Highly Selective and Efficient Synthesis of 7-Aminoquinolines and Their Applications as Golgi-Localized Probes

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S Supporting Information

ABSTRACT: Quinoline derivatives have extensively been used for both pharmaceutical agents and bioimaging. However, typical synthesis of quinoline derivatives is generally through strong acid/base-catalyzed or metal-catalyzed methods at high temperatures. Here we report a catalyst-free synthesis of 2,4-disubstituted 7-aminoquinolines with high selectivity and good yields via the introduction of a trifluoromethyl group. It is discovered that quinolines containing both amino and trifluoromethyl groups exhibit strong intramolecular charge-transfer fluorescence with large Stokes shifts. We further applied the obtained quinolines to live-cell imaging and found that some of the derivatives can target specifically Golgi apparatus in various cell lines (HeLa, U2OS, and 4T1 cells) in vitro and the colocalization with commercial Golgi marker is retained during the mitosis in HeLa cells. Moreover, the quinoline dyes can also be used for Golgi apparatus imaging with two-photon fluorescence microscopy. These results provide new insights into developing low cost Golgi-localized probes.

KEYWORDS: Quinoline, selective synthesis, intramolecular charge transfer, fluorescence, cell imaging

Quinolines and their derivatives play a crucial role in organic chemistry due to the applications in pharmaceuticals as well as advanced functional materials.^{1–4} As the important “star molecules” in various research areas, quinolines continued to receive extensive research interests in the past few years, particularly as the core scaffold to construct medicine molecules^{5–8} and fluorescent probes for sensing.^{9–13} Given the importance of the quinoline scaffold in the fields of both pharmaceutical and organic chemistry, synthesis of quinoline derivatives has received tremendous attention since Skrap first reported the classical synthetic method of quinoline in 1880.¹⁴ Over the past few decades, numerous methods based on various mechanisms, including Conrad–Limpach–Knorr,¹⁵ Friedländer,¹⁶ Doebner–von Miller,¹⁷ Pfitzinger,¹⁸ or Combes,¹⁹ have been developed for the preparation of substituted quinolones. However, multiple synthetic steps and harsh reaction conditions, such as high temperatures, strong base, acid or metal catalysts, still limit the applications of these strategies. Therefore, direct catalyst-free approaches with good yields remain highly valuable to broaden the application of quinoline derivatives.

As one of the common cellular organelles, Golgi apparatus is the major collecting, processing, and dispatching station of proteins to be modified and delivered for secretion.²⁰ Since

involved in such vital intracellular activities, disruption of Golgi apparatus functions could cause many organ lesions such as eye, kidney, and liver diseases.²¹ Thus, it is of great significance to develop specialized probes to mark Golgi apparatus. Considering most commercial Golgi markers generally are difficult to be synthesized with complicated structures or high cost,^{22–24} the development of Golgi-localized small molecule probes has still remained challenging. The application of quinoline derivatives as cell organelle probes is rarely explored, even though it has been widely applied to construct medicine molecules and analyte probes. Moreover, quinoline primarily fluoresces in the near UV region, it is desirable to shift its absorption and emission signals to longer wavelengths without significantly extending the molecular size for biosensing and bioimaging. In this context, charge-transfer state could be used as an effective strategy to mediate excited states.^{25,26} As a strongly electron-withdrawing group, trifluoromethyl group has been used to form charge-transfer states with electron-donating groups.^{27–29} Meanwhile, biological and medicinal studies have

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demonstrated that fluorine-containing compounds also exhibit enhanced biological properties.^{30–32}

Considering both feasible synthetic routines and biological applications of quinolines, we propose here to conduct a catalyst-free reaction of *m*-phenylenediamine with unsymmetric 1,3-diketones containing a trifluoromethyl group to synthesize various substituted 7-aminoquinolines as novel fluorophors in good yields. Introduction of such a trifluoromethyl group avoids the use of concentrated acid to promote the condensation as well as the subsequent treatment with excess amount of base to liberate the quinoline as previously reported.³³ And the strongly electron-withdrawing trifluoromethyl group also potentially enhances intramolecular charge transfer (ICT) state of the 7-aminoquinolines between the strongly electron-donating amine group and the trifluoromethyl group, thus shifting the absorption and emission of the compounds to the longer wavelengths in polar media.

