Fluorescent 6-Hydroxy- and 6,7-Dihydroxy-4-trifluoromethylcarbostyrils and Formation of O-Carboxymethylated Derivatives via O-Succinimide Esters

Georg Uray, Naresh S. Badgujar, Sona Kováčková and Wolfgang Stadlbauer*

Department of Chemistry, Organic and Bioorganic Chemistry, Karl-Franzens University of Graz
Heinrichstrasse 28, A-8010 Graz, Austria/Europe
wolfgang.stadlbauer@uni-graz.at
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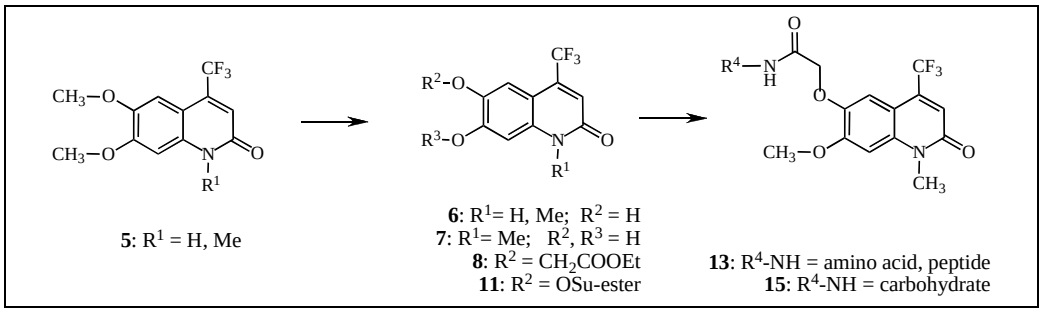

Stepwise demethylation of fluorescent 6,7-dimethoxy-3-trifluoromethylcarbostyrils **5** leads to 6-hydroxy derivatives **6** and 6,7-dihydroxyderivative **7**. Phenolate formation shifts excitation and emission maxima from 370 and 430 nm to 430 and 480 nm for the anion of **6** and as far as 500 and 580 nm for the dianion of **7**. Dependence of fluorescence quantum yield on media and polar structure, varying from 0.02 to 0.51, is discussed. O-Alkylation of **6** with alkyl bromoacetate yields esters of type **8** in good yield. Reactive succinimidoyl (OSu) esters of type **11** were prepared after saponification to acids **9.** With amino acids or their esters, peptides and aminoglucose, linking to labeled derivatives **13** or **15** could be achieved under mild conditions in slightly basic aqueous media.

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Luminescence properties of most carbostyrils (quinolin-2(1*H*)-ones) have the disadvantage of shorter absorption and emission wavelengths compared with coumarins [1]. Recently we reported systematic studies about the fluorescence properties of differently substituted carbostyrils [2] which revealed that suitable structure elements 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 makes them also interesting to be used in sensor devices utilizing the new blue laser diodes. In contrast to many other fluorescent dyestuffs, such push-pull substituted carbostyrils have the important advantage that they are highly stable against chemicals (compared with coumarins [3] or fluorescein type dyes), thermal and photochemical stress (e.g. compared with azodyes) and they are insensitive to oxygen quenching (e.g. compared with 1,10-phenanthroline complexes).

The above mentioned dyes are frequently used as fluorescent labels for natural polymers [4]. Recently we described the introduction of reactive linker groups at the N1 position of 6,7-dimethoxy-4-trifluoromethyl-carbostyrils which allowed labeling of natural substrates such as amino acids, proteins, amino-carbohydrates or amino-polysaccharides without any blueshift [5]. These compounds showed very good photophysical properties, such as an absorption maximum close to the visible ($\lambda \geq$ 370 nm), large Stokes shifts ($\lambda_F \geq$ 450 nm), sufficient high extinction coefficients (ε about 10^4) and high fluorescence quantum yields (Φ_F up to 0.5). The disadvantage of dimethoxy derivatives in terms of slightly shorter absorption and emission wavelengths compared with aminocarbostyrils ($\lambda \sim$ 440 nm absorption and $\lambda \sim$ 540 nm emission wavelengths) is counterbalanced by advantages such as largely pH-independent photophysical properties and high chemical stability.

