Syntheses and Fluorescent Properties of 2-Amino Substituted 6,7-Dimethoxy-4-(trifluoromethyl)quinolines

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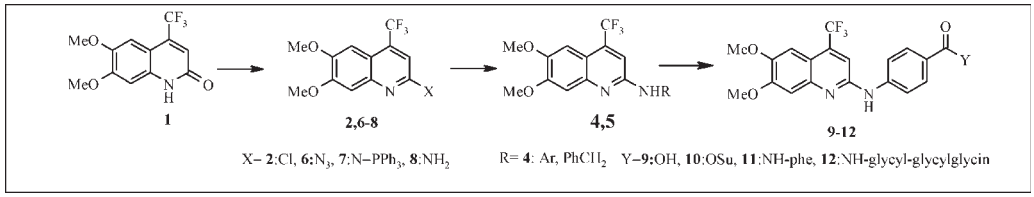

2-Amino-substituted 6,7-dimethoxy-4-trifluoromethyl-quinolines were synthesized from the 2-oxo compound **1** *via* 2-chloroquinoline **2** and aminated with anilines or benzylamine to give highly fluorescent molecules **4**, 5. 2-Aminoquinoline **8** was obtained *via* azidation of **2**–**6**, reaction to the phosphazene **7**, and hydrolysis. 4-Ethoxycarbonyl derivative **4b** is suitable for linking appropriate biomolecules. The construction of a linking group was achieved by conversion of **4b** *via* carboxylic acid **9** to the reactive *O*-succinimide ester **10**, which reacts easily with amino acids or peptides to amides **11** and **12**. The fluorescent properties were investigated and are comparable with derivatives of **1**.

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INTRODUCTION

Coumarins and carbostyrils with push-pull systems are studied extensively as fluorescent dyes [1]. However, many carbostyrils (2-quinolones) show disadvantages in luminescence properties compared with coumarins because of shorter absorption and emission wavelengths [2]. Recently, we reported a series of studies about the fluorescence properties of differently substituted carbostyrils [3] with suitable structure elements which shifted the wavelengths up to 440 nm absorption and 540 nm emission maxima. These structure elements were electron donating substituents such as amino or methoxy groups in both positions 6 and 7 and an electron deficient substituent in position 4. Such properties make this compound class also interesting for the use in sensor and electroluminescence devices [4,5]. The advantage of 3,4-dimethoxycarbostyril derivatives was shown recently in their use as fluorescence resonance energy transfer systems [6], in the study of luminescence resonance transfer techniques [7a] and incorporated in a time resolved pH sensor as covalently attached europium complex [7b].

In our earlier articles [3a–f], we described the synthesis of highly fluorescent push-pull substituted carbostyrils (type **I**) with donor substituents at positions 6 and 7 and acceptor substituents at position 4 having widely pH independent properties, large Stokes shifts and medium to high-quantum yields. The functionalization to *O*-succinimidyl (OSu) esters at N-1 and 6-O and labelling of biopolymers such as peptides and carbohydrates was carried out without any blue-shift, resulting in absorbing close to the visible range and emitting in aqueous solution at 430–450 nm, suitable for biochemistry and medicine.

After the variation of substituents at positions 4, 6, and 7, we report in this article about the investigation on the synthesis and properties of 2-aminoquinolines **III**[3g]. In contrast to type **II** structures [3b], 2-aminoquinolines **III** have a possible tautomeric 2-imino structure **IV** as potential fluorescent compounds (Scheme 1).