We first tested the reaction of *m*-phenylenediamine with 4,4,4-trifluoro-1-phenylbutane-1,3-dione. As shown in Scheme 1, after a chloroform solution of the two compounds were

Scheme 1. Syntheses of 7-Aminoquinolines

heated at reflux for ~10 h, rotary evaporation of the solvent directly led to light green needle crystals of the product in 88% yield. No strong acid or other catalyst was needed to promote this reaction. Surprisingly, this reaction was found to be able to proceed in a solvent-free solid state! The two starting reactants were thoroughly ground in a mortar, and the resulted pale mixture turned light green overnight at room temperature in the air. ¹HNMR spectroscopic analyses confirm the only product structure of **1a**, avoiding the formation of regioisomeric products that one would expect for the reaction of *m*-phenylenediamine with unsymmetric 1,3-diketones. Here, we propose the reaction routine in Scheme 2: the first step is the nucleophilic addition (NA) between one amine group of *m*-phenylenediamine and the ketone group adjacent to trifluoromethyl group, due to its strong electronegativity. Then a second condensation of the other ketone group with the aromatic ring at 6-position, not 2-position, follows, contributing to the octet rule, to form the final single product **1a**. Therefore, using such trifluoromethyl substituted 1,3-diketones has directed a highly selective and efficient condensation to form the 4-CF₃-substituted 7-aminoquinoline as a single product.

Scheme 2. Proposed Formation Mechanism of 7-Aminoquinolines

In a similar way, we also conducted the reaction with various substituents on the unsymmetric trifluoromethylated 1,3-diketones to test the versatility of the method to introduce a trifluoromethyl group. Compounds **1b–1d** were successfully obtained from the corresponding unsymmetric 1,3-diketones in good yields, demonstrating the strategy could be widely applied. Moreover, when *m*-phenylenediamine was reacted with hexafluoroacetylacetone, the reaction condition can be so mild that the product **1d** could even be produced in water at room temperature (Figure S1), which indicates that the two trifluoromethyl groups further accelerate the reaction.

We then studied the fluorescence ICT properties of the 2,4-disubstituted 7-aminoquinolines in various solvents. For comparison, we prepared 7-methoxyquinoline **2** with a methoxy group that is less electron-donating than the amine group and 7-amino-2,4-dimethylquinoline **ADMQ** with two methyl groups that are less electron-withdrawing than the trifluoromethyl group, and compared their optical properties with the new quinolines. A summary of the optical characterizations of compounds **1a–d**, **2**, and **ADMQ** is presented in Table 1. The absorption and emission spectra are also provided (Figures 1 and S2–S7), along with photos showing the solvatochromic fluorescent emissions (Figures S8–S13). In general, the trifluoromethyl-substituted 7-aminoquinolines (**1a–1d**) show rather strong absorption in the near UV to blue light region. Absorption maxima exhibit gradual bathochromic shifts as the solvent polarity increases, e.g., $\lambda_{\text{max}} = 365\text{--}368\text{ nm}$ in *n*-hexane and $\lambda_{\text{max}} = 389\text{--}399\text{ nm}$ in methanol. The visual emission color changes from violet in *n*-hexane ($\lambda_{\text{em}} = 407\text{--}435\text{ nm}$) to greenish yellow ($\lambda_{\text{em}} = 507\text{--}537\text{ nm}$) in MeOH, indicating increased excited-state dipole moments of these molecules. Presumably this is due to an ICT process from the $-\text{NH}_2$ lone pair to the vicinity of the electron-withdrawing $-\text{CF}_3$ group. As a result, when $-\text{NH}_2$ is replaced with a less powerful electron-donating $-\text{OCH}_3$ group, or the strong electron-withdrawing group $-\text{CF}_3$ with an electron-donating $-\text{CH}_3$ group, the quinoline compounds **2** and **ADMQ** emit in the violet region in all the solvents ($<420\text{ nm}$), suggesting that the lowest transition consists of more $\pi\text{--}\pi^*$. Time-correlated fluorescence lifetimes were also measured in different solutions (Table 1). With increasing solvent polarity, fluorescence lifetimes of the 7-aminoquinolines first lengthen (e.g., **1d**: 4.96 to 20.0 ns from *n*-hexane to ethyl acetate) in moderately polar solvents but start to shorten in strongly polar solvents (e.g., **1d**: 7.49 ns in methanol). The trend is typical of ICT compounds discussed in a previous publication.³⁴ Briefly speaking, the initially lengthened lifetimes