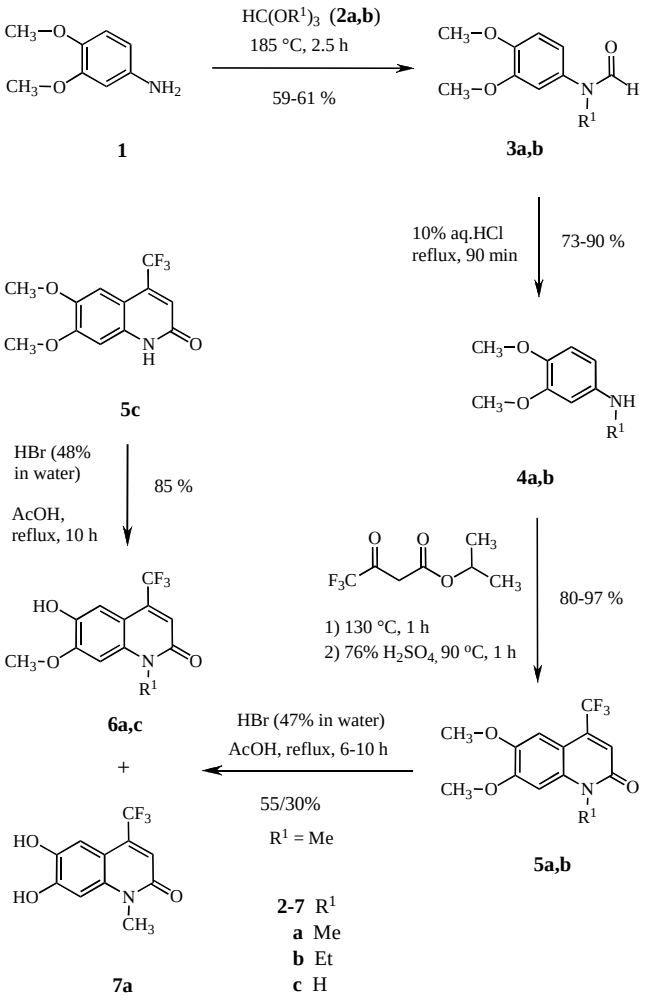
In this paper we present a strategy of the functionalization in compounds of type **5** proceeding *via* a stepwise ether cleavage of the methoxy groups in position 6 and 7. After functionalization at position 6 using α-halogen substituted carboxylates and activation as O-succinimidoyl (OSu) esters we show the possibility to label natural substrates such as amino acids and amino-carbohydrates under mild aqueous conditions.

Furthermore, the effects of variation of the electron density on the oxygens in position 6 and 7 on luminescence properties are investigated.

RESULTS AND DISCUSSION

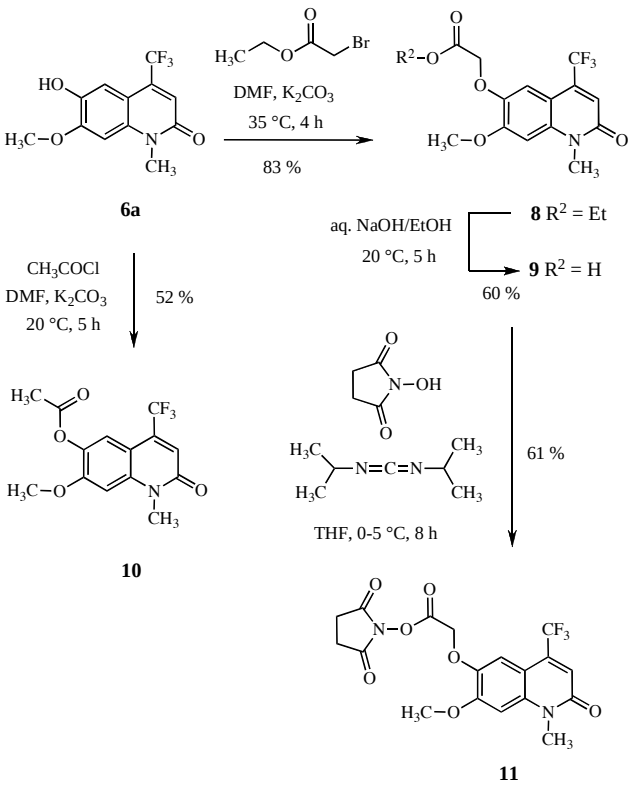
We started the synthesis of N-alkylcarbostyrils **5a,b** from dimethoxyanilines **4a,b**, which were obtained from