RESULTS AND DISCUSSION

For our study, we selected 6,7-dimethoxy-4-trifluoromethyl-2-quinolone **1** as the starting compound, with methoxy groups as the donor and a trifluoromethyl group as the acceptor substituents. The synthesis of the carbostyril ring system was achieved by cyclocondensation of 3,4-dimethoxyaniline with trifluoro-methyl-acetoacetate as described recently [3b,c]. The conversion of the 2-oxo group to the reactive 2-chloro moiety in compound **2** was achieved with phosphoryl chloride. Conventional heating required a reaction time of 12 h and produced many by-products. The application of

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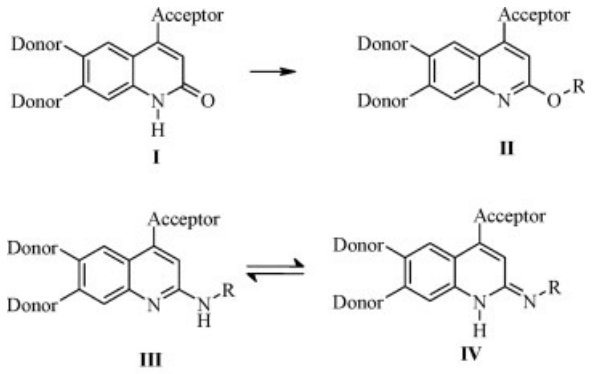
Scheme 1



microwave heating allowed the isolation of chloroquinoline **2** after 30 min with similar yields but better purity (Scheme 2).

The conversion of the 2-chloro group in **2** to a free 2-amino group was achieved in a three step reaction by exchange of the 2-chloro substituent against the 2-azido group in dimethylformamide at 80°C using Kryptofix-5 as catalyst, to give 2-azidoquinoline **6**. According to IR spectra the azide **6A** exists predominantly in its tautomeric tetrazolo structure **6T** similar as shown in many investigations [8]. The Staudinger reaction with triphenylphosphane gave the corresponding phosphazene **7**, which is hydrolyzed by acid catalysis with hydrochloric acid in water/methanol to give the free 2-aminoquinoline **8** in an overall yield of about 67%. The aminoquinoline **8**, however, did not show sufficient fluorescent properties for further applications, probably caused by the predominant tautomeric amino-structure of type **III**, so this way was not continued.

On the other hand, 2-arylamino and 2-benzyl-aminoquinolines **4a-c** and **5**, which were obtained from the 2-chloro derivative with the appropriate anilines **3a-c** or benzylamine in a one step reaction in 62–66% yield, showed good fluorescence properties (possibly deriving from the formation of a tautomeric imino structure in the state of fluorescence excitation); see Table 1. Surprisingly, the benzylamino derivative **5** showed similar fluorescence properties as the arylamino derivatives **4**, which means, that the influence of the aryl group attached to the 2-amino group (forming an azomethine-type structure as imino tautomer) has no remarkable influence on luminescence properties. However, products with substituted benzylamines were not stable enough for further investigation (Scheme 3).

Spectral assignment of **4** and **5** to an amino- or imino-structure was not possible, because differences caused by solvent influences are strong and the ^{1}H NMR signals of NH ranged between 5.2 and 10.9 ppm with chloroform as the solvent.

Using suitable substituted derivatives such as 4-(2-quinolinylamino)benzoate **4b** (R^2 = COOEt) allowed the introduction of linker groups attached at the phenyl ring at the amino/imino-position 2. For the construction of linker groups to aminogroups of natural products, a reactive *O*-succinimide ester (OSu-ester) was planned because OSu-esters attached to heterocycles are known to be easily available, stable, and useful to link to biological samples. The synthesis was achieved by saponification of the ethyl ester group of **4b** to the free carboxylic acid **9** in ethanolic sodium hydroxide solution, and re-esterification with *N*-hydroxysuccinimide in the presence of carbodiimide, which gave the active OSu ester **10** in good yields.

The OSu ester **10** reacted smoothly under biological conditions in buffered aqueous DMSO solution below 50°C with biomolecules such as aminoacids and peptides. We synthesized two fluorescence marked