Table 1. Optical Properties of Quinoline Compounds 1a–1d, 2, and ADMQ in Different Solutions

solvent ^a	A	B	C	D	E	F	G	H
ϵ^b	1.88	2.38	4.81	6.02	7.58	8.93	20.56	32.66
1a $\lambda_{\max}$ (nm) ^c	368	375	371	384	389	373	387	389
λ_{em} (nm) ^d	407	442	468	472	473	449	483	507
τ_F (ns) ^e	2.89	4.56	5.82	7.22	8.04	3.63	8.93	7.84
1b $\lambda_{\max}$ (nm)	367	375	372	387	391	374	389	392
λ_{em} (nm)	409	452	469	477	480	446	487	513
τ_F (ns)	3.89	5.17	4.55	6.13	6.66	4.30	7.01	6.72
1c $\lambda_{\max}$ (nm)	365	374	372	382	387	373	386	391
λ_{em} (nm)	435	475	500	503	512	475	517	537
τ_F (ns)	4.24	12.9	13.7	15.6	15.9	12.2	14.7	5.50
1d $\lambda_{\max}$ (nm)	368	383	379	393	397	380	396	399
λ_{em} (nm)	413	461	484	489	495	464	501	527
τ_F (ns)	4.96	15.7	17.5	19.5	20.0	16.7	19.7	7.49
2 $\lambda_{\max}$ (nm)	336	341	341	341	342	341	342	341
λ_{em} (nm)	376	398	392	402	402	396	406	417
τ_F (ns)	0.68	3.97	2.25	4.18	4.16	2.57	5.19	7.58
ADMQ $\lambda_{\max}$	339	344	350	347	344	343	349	351
λ_{em} (nm)	374	393	407	401	398	390	408	429
τ_F (ns)	0.02	3.73	6.08	4.55	2.10	2.88	5.28	0.17

^aA, *n*-hexane; B, toluene; C, chloroform; D, ethyl acetate; E, tetrahydrofuran; F, dichloromethane; G, acetone; H, MeOH. ^bDielectric constant of the solvent. ^c $\lambda_{\max}$ = absorption maximum in solution. ^d λ_{em} = emission maximum in solution (excited at 365 nm). ^e τ_F = pre-exponent-weighted fluorescence lifetime.

Figure 1. Normalized absorption (solid line) and emission spectra (dashed line) of **1c**, **2**, and **ADMQ** in methanol solutions.

are due to a more forbidden ICT character in moderately polar solvents compared to a pure π – π^* transition because the origin and destination orbitals do not entirely overlap in space. Meanwhile, when ICT becomes more dominating in very polar solvents, more dramatic electron redistribution between the donor and acceptor moieties in the excited state can result in subsequent large nuclear reorganization.³⁵ The apparent emission lifetime can thus be compromised with increased thermal quenching.