the commercially available 4-aminoveratrol **1** by a selective monoalkylation with the corresponding orthoformates **2** *via* a Chapman rearrangement [6]. In the first reaction step the formamides **3** were obtained, which gave on acidic hydrolysis *N*-alkyl-3,4-dimethoxyanilines **4** in good yields. This reaction sequence was performed similar to a text-book procedure [7]; other mono-alkylation approaches described in the literature did not show any advantages [8]. The reaction of alkylanilines **4** with isopropyl trifluoroacetoacetate was performed as described previously [2,5,9] and gave as the intermediates the corresponding trifluoroaceto-acetanilides. These intermediates cyclized without isolation on heating with sulfuric acid as catalyst to give mainly 6,7-dimethoxy-4-trifluoromethyl-2-quinolones **5a,b**, together with a small amount of the isomer 6,7-dimethoxy-2-trifluoromethyl-4-quinolones in a 20:1 ratio. Simple recrystallization afforded pure 2-quinolones **5a,b**.



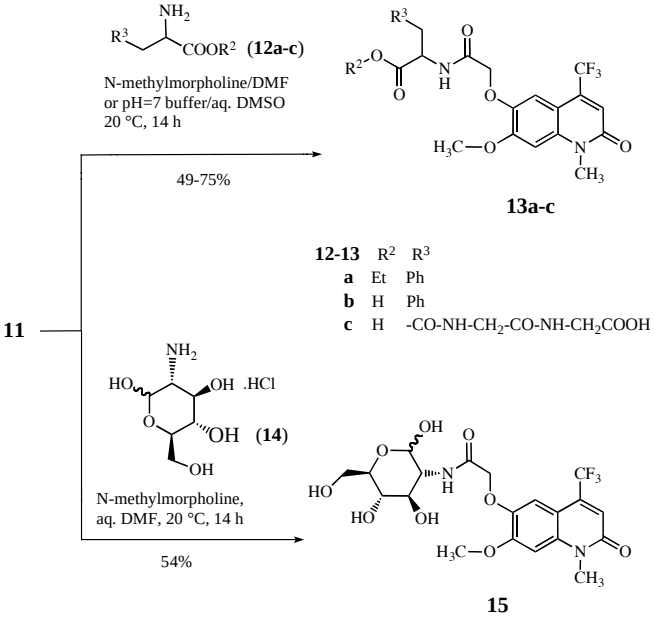
Ether cleavage of *N*-methyl-dimethoxycarbostyril **5a** with 47 % hydrobromic acid in water gave a mixture of the mono- and di-demethoxylated products **6a** and **7a** in a 5:3 ratio, which were separated by dry-flash column chromatography [10]. Similar results were obtained with the N-ethyl-derivative **5b**, however with lower yields and worse ratio of **6b**; this reaction sequence was not investigated further. Variation of the concentration of hydrobromic acid and of the reaction time did not give significantly other ratios of **6a**/**7a**, but either lower overall yields or by-products; complete di-demethoxylation of **5a** was achieved when hydroiodic acid was used as the reagent. N-Unsubstituted carbostyril **5c** [2,5] reacted mainly to the mono-demethylated product and gave **6c** in 85% yield. The position of mono-demethoxylation in compounds **6a** and **6c** was determined by NMR experiments. The HMBC experiments showed that exclusively in both reactions a regioselective 6-mono-demethylation took place.

The introduction of the linker group was started by alkylation of 6-hydroxycarbostyril **6a** with 2-bromo-acetate under basic conditions, which gave in 83% yield the desired 6-quinolinyloxy-acetate **8**. A similar reaction of the N-unsubstituted 6-hydroxycarbostyril **6c** gave a mixture of N- and O-mono- and dialkylated products and was not investigated further. To study the influence of O-acylation on fluorescence properties, 6-quinolinyl acetate **10** was prepared from 6-hydroxycarbostyril **6a** by acetylation with acetylchloride.



Next we achieved the preparation of the reactive succinimidoyl active ester **11** (OSu ester), which has in

aqueous solution the advantage of both stability and high reactivity with amino groups [11]. Hydrolysis of 6-quinolinyloxy-acetate **8** in aqueous-ethanolic sodium hydroxide gave in good yields 6-quinolinyloxy-acetic acid **9** which yielded the desired compound **11** after reaction with N-hydroxysuccinimide/diisopropylcarbodiimide in dry tetrahydrofurane.