Scheme 2

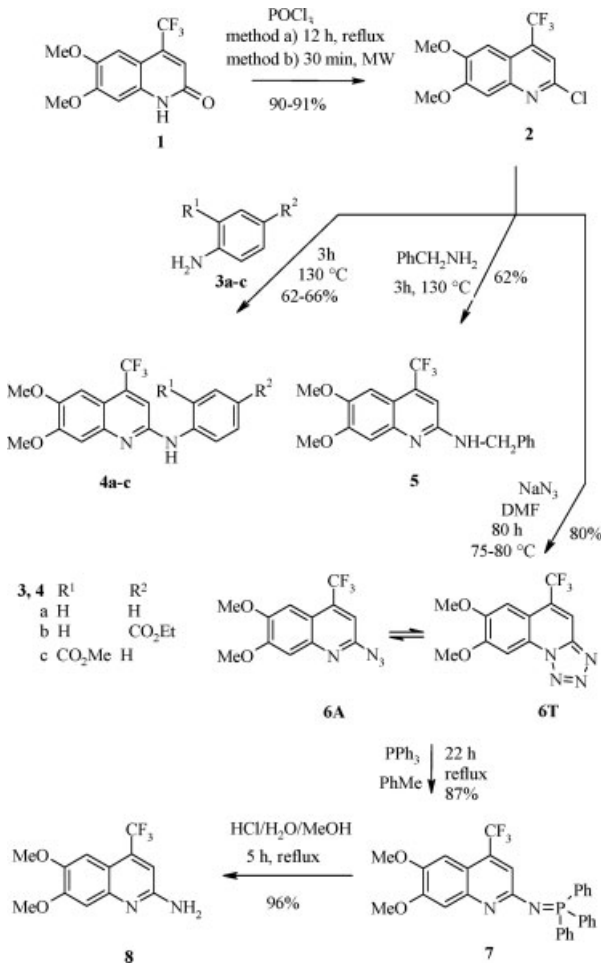


Table 1

Photophysical data for UV spectra, the electronic excitation (exc), and fluorescence (flu) of carbostyrils **4–12**.

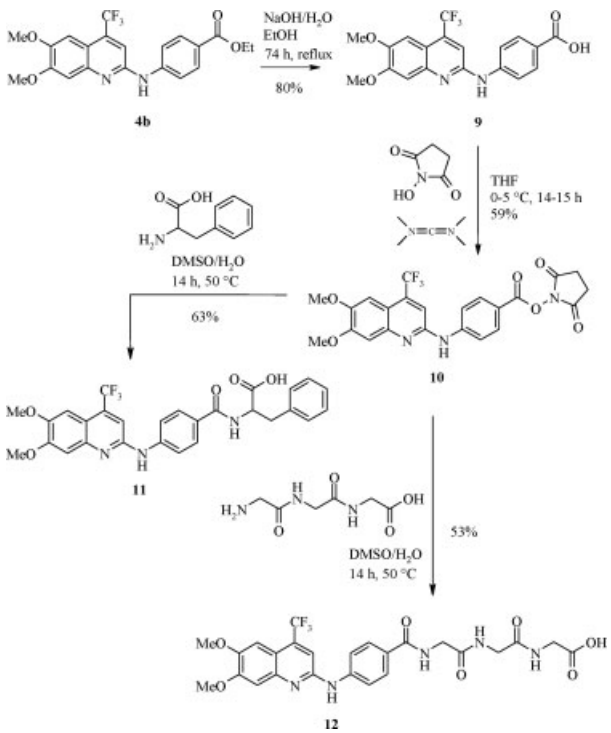
No.	UV (λ_{max})	ε	λ_{exc} [a]	λ_{flu}	Stokes shift	Φ_F
4a	384	9500	380	450	70	0.152
4b	392	13400	380	433	53	0.100
4c	398	18000	394	440	46	0.182
5	375	8600	380	440	60	0.297
9	391	10200	380	433	53	0.072
10	393	9900	380	417	37	0.100
11	393	9900	380	432	52	0.060
12	392	9000	378	433	53	0.033

Solvent: DMSO, Solvent temperatures: 25 °C; λ in nm.
[a] Wavelength of excitation.

examples, the phenylalanine derivative **11** and the glycyl-glycyl-glycin **12** linked at the amino group of the amino acid with the linker molecule.