In order to gain further understanding on the optical properties of these compounds, quantum chemistry calculations were performed with the Gaussian09 package. The optimized geometry and electronic structures were simulated with density function theory (DFT) at the B3LYP/6-31G level (Figure 2). The frontier orbitals of compounds **1a–1d** possess close energy levels, while the highest occupied molecular orbital (HOMO) of **2** is much lower in energy. The higher HOMOs for **1a–1d** are evidently caused by the presence of the amino group since the starting material *m*-phenylenediamine (**1**) has a comparable HOMO energy level. As shown in Figure 2, for 7-aminoquinolines **1a–1d**, the HOMOs and the

Figure 2. Calculated main origin and destination orbitals involved in the lowest singlet transition states of compounds **1** (*m*-phenylenediamine), **1a**, **1c**, and **2**. Blue and red circles represent regions with the highest electron density in the ground and in the excited states, respectively.

lowest unoccupied molecular orbitals (LUMOs) are more concentrated on the amino group and near the $-\text{CF}_3$ group, respectively, indicating a strong ICT character. For **2**, however, the overlap of the HOMO and the LUMO is significantly better and is thus more likely to exhibit a vertical π – π^* state as the lowest transition. Therefore, both the trifluoromethyl group and amino group are essential to form valid ICT states among the new quinolones.

On account of the extensive applications of quinolines in bioimaging and the substantial ICT character of these 7-aminoquinolines, we then explored their feasibilities as fluorescent cell imaging agents. All the ICTQs (intramolecular charge transfer quinolines **1a–1d**, **2** $\mu\text{g/mL}$) in buffer solutions were added to U2OS cells growing at 37 °C in a 5% CO_2 incubator. We found that **1a** and **1b** exhibited the best brightness and photostability. After 30 min, the live cells were taken under a fluorescence microscope for one-photon imaging. Surprisingly, the compounds tended to specifically locate in the peri-nuclear region of the cells, which might be

the Golgi apparatus after being internalized (Figures 3a and S14a). In order to exclude the specialty of one kind of cells, we

Figure 3. Confocal fluorescence micrographs showing stained Golgi apparatuses by **1a** (a, d, g; $\lambda_{\text{ex}} = 488$ nm; emission range 489–580 nm) and BODIPY TR Ceramide (b, e, h; $\lambda_{\text{ex}} = 633$ nm; emission range 634–740 nm), and the merged images (c, f, i). Scale bar: 10 μm .

also conducted the experiments with two other cell lines (HeLa and 4T1 cells) under the same conditions. As shown in Figure 3d, g, **1a** and **1b** (Figure S14d,g) present similar locations in the Golgi apparatus with strong green emission, which demonstrates that our quinolone dyes possess versatile cell imaging properties. IC_{50} tests were also conducted to evaluate the toxicity of **1a** and **1b** (Figure S15). The calculated IC_{50} values for **1a** and **1b** are 3.37 and 3.44, respectively; thus, the half maximal inhibitory concentrations are 2.34 and 2.72 $\mu\text{g}/\text{mL}$, respectively. Since the experimental concentration of **1a** and **1b** is 2 $\mu\text{g}/\text{mL}$ in the present work, no obvious cytotoxicity for these two dyes was noted during all of the cell culture experiments.

To investigate the cellular location specificity of **1a** and **1b**, the cells were cross-stained with BODIPY TR Ceramide, a commercial red-emissive marker for the Golgi apparatus, and examined under a Zeiss LSM 710 confocal microscope. All the images for the three cell lines exhibit a complete distribution overlap with the Pearson's correlation coefficients, R_r larger than 0.50 (Figure 3c, f, i and Figure S14c, f, i). Those high R_r values demonstrate that **1a** and **1b** exhibit excellent specificity for Golgi apparatus.³⁶ An anti-giantin antibody of Golgi apparatus was also cross-stained with **1a** and **1b** to test their specificity for Golgi apparatus in HeLa cells (Figure S16). The R_r values are 0.65 and 0.83 for **1a** and **1b**, respectively, confirming their highly target-specific Golgi apparatus properties. Further, we also examined the colocalization of our dye **1a** and BODIPY TR Ceramide during the mitosis in living HeLa cells. The imaging results of different subphases are presented in Figure 4. The R_r values for prophase, metaphase, anaphase, and telophase were found to be 0.77, 0.85, 0.63, and 0.86, respectively, showing that **1a** and BODIPY TR Ceramide still show good distribution overlap in different subphases of mitosis. We preliminarily ascribe the highly target-specific

Figure 4. Subcellular localizations in synchronously dividing HeLa cells of **1a** (a, d, g; $\lambda_{\text{ex}} = 488$ nm; emission range 489–580 nm) and BODIPY TR Ceramide (b, e, h, k; $\lambda_{\text{ex}} = 633$ nm; emission range 634–740 nm), and the merged images (c, f, i, l). Scale bar: 5 μm .