Linkage of fluorescent dyes with biopolymers such as proteins or polysaccharides is a method used for many purposes; *e.g.* refs [4b,4i,11b,12], and was already successfully applied with similar N1-linked carbostyrils [5]. The reaction of OSu ester **11** with phenylalanine ester **12a** or phenylalanine **12b** was performed either in dimethylformamide as the solvent and *N*-methyl-morpholine as basic catalyst, or in aqueous dimethyl-sulfoxide as the solvent and pH 7 buffer as the base. It afforded in all cases in about 49-75% yield the carbostyrils **13a** or **13b**, linked with the amino group of phenylalanine derivative. In the same manner, the tripeptide glycyl-glycyl-glycine (**13c)** reacted both in DMF and in aqueous DMSO solution with OSu-ester **11** to the peptide linked carbostyril **13c** in 54-56% yield. Aminoglucose (**14**) gave with **11** in 54 % yield the glucose-linked carbostyril **15**.

It must be emphasized that all these linking reactions could be carried out at conditions which prevent any renaturation of natural products: the reaction temperature was in all cases 20 °C, which is an important and necessary fact when natural products are used as substrates. A further important fact is that all linking reactions with amino acids and peptides could be performed at biochemical conditions in aqueous dimethylsulfoxide as the solvent and with aq. pH7 buffer.

Electronic spectra. Absorption spectra of all new O-alkyl substituted carbostyrils (including those already linked to amino acids, peptides and carbohydrates) are very similar with λ_{max} = 366–377 nm in DMSO and 355-360 nm in water. In Table 1 are excitation maxima listed which are for all alkylated species almost equal. We also found that there is no significant difference to the N-linked 6,7-dimethoxycarbostyrils described earlier [5]. Interestingly, extinction coefficients are about 10-30% larger comparing N1-derivatives with the new O6-isomers varying between 9000 and 13000 in DMSO and 10000-16000 in water [5]. As also previously observed with emission spectra of N1-linked derivatives, the new O6 alkylated isomers give maxima in a narrow range around 440 nm in DMSO and 430 nm in water. Hence the Stokes' shifts λ_F = 61-75 nm are sufficiently high and again similar to the N-linked carbostyrils [5].

Unexpectedly, fluorescence quantum yields, which were found in DMSO to have values of Φ_F = 0.34 and 0.47 for "standard" 6-O-methylcarbostyrils **5a** and **5c**, were lowered in water for the N-methyl derivative **5a** by about 50% (Table 1). The same trend was observed in water for 6-O-CH_2CO linked derivatives **8**, **11** and **13a-c**, with values of Φ_F = 0.08–0.14 (vs. 0.11– 0.27 for the N1-analogues). As an exception, the glucosamine derivative **15** emitted 30% stronger than the N1-analogue. In contrast, in DMSO measured differences in quantum yields were found to be individually different between N1 and O6 derivatives, sometimes better in O6 derivatives (**8** and **15**), and significantly smaller for OSu ester **11** (0.14 vs. 0.40).

Spectral data of acetyloxycarbostyril **10** were explored because the structure could serve as a model compound in enzymatic hydrolysis (*e.g.* the activity of hydrolases in water). Comparison of **10** with **5a** and **6a** shows that both excitation and emission spectra suffered a blue-shift of about 20-38 nm (see Table 1). The epsilon values are rather high (11600 in DMSO and 14100 in water), however the quantum yields are low with about 0.03 both in DMSO and water.

Interesting are the electronic spectra of 6-hydroxy- and 6,7-dihydroxycarbostyrils **6** and **7** (Figure 1). Monophenol **6**, fluorescing in DMSO solution just as 6,7-dialkylated analogues, shows in water only about 6% of the DMSO quantum yield (0.02). The anion, however shows the "usual" water quantum yield of 0.16, absorbing at 395 nm and emitting at 465 nm. A study of the pH-dependence of **6a** (Figure 2) revealed a pK_a of about 8.3, well in the range of expectation [13]. Interestingly, a recent publication dealing with the excited state "super" acidity of 6-hydroxyquinoline-N-oxides describes the photoisomerization to 6-hydroxyquinoline-2-ones *via* adiabatic photo-induced proton transfer confirming the photo stability of carbostyrils [14]. Carbostyril **6c**, having

a second dissociable group at NH1/OH2, has the best quantum yield of all investigated compounds (0.50) in DMSO and is again quenched in water. 6,7-Dihydroxy-carbostyril **7a** has in water and DMSO equal fluorescence properties, but the monoanion of **6a** and the dianion of **7a** (both measured at pH = 13) have very weak fluorescence. However, measured in DMSO with the addition of traces of powdered potassium hydroxide, monoanion of **6a** and dianion of **7a** show values of unprecedented redshift in the carbostyril series (Figure 1). Excited at 490 nm, emission of $\mathbf{7a}^{2-}$ occurs with a quantum efficiency of 0.02 at 580 nm (monoanion 430 nm and 490 nm, quantum efficiency 0.07).