Electronic spectra. Absorption spectra of recently synthesized 4-(trifluoromethyl)carbostyrils [3b,c] were rather similar with $\lambda_{max} \sim 350–380$ nm in DMSO or water; there was also no great difference between NH- and N-alkyl derivatives, which means, that in all cases the tautomeric amide group (N1-C2) of structure **I** is predominant. In the 2-amino/imino series (structures **III/IV**) comparable absorption wavelengths were obtained (Table 1): The UV wavelengths are slightly higher (375–398 nm), the Stokes' shifts are in the region 50–70 nm. However, the fluorescence quantum yields, which were high for any N1-alkylated analyte of type **I** [3b,c], decreased from $\Phi_F = 0.1$ in the ester **4b** to $\Phi_F = 0.03–0.06$ in linked 2-amino analogues **11**,**12**. Ester **4c** shows a higher ε value because of the asymmetric structure, which causes changes in dipole properties.

Scheme 3



CONCLUSION

We could show that the conversion of the carbostyril **1** to its 2-aza analogues **4** and **5** can be achieved in good yields to obtain subsequently OSu ester **10** with comparable fluorescence spectral properties, however, with too low-quantum yield values for the use in analytical tasks. From the 6,7-dimethoxy-4-(trifluoro-methyl)-carbostyril series until now investigated, only N1-alkylated carbostyrils of structure type **I** [3c] gave quantum yields high enough for this purpose.

EXPERIMENTAL

Melting points were determined using a Stuart SMP3 Melting Point Apparatus in open capillary tubes. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX 360 instrument (360 or 90 MHz) or on a Bruker Avance DRX 500 instrument (500 or 125 MHz). Chemical shifts are given in ppm (δ) from the internal TMS standard. IR spectra were recorded using a Mattson Galaxy Series FTIR 7020 instrument with potassium bromide discs. Elemental analyses were performed at the Microanalytical Laboratory of the University of Vienna, Austria. Mass spectra were obtained from a HP 1100 LC/MSD mass spectral instrument (positive or negative APCI ion source, 50–200 V, nitrogen). UV/Vis spectra were recorded on a Shimadzu UV/Vis scanning spectrophotometer UV-2101 PC; concentration: 0.01 mg/mL. Excitation and emission spectra were recorded using a Shimadzu RF-5001 PC spectrofluorometer, concentration: 0.001 mg/mL. Determination of quantum yields: emission signals were set in relation to the known signal of quinine sulfate at pH 1. Analytical HPLC was performed on a Shimadzu LC 20 system equipped with a diode array detector (215 and 254 nm) on a Pathfinder AS reversed phase (4.6150 mm, 5 μm) column, running an acetonitrile/water gradient (30–100% acetonitrile).

Microwave-assisted syntheses were carried out in an Emrys Synthesizer at 2450 MHz (Biotage AB, Uppsala). All reactions were monitored by thin layer chromatography (TLC) on 0.2-mm silica gel F-254 (Merck) plates using UV light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures. All optical measurements were performed using analytical grade solvents.

2-Chloro-6,7-dimethoxy-4-(trifluoromethyl)quinoline (2)

Method A. A mixture of 6,7-dimethoxy-4-(trifluoromethyl)-quinolone (**1**) [3c] (2.73 g, 10 mmol) and phosphoryl chloride (7.60 g, 50 mmol) was heated under reflux for 12 h. The reaction mixture was cooled to room temperature and poured onto crushed ice (250 g) and kept for 30 min. The solid obtained was filtered by suction, washed with excess of water to afford 2.65 g (91% yield) of colorless needles.

Method B. A mixture of 6,7-dimethoxy-4-(trifluoromethyl)-quinolone (**1**) (0.273 g, 1 mmol) and phosphoryl chloride (3.0 g, 20 mmol) was heated at 120°C for 30 min by microwave irradiation in a sealed tube. After cooling to room temperature, the reaction mixture was worked up as described in method A. The yield was 0.260 g (90%), colorless needles, m.p. 134–136°C (ethanol); IR: 3468 m, 2978 w, 1619 m, 1593 m cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.05 (2 s, 6H, 2 OMe), 7.29 (s, 1H, 3-H), 7.43 and 7.56 (2 s, 2H, ArH); *Anal.* Calcd. for $C_{12}H_9ClF_3NO_2$ (291.66): C, 49.42; H, 3.11; N, 4.80; Found C, 49.21; H, 2.90; N, 4.58.

