, which was directly used without further purification for the synthesis of **22**. M.p. 178°

(EtOH). IR: 3090, 3060, 1615, 1585, 1545, 1520, 1490, 1370, 1350, 1300, 1190. ^{1}H-NMR ($CDCl_3$): 8.30 (*d*, CH); 8.57 (*dd*, CH); 9.03 (*d*, CH); 9.04 (*d*, CH); 9.05 (*d*, CH).

1,4-Diethyl-1,2,3,4-tetrahydro-6-nitroquinoxaline (**22**). Crude **21** (2.60 g, 14.8 mmol) and $NaBH_4$ (5.62 g, 148 mmol) were placed in dioxane (40 ml), and AcOH (25 ml, 0.44 mol) was slowly added under stirring at r.t. After 1 h at r.t., the mixture was heated to 90°. To ensure complete reaction, more $NaBH_4$ (5.62 g, 148 mmol) was added to the hot mixture over a period of 4 h. After altogether 15 h at 90°, the product was extracted with CH_2Cl_2 and purified by dry-column FC (toluene/acetone mixtures of increasing polarity): 2.90 g (83%) of **22**. M.p. 59°. IR: 2972, 2931, 2873, 1576, 1530, 1494, 1372, 1300. ^{1}H-NMR ($CDCl_3$): 1.207 (*t*, Me); 1.213 (*t*, Me); 3.29 (*t*, CH_2); 3.37 (*q*, CH_2); 3.44 (*q*, CH_2); 3.51 (*t*, CH_2); 6.43 (*d*, arom. H); 7.38 (*d*, arom. H); 7.66 (*dd*, arom. H).

*1,4-Diethyl-1,3,4,6-tetrahydro-9-(trifluoromethyl)pyrido[2,3-g]quinoxalin-7(2*H*)-one* (**23b**). Compound **22** (620 mg, 2.64 mmol) in anh. EtOH (15 ml) was reduced by shaking with H_2 (40 psi) at 20° for 20 h in the presence of 10% Pd/C. The catalyst was removed, the mixture was concentrated, and the air-sensitive intermediate (6-amino-1,4-diethyl-1,2,3,4-tetrahydroquinoxaline) was reacted with isopropyl 4,4,4-trifluoro-2-oxobutanoate (790 mg, 4 mmol) in the presence of anh. $ZnCl_2$ (550 mg, 4 mmol) at 180° for 15 min. Workup by dry-column FC (SiO_2; AcOEt) afforded 630 mg (73%) of **23**. M.p. 255° (CH_2Cl_2). IR: 2950, 1669, 1528, 1447, 1341, 1255,1159, 1125. ^{1}H-NMR ($CDCl_3$): 1.20 (*t*, Me); 1.23 (*t*, Me); 3.28 (*t*, CH_2); 3.36 (*q*, CH_2); 3.44 (*q*, CH_2); 3.49 (*t*, CH_2); 6.43 (*s*, arom. H); 6.39 (*s*, arom. H); 6.75 (*s*, arom .H); 12.01 (*s*, NH). Anal. calc. for $C_{16}H_{18}F_3N_3O$: C 59.07, H 5.58, N 12.92; found: C 59.21, H 5.65, N 12.80.

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