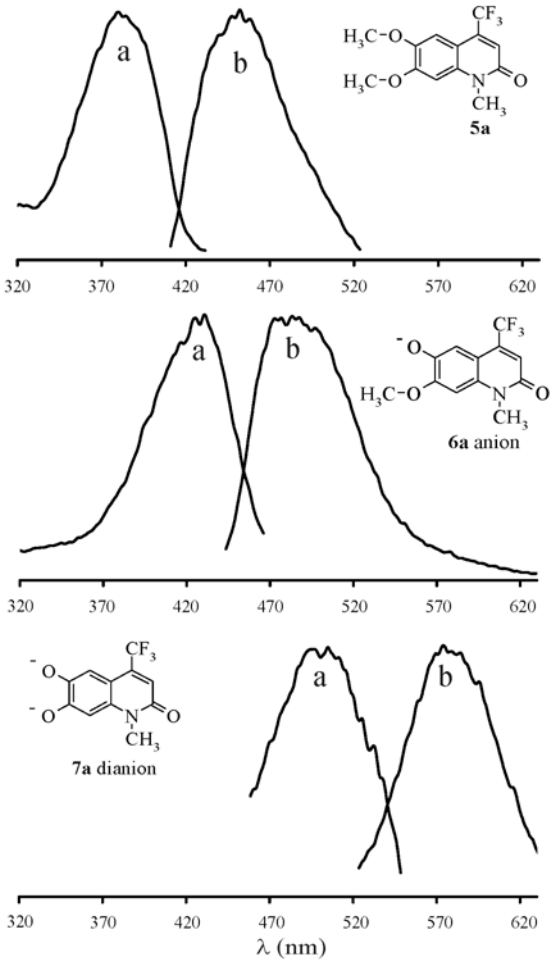


Figure 1: Absorption (a) and emission (b) spectra of **5a** and the anions of **6a** and **7a** in DMSO.

CONCLUSION

All these findings reveal that easily prepared N1-protected 6-hydroxy-7-methoxy-4-trifluoromethyl-carbostyrils lead to interesting derivatives with tunable fluorescence properties, useful to label biological interesting substrates under mild conditions. Quantum yields of the new OCH_2CO- in comparison to N-CH_2CO-linked products are in some cases lower. They are understandable considering the double push function in position 6 and 7 being more sensible to ionic quenching phenomena. In these cases, comparison of experimental data lead to better understanding of the complicated fluorescence decay pathways.

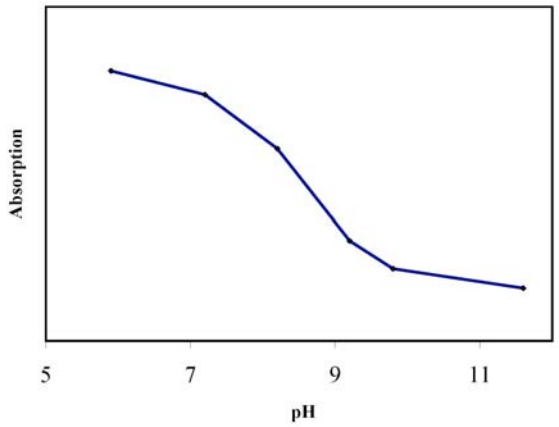


Figure 2: UV-Absorption of **6a** at 365 nm at pH 5 – 11

EXPERIMENTAL

Melting points were determined using a Stuart SMP3 Melting Point Apparatus in open capillary tubes. ^{1}H 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 (150-W Xe lamp, 6 selectable slits: 1.5, 3, 5, 10, 15, 20 nm, R452-01 photo-multiplier; monochromator: ion-blazed holographic concave grating F/2.5); concentration: < 10^{-5} mol/L. Determination of quantum yields: emission signals were set in relation to the known signal of quinine sulphate 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).

All reactions were monitored by thin layer chromatography 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.

Table 1

Photophysical Data for the Electronic Excitation (exc) and Fluorescence (flu) of Carbostyrils **5-15**; solvent temperatures: 25 °C; λ in nm.