6,7-Dimethoxy-*N*-phenyl-4-(trifluoromethyl)quinolin-2-amine (4a). A mixture of 2-chloroquinoline **2** (0.291 g, 1 mmol) and aniline (**4a**) (0.186 g, 2 mmol) was heated for 3 h to 130°C. The reaction mixture was cooled to room temperature, the formed solid filtered and digested with diethylether (100 mL). The ether solution was taken to dryness under reduced pressure and the oily residue purified by dry flash column chromatography [9] using toluene as the eluent. The yield was 0.230 g (66%), pale yellow needles, m.p. 147–148°C (ethanol); IR: 3438 m, 3385 s, 1630 m, 1618 m, 1599 m cm^{-1}, ^1H NMR ($CDCl_3$): δ 4.00 and 4.03 (2 s, 6H, 2 OMe), 6.92 (s, b, 1H, 2-NH), 7.11–7.17 (m, 2H, ArH), 7.21–7.27 (m, 2H, ArH), 7.38 (t, J = 7.5 Hz, 2H, ArH), 7.54 and 7.57 (2 s, 2H, ArH);*Anal.* Calcd. for $C_{18}H_{15}F_3N_2O_2$ (348.33): C, 62.07; H, 4.34; N, 8.07; Found C, 62.02; H, 4.16; N, 7.95.

Ethyl 4-{[6,7-dimethoxy-4-(trifluoromethyl)quinolin-2-yl] amino}benzoate (4b). A mixture of 2-chloroquinoline **2** (2.91 g, 10 mmol) and ethyl 4-aminobenzoate (**3b**) (3.30 g, 20 mmol) was heated for 3 h to 130°C. The reaction mixture was cooled to room temperature, the formed solid filtered by suction, washed with ethanol (100 mL), and dried. The yield was 2.85 g (65%), yellow needles, m.p. 210–211°C (ethanol); IR: 3357 s, 3215 m, 2926 m, 1682 s, 1619 m, 1602 s cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39 (t, J = 7.5 Hz, 3H, Me), 4.02 and 4.07 (2 s, 6H, 2 OMe), 4.35 (q, J = 7.1 Hz, 2H, CH_2), 6.96 (s, 1H, NH), 7.16 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.29 (s, 1H, ArH), 7.73 (d, J = 7.5 Hz, 2H, ArH), 8.07 (d, J = 7.5 Hz, 2H, ArH); MS: m/z (%) = 421 (21, M + 1), 420 (100, M^+);*Anal.* Calcd. for $C_{21}H_{19}F_3N_2O_4$ (420.39): C, 60.00; H, 4.56; N, 6.66; Found C, 59.92; H, 4.28; N, 6.65.

Methyl 2-{[6,7-dimethoxy-4-(trifluoromethyl)quinolin-2-yl]amino}benzoate (4c). A mixture of 2-chloroquinoline **2** (0.291 g, 1 mmol) and methyl anthranilate (0.302 g, 2 mmol) was heated for 3 h to 130°C. The mixture was cooled, the formed solid filtered by suction, washed with ethanol (100 mL), and dried. The yield was 0.252 g (62%), yellow needles, m.p. 188–189°C (ethanol); IR: 3266 m, 1684 s, 1601 m, 1570 w, 1536 m cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.97, 4.02, and 4.07 (3 s, 9H, 3 OMe), 6.98 (t, J = 8.3 Hz, 1H, ArH), 7.17 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.33 (s, 1H, ArH), 7.60 (t, J = 8.1 Hz, 1H, ArH), 8.07 (d, J = 8.3 Hz, 1H, ArH), 9.19 (d, J = 8.6 Hz, 1H, ArH), 10.96 (s, 1H, NH); MS: m/z (%) = 407 (20, M + 1), 406 (100, M), 375 (15), 374 (33); *Anal.* Calcd. for $C_{20}H_{17}F_3N_2O_4$ (406.36): C, 59.12; H, 4.22; N, 6.89; Found C, 58.83; H, 4.56; N, 6.54.