Golgi imaging in vitro of **1a** and **1b** to the basicity of pyridyl moiety, considering that the Golgi apparatus is slightly acidic (6.0–6.7).³⁷ Together, these colocalization results confirm that **1a** and **1b** have the same intracellular localization as BODIPY TR Ceramide and can be potentially used as low cost Golgi probes to replace the more costly commercial ones.

Compared to one photon UV-excitation, two-photon microscopy (TPM), which utilizes a longer wavelength excitation source, owns the advantages of negligible background signal, deeper tissue penetration depth, reduced phototoxicity, and photobleaching.³⁸ It is well-known that a strong ICT state is typically associated with two-photon absorption (TPA) characteristics, which can be beneficial for bioimaging applications.^{39,40} Given their remarkable ICT character, we also tested **1a** and **1b** for two-photon imaging capability in U2OS cells. The absorption maxima of the fluorophores are ~ 400 nm in protic solvents, indicating that the optimal TPA wavelength is in the 780–800 nm range. To our delight, despite their small sizes, both of these two dyes exhibited very strong two-photon induced emission under the 790 nm laser excitation (Figure 5). The merged images also show perfect colocalizations in the Golgi apparatus with BODIPY TR Ceramide. The R_r values are 0.63 and 0.68 for **1a** and **1b**, respectively. These initial results have demonstrated the imminent application potential of these ICTQs as both one- and two-photon fluorescence cell imaging.

In summary, we have conducted a highly selective and efficient condensation of *m*-phenylenebenzene with unsymmetric 1,3-diketones to generate 2,4-disubstituted 7-aminoquinolines, by incorporating a strongly electron-withdrawing trifluoromethyl group. The introduction of such a trifluoromethyl group avoids the use of strong acid or other catalyst and also enhances the ICT process within 7-aminoquinolines

Figure 5. Two-photon fluorescence micrographs showing stained Golgi apparatuses within U2OS cells by **1a** (a) and **1b** (d) ($\lambda_{\text{ex}} = 790$ nm; emission range 371–580 nm); one-photon fluorescence micrographs showing stained Golgi apparatuses by BODIPY TR Ceramide (b, e, $\lambda_{\text{ex}} = 633$ nm; emission range 634–740 nm); merged images showing almost perfect overlaps between the quinoline and BODIPY TR Ceramide dyes (c, f). Scale bar: 10 μm .

from the strongly electron-donating amine group and the strongly electron-withdrawing trifluoromethyl group. These novel 7-aminoquinolines show large bathochromic shift going from nonpolar solvents to highly polar solvents. Interestingly, two of the new 7-aminoquinolines appear to exhibit high specificity for the Golgi apparatus as demonstrated by colocalization experiments with a commercial Golgi apparatus marker, BODIPY TR Ceramide, in various cell lines (HeLa, U2OS, and 4T1 cells). Furthermore, the dyes have exhibited potentials in both one- and two-photon fluorescence cell imaging. These preliminary findings provide new insights into developing low cost probes and drug delivery engineering with small quinoline molecules for Golgi apparatus. Currently, we are exploring the synthesis of red-emitting ICT quinolines for more useful life science applications.

■ ASSOCIATED CONTENT

Supporting Information

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Detailed experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

ICT, intramolecular charge transfer; ADMQ, 7-amino-2,4-dimethylquinoline; ICTQs, intramolecular charge transfer quinolines; TPA, two-photon absorption; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital.

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