No.	λ_{exc} (DMSO)	ε (DMSO)	λ_{flu} (DMSO)	Φ_F (DMSO)	Φ_F N1*	λ_{exc} (water)	ε (water)	λ_{flu} (water)	Φ_F (water)	Φ_F N1*
5a	365	9700	435	0.34		365	10100	428	0.16	
5c	368	9400	438	0.47		365	10400	428	0.45	
6a	380	9100	450	0.33		361	10200	430	0.02	
6a $^-$	400	10000	470	0.29		395	9000	465	0.16	
6c	377+400	9600	450	0.50		358	9900	460	0.03	
7a	384	9600	455	0.16		354	9900	420	0.13	
8	365	10400	430	0.41	0.31	354	11700	420	0.08	0.21
9	380	10800	450	0.22	0.32	360	12900	428	0.11	0.27
10	350	11600	410	0.03		345	14100	397	0.03	
11	376	10500	438	0.14	0.40	356	12100	426	0.14	0.25
13a	366	11300	430	0.33	0.33	354	12600	420	0.10	0.25
13b	366	13500	433	0.27	0.36	354	15600	420	0.13	0.22
13c	371	9600	433	0.28	0.33	365	11400	420	0.14	0.26
15	366	11300	433	0.29	0.22	354	13400	420	0.13	0.11

* Quantum yields of N1-isomer 6-methoxy-1-alkyl-carbostyrils [5]

3,4-Dimethoxyaniline (**1**): This compound is commercially available.

***N*-(3,4-Dimethoxyphenyl)-*N*-methylformamide** (**3a**). A mixture of 3,4-dimethoxyaniline (**1**) (29.90 g, 195 mmol), trimethyl orthoformate (**2a**) (32.0 g, 300 mmol) and concentrated sulfuric acid (1.5 g) was slowly heated under stirring to 103-105 °C and the formed methanol was distilled over a short Vigreux column. During 2.5 hours the bath temperature was increased to 170-185 °C until no more methanol was formed, then the mixture was kept at this temperature for further 60 min, and then cooled to 50 °C. Distillation under reduced pressure (bp 180-190 °C/15 mbar) afforded a yield of 23.2 g (61%) of a yellow oil, hplc purity 94%; ir: 3550-3450 m, 2960-2910 s, 2836 s, 1673 s, 1596 s, 1516 s cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.28 (s, 3 H, NMe), 3.89 (s, 6 H, 2 OMe), 6.69 (s, 1 H, 2-H), 6.73 (d, J = 8.6 Hz, 1 H, 1 ArH), 6.85 (d, J = 8.4 Hz, 1 H, ArH), 8.36 (s, 1 H, CH=O); MS: m/z (%) = 195 (80) [M].

***N*-(3,4-Dimethoxyphenyl)-*N*-ethylformamide** (**3b**). A mixture of 3,4-dimethoxyaniline (**1**) (10.00 g, 65 mmol) and triethyl orthoformate (**2b**) (18.0 g, 120 mmol) were brought to reaction and worked up as described for **3a**. Distillation (bp 145-148 °C/10 mbar) gave a yield of 8.07 g (59%) of a yellow-orange liquid, hplc purity 93%; ^1H nmr ($CDCl_3$): δ 1.23 (t, J = 7.1 Hz, 6 H, ethyl-CH_3), 3.15 (q, J = 7.5 Hz, 2 H, ethyl-CH_2), 3.80 and 3.85 (2 s, 2x3 H, 3-OMe and 4-OMe), 6.18 (d, J = 6.2 Hz, 1 H, 1 ArH), 6.24 (s, 1 H, 2-H), 6.79 (d, J = 8.4 Hz, 1 H, 1 ArH), 8.30 (s, 1 H, CH=O); MS: m/z (%) = 209 (76) [M].

3,4-Dimethoxy-*N*-methylbenzenamine (**4a**). A mixture of the formamide **3a** (22.5 g, 115 mmol) and 10% hydrochloric acid (70 mL) was stirred and heated under reflux for 90 min. Then the mixture was cooled to room temperature, neutralized and saturated with potassium carbonate. The amine separated as colorless oil and was extracted with diethylether (6 x 70 mL), the ether phase was washed with ice/water (80 mL) and dried over potassium carbonate. The solvent was removed *i. vac*. and the orange product distilled under reduced pressure (bp 153-155 °C, 15 mbar) to yield 14.0 g (73%) of a slightly yellow liquid, hplc purity 95%; lit. bp: 153-155 °C (12 mm Hg) [8g]; ^1H nmr ($CDCl_3$): δ 2.81 (s, 3 H, NMe), 3.81 and 3.84 (2 s, 2x3 H, 2 OMe), 6.16 (d, J = 6.1 Hz, 1 H, 1 ArH), 6.25 (s, 1 H, 2-H), 6.78 (d, J = 8.5 Hz, 1 H, 1 ArH); MS: m/z (%) = 167 (100) [M].