***N*-Benzyl-6,7-dimethoxy-4-(trifluoromethyl)quinolin-2-amine (5).** A mixture of 2-chloroquinoline **2** (0.291g, 1 mmol) and benzylamine (0.214 g, 2 mmol) was heated for 3 h to 130°C. The reaction mixture was cooled to room temperature, the formed solid filtered, dissolved in water (100 mL), and brought to pH 13 with conc. aq. sodium hydroxide solution. The aqueous solution was extracted with diethylether (3 × 30 mL), the ether solution taken to dryness under reduced pressure and the oily product purified by dry flash column chromatography [9] using toluene as eluent. The yield was 0.224 g (62%), pale yellow needles, m.p. 98–99°C (ethanol); IR: 3435 s, 3253 m, 1632 s, 1514 m cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.98 and 4.02 (2 s, 6H, 2 OMe), 4.71 (d, J = 5.8 Hz, 2H, CH_2), 5.04 (s, 1H, NH), 6.84 (s, 1H, ArH), 7.18 (s, 2H, ArH), 7.31–7.43 (m, 5H, PhH); MS: m/z (%) = 363 (25, M + 1), 362 (100, M), 361 (12, M − 1), 272 (8); *Anal.* Calcd. for $C_{19}H_{17}F_3N_2O_2$ (362.35): C, 62.98; H, 4.73; N, 7.73; Found C, 62.79; H, 4.57; N, 7.72.

7,8-Dimethoxy-5-(trifluoromethyl)tetrazolo[1,5-a]quinoline (6). A suspension of 2-chloroquinoline **2** (0.291 g, 1 mmol), sodium azide (0.260 g, 4 mmol), and Kryptofix-5 (0.01 g) in dimethylformamide (7 mL) was heated under TLC monitoring for about 80 h to 75–80°C. Then the mixture was cooled to room temperature and poured into ice/water (100 mL), the formed solid filtered by suction and washed with cold water (100 mL). The yield was 0.240 g (80%), brownish needles, m.p. 237–239°C (ethanol); IR: 1617 w, 1528 m, 1505 w cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.08 and 4.18 (2 s, 6H, OMe), 7.51 (s, 1H, ArH), 8.18 (s, 1H, ArH), 8.23 (s, 1H, ArH); MS: m/z (%) = 299 (14, M + 1), 298 (100, M), 272 (13); *Anal.* Calcd. for $C_{12}H_9F_3N_4O_2$ (298.23): C, 48.33; H, 3.04; N, 18.79; Found: C, 48.08; H, 3.01; N, 18.48.

6,7-Dimethoxy-4-(trifluoromethyl)-*N*-(triphenylphosphoranylidene)quinolin-2-amine (7). A mixture of tetrazolo[1,5-a]quinoline **6** (0.298 g, 1 mmol), and triphenylphosphane (0.524 g, 2 mmol) in toluene (8 mL) was heated under TLC monitoring for about 22 h under reflux. The solvent was removed under reduced pressure and the oily residue triturated with cyclohexane. The formed solid was filtered by suction, and washed with cyclohexane until the excess of triphenylphosphane was removed. The yield was 0.260 g (87%), brownish prisms, m.p. 183–184°C (methanol); IR: 1606 m, 1509 m cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.88 and 3.93 (2 s, 6H, 2 OMe), 6.67 (s, 1H, ArH), 7.14 (s, 1H, ArH), 7.37 (s, 1H, ArH), 7.44–7.48 (m, 6H, ArH), 7.52–7.56 (m, 3H, ArH), 7.86–7.92 (m, 6H, ArH); *Anal.* Calcd. for $C_{30}H_{24}F_3N_2O_2P$ (532.51): C, 67.67; H, 4.54; N, 5.26; Found: C, 67.94; H, 4.65; N, 5.06.