***N*-Ethyl-3,4-dimethoxybenzenamine** (**4b**). A mixture of the formamide **3b** (8.00 g, 38.5 mmol) and 10% hydrochloric acid (50 mL) was brought to reaction and worked-up as described for **4a**. The yield was 6.22 g (90%) of a yellow-brown liquid, hplc purity 96%, bp 150-154 °C/15 mbar; lit. bp: 145-151 °C (6-8 mm Hg) [8e], 116-119 °C (2.5 mm Hg) [8d]; ir: 3380 m, 2960 s, 2930 s, 2900 sh, 2830 m, 1620 s, 1595 m cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.10 (t, J = 7.5 Hz, 3 H, ethyl-CH_3), 2.92 (q, J = 7.5 Hz, 2 H, ethyl-CH_2), 3.65 and 3.71 (2 s, 2x3 H, 3-OMe and 4-OMe), 5.11 (s, 1 H, NH), 6.02 (d, J = 7.5 Hz, 1 H, 1 ArH), 6.30 (s, 1 H, 2-H), 6.72 (d, J = 7.3 Hz, 1 H, 1 ArH); MS: m/z (%) = 181 (100) [M].

6,7-Dimethoxy-1-methyl-4-trifluoromethylquinolin-2(1*H*)-one (5a). To isopropyl 4,4,4-trifluoroacetoacetate (10.30 g, 52 mmol) at 130 °C in an open flask dimethoxyaniline **4a** (4.34 g, 26 mmol) was added dropwise under stirring; the reaction mixture was kept for 1 hour at this temperature and then cooled to 40-45 °C. The excess ester was removed *i. vac*. to give *N*-methyl-*N*-(4,4,4-trifluoroacetoacetyl)-3,4-dimethoxyanilide as a yellow oily residue. The intermediate was cyclized without isolation: 76% sulfuric acid (9 mL) was added to the reaction mixture while keeping the temperature below 95 °C. After 1 hour at 90 °C, the reaction mixture was cooled to room temperature, water (300 mL) was added with stirring, and a light yellow-green precipitate was formed, which was filtered and washed with water until neutral to afford 7.20 g (97%) of light yellow prisms, mp 230-231 °C (ethanol); ir: 3550-3450 s, 1662 s, 1624 w, 1599 m, 1561 w cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.77 (s, 3 H, NMe), 3.96 and 4.04 (2 s, 2x3 H, 6-OMe and 7-OMe), 6.84 (s, 3-H), 7.00 (s, 8-H), 7.22 (s, 5-H); uv (DMSO): λ_{max} (nm) = 365; (water): 365. *Anal.* Calcd. for $C_{13}H_{12}F_3NO_3$ (287.24): C, 54.36; H, 4.21; N, 4.88. Found: C, 54.49; H, 4.18; N, 4.89.

1-Ethyl-6,7-dimethoxy-4-trifluoromethylquinolin-2(1*H*)-one (5b). A mixture of isopropyl 4,4,4-trifluoroacetoacetate

(7.33 g, 37 mmol), dimethoxyaniline **4b** (2.99 g, 16.5 mmol) and 76% sulfuric acid (7 mL) was brought to reaction and worked-up as described for **5a** to afford 3.98 g (80%) of colorless prisms, mp 166.4-166.9 °C (ethanol); ir: 2980 w, 2930 w, 1660 s, 1630 m, 1600 w cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.41 (t, J = 7.1 Hz, 3 H, ethyl-CH_3), 4.04 and 4.38 (s, 2x3 H, 6-OMe and 7-OMe), 4.41 (q, J = 7.2 Hz, 2 H, ethyl-CH_2), 6.87 (s, 1 H, 3-H), 6.99 (s, 1 H, 8-H), 7.22 (s, 1 H, 5-H); uv (DMSO): λ_{max} (nm) = 370; (water): 360. *Anal.* Calcd. for $C_{14}H_{14}F_3NO_3$ (301.27): C, 55.82; H, 4.68; N, 4.65. Found: C, 56.01; H, 4.60; N, 4.58.