6,7-Dimethoxy-4-(trifluoromethyl)quinolin-2-amine (8). A mixture of *N*-(triphenylphosphoranylidene)quinolin-2-amine **7**

(0.532 g, 1 mmol) and conc. hydrochloric acid (7 mL) in methanol (8 mL) was heated under TLC monitoring for 5 h under reflux. The reaction mixture was cooled to room temperature, the formed solid filtered by suction and washed with excess of water until pH of 7 was reached. The yield was 0.262 g (96%), yellowish green crystals, m.p. 283–284°C (ethanol); IR: 3345 s, 3090 s, 1680 s, 1647 m, 1618 w, 1520 m cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.87 and 3.94 (2 s, 6H, OMe), 7.09 (s, 1H, ArH), 7.32 (s, 1H, ArH), 7.38 (s, 1H, ArH), 8.62 (s, b, 2H, NH_2); *Anal*. Calcd. for $C_{12}H_{11}F_3N_2O_2$ (272.23): C, 52.95; H, 4.07; N, 10.29; Found: C, 52.65; H, 3.78; N, 10.02.

4-{[6,7-Dimethoxy-4-(trifluoromethyl)quinolin-2-yl]amino} benzoic acid (9). A mixture of 4-(quinolin-2-yl)aminobenzoate **4b** (0.420 g, 1 mmol) and 1*M* aq. sodium hydroxide solution (2 mL) in ethanol (20 mL) was heated for 7 h under reflux, then the solvent was removed under reduced pressure and the residue dissolved in water (10 mL) under cooling. The mixture was acidified with conc. hydrochloric acid to pH = 1–2, the resulting precipitate filtered by suction and washed with excess of water. The yield was 0.310 g (80%), yellow prisms, m.p. 275–276° C (ethyl acetate); IR: 3457 s, 2940 w, 1677 s, 1624 w, 1600 s, 1526 s cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.87 and 3.96 (2 s, 6H, 2 OMe), 7.10 (s, 1H, ArH), 7.36 (s, 1H, ArH), 7.38 (s, 1H, ArH), 7.91 (d, J = 8.6 Hz, 2H, ArH), 8.04 (d, J = 8.6 Hz, 2H, ArH), 9.95 (s, 1H, NH), 12.54 (s, 1H, OH); MS: m/z (%) = 393 (18, M + 1), 392 (100, M), 377 (12); *Anal*. Calcd. for $C_{19}H_{15}F_3N_2O_4$ (392.34): C, 58.17; H, 3.85; N, 7.14; Found: C, 57.82; H, 3.76; N, 7.00.

1[(4-{[6,7-Dimethoxy-4-(trifluoromethyl)quinolin-2-yl]amino}benzoyl)oxy]pyrrolidine-2,5-dione (OSu-ester) (10). *N*-Hydroxysuccinimide (0.115 g, 1 mmol) was added slowly with stirring at 0°C to a solution of 4-(quinolin-2-yl)amino-benzoic acid **9** (0.392 g, 1 mmol) in dry tetrahydrofuran (20 mL). Then *N,N*-diisopropylcarbodiimide (0.125 g, 1 mmol) was added dropwise with stirring at 0–5°C which formed a yellowish-white precipitate. This mixture was stirred further at 0–5°C for 14–15 h. The solvent was removed under reduced pressure and the solid residue obtained was digested in dry tetrahydrofuran (10 mL), filtered and washed well with dry tetrahydrofuran. Then the solid was stirred in dry ethanol (50 mL) at room temperature for 30 min to remove *N,N*-diisopropylurea formed during the reaction. Suction filtration afforded 0.288 g (59%) of OSu-ester, pale yellow prisms, m.p. 268–269°C (ethanol); IR: 3435 s, 3340 s, 3212 m, 1765 s, 1723 s, 1618 w, 1598 s, 1578 w cm^{-1};^1H NMR ($CDCl_3$): δ 2.93 (s, 4H, 2 CH_2), 4.03 and 4.09 (2 s, 6H, 2 OMe), 7.22 (s, 1H, ArH), 7.25 (s, 1H, ArH), 7.33 (s, 1H, ArH), 7.77 (d, J = 8.4, 2H, ArH), 8.16 (d, J = 8.6, 2H, ArH); MS: m/z (%) = 490 (25, M + 1), 489 (100, M), 392 (10); *Anal*. Calcd. for $C_{23}H_{18}F_3N_3O_6$ (489.41): C, 56.45; H, 3.71; N, 8.59; Found: C, 56.44; H, 3.89; N, 8.30.

***N*-(4-{[6,7-Dimethoxy-4-(trifluoromethyl)quinolin-2-yl]amino}benzoyl)phenylalanine (11).** To a solution of (D,L)phenylalanine (38 mg, 0.2 mmol) in dimethyl-sulfoxide/water (9:1, 2.5 mL), a solution of OSu-ester **10** (98 mg, 0.2 mmol) in dimethylsulfoxide/water (9:1, 2.5 mL) was added dropwise at room temperature. Then aq. pH 7 buffer (0.75 mL) was added, the mixture stirred for 14 h at 50°C, poured into water (25 mL) and then acidified with conc. hydrochloric acid to pH = 1–2. A solid separated, which was filtered by suction and washed with excess of water to afford 85 mg (63%) of yellow prisms, m.p. 272–273°C (acetone); IR: 3366 w, 2933 m, 1647 w, 1625 w, 1603 s, 1575 w cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.33 and 3.41 (2 dd, J = 5.7 and 13.9 Hz, 2H, CH_2), 3.99 and 4.05 (2 s, 6H, 2 OMe), 5.09 (dd, 5.8 and 6.7 Hz, 1H, CH), 6.87 (d, J = 5.9 Hz, 1H, amide-NH), 7.18–7.24 (m, 6H, ArH), 7.30 and 7.33, (2 s, 2H, ArH), 7.37 (d, J = 8.2 Hz, 2H, ArH), 7.75 (d, J = 8.3 Hz, 2H, ArH), 10.20 (s, 1H, 2-NH); MS: m/z (%) = 541 (11, M + 2), 540 (47, M + 1), 539 (100, M), 538 (35, M − 1), 391 (14); *Anal*. Calcd. for $C_{28}H_{24}F_3N_3O_5$ (539.52): C, 62.34; H, 4.48; N, 7.79; Found C, 61.91; H, 4.37; N, 7.63.

***N*-(4-{[6,7-Dimethoxy-4-(trifluoromethyl)quinolin-2-yl]amino}benzoyl)glycylglycylglycine (12).** To a solution of glycyl-glycyl-glycine (38 mg, 0.2 mmol) in dimethyl-sulfoxide/water (9:1, 2.5 mL), a solution of OSu-ester **10** (98 mg, 0.2 mmol) in dimethylsulfoxide/water (9:1, 2.5 mL) was added dropwise at room temperature. Then aq. pH 7 buffer (0.75 mL) was added, the mixture stirred for 14 h at 50°C, poured into water (25 mL), and then acidified with conc. hydrochloric acid to pH = 1–2. A solid separated, which was filtered by suction and washed with excess of water to afford 75 mg (53%) of yellow prisms, m.p. 238–239°C (acetone); IR: 3338 s, 3306 s, 3117 m, 3088 m, 2961 w, 2925 m, 1721 s, 1662 s, 1625 w, 1605 s, 1568 w, 1531 s cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.76–3.78 (m, 4H, 2 CH_2), 3.87 (s, 3H, OMe), 3.90 (d, J = 5.4 Hz, 2H, CH_2), 3.97 (s, 3H, OMe), 7.11 (s, 1H, ArH), 7.35 and 7.39 (2 s, 2H, ArH), 7.88 (d, J = 8.6 Hz, 2H, ArH), 8.01 (d, J = 8.3 Hz, 2H, ArH), 8.17–8.24 (m, 2H, amide-NH), 8.64 (t, J = 5.3 Hz, 1H, amide-NH), 9.91 (s, 1H, 2-NH); MS: m/z (%) = 564 (14, M + 1), 563 (42, M), 507 (17), 450 (25), 449 (100), 392(85); *Anal*. Calcd. for $C_{25}H_{24}F_3N_5O_7$ (563.49): Calcd. C, 53.29; H, 4.29; N, 12.43; Found C, 53.63; H, 4.29; N, 12.56.

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