6,7-Dimethoxy-4-trifluoromethylquinolin-2(1*H*)-one (5c). This compound was prepared according to ref. [5].

6-Hydroxy-7-methoxy-1-methyl-4-trifluoromethyl-quinolin-2(1*H*)-one (**6a**). A mixture of dimethoxyquinolone **5a** (1.44 g, 5 mmol) and hydrobromic acid (47% in water, 10 mL, 60 mmol) in glacial acetic acid (15 mL) was heated under reflux, until starting material was dissolved. The mixture was then heated for further 6-8 hours until no starting material could be detected (checked by TLC monitoring). Then the mixture was cooled to room temperature, poured into ice/water (250 mL) and filtered by suction. The yellow precipitate (1.10 g, 85%) was purified by dry column flash chromatography [10] (Merck silica gel 60 H; elution with chloroform). The yield was 0.71 g (55%) of pale yellow prisms, mp 245-246 °C (chloroform); ir: 3156 w, 3089 m, 1658 s, 1632 w, 1586 m cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.67 (s, 3 H, NMe), 3.97 (s, 3 H, 7-OMe), 6.86 (s, 1 H, 3-H), 7.05 (s, 1 H, 8-H), 7.21 (s, 1 H, 5-H), 9.65 (s, 1 H, OH, D_2O exchangeable); uv (DMSO): λ_{max} (nm) = 380, 308; (water): 361; MS: m/z (%) = 273 (90) [M]. *Anal.* Calcd. for $C_{12}H_{10}F_3NO_3$ (273.21): C, 52.75; H, 3.69; N, 5.13. Found: C, 52.74; H, 3.53; N, 5.09.

6-Hydroxy-7-methoxy-4-trifluoromethylquinolin-2(1*H*)-one (**6c**). Dimethoxyquinolone **5c** (1.37 g, 5 mmol) was brought to reaction with hydrobromic acid (47% in water, 5 mL, 30 mmol) in glacial acetic acid (5 mL) as described for **6a**. Then the mixture was cooled to room temperature, poured into ice/water (300 mL) and filtered by suction. The residue was dissolved in 0.1 *M* aq. sodium hydroxide, extracted with diethylether (300 mL) and acidified with hydrochloric acid to pH = 2-3. The precipitate was filtered by suction, washed with water and purified by dry column flash chromatography [10] (Merck silica gel 60 H; elution with chloroform/acetone 9:1), which afforded 1.10 g (85%) of colorless prisms, mp 292-295 °C (ethyl acetate); ir: 3200-2850 m, 1665 s, 1638 sh, 1607 m, 1523 s cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.84 (s, 3 H, 7-OCH_3), 6.72 (s, 1 H, 3-H), 6.93 (s, 1 H, 8-H), 7.06 (s, 1 H, 5-H), 9.52 (s, 1 H, OH), 12.03 (s, 1 H, NH); ^{13}C nmr (DMSO): δ 56.3 (7-OMe), 98.9 (8-C), 107.0 (4a-C), 108.3 (5-C), 118.3 (3-C), 123.6 (q, J = 270 Hz, CF_3), 135.4 (8a-C), 136.4 (q, 27 Hz, 4-C) 143.6 (C-6), 152.7 (7-C), 160.3 (2-C=O); HMBC ($CDCl_3$): $\delta^{13}C$-δ^1H = 118.3-6.72 (3-C), 108.3-7.06 (5-C), 152.7-3.84 (7-C), 98.9-6.93 (8-C); uv (DMSO): λ_{max} (nm) = 377; (water): 358; MS: m/z (%) = 260 (15), 259 (80) [M], 244 (100), 215 (8). *Anal.* Calcd. for $C_{11}H_8F_3NO_3$ (259.19): C, 50.98; H, 3.11; N, 5.40. Found: C, 50.63; H, 3.04; N, 5.26.

6,7-Dihydroxy-1-methyl-4-trifluoromethylquinolin-2(1*H*)-one (**7a**). This compound was obtained from dimethoxyquinolone **5a** (1.44 g, 5 mmol) and hydrobromic acid (47% in water, 10 mL, 60 mmol) following to the procedure of **6a**. After separation of **6a** by dry column flash chromatography [10] (Merck silica gel 60 H), elution with acetone afforded 0.39 g (30%) of pale yellow prisms of **7a**, mp 323-325 °C (chloroform); ^1H nmr (DMSO-d_6): δ 3.56 (s, 3 H, NMe), 6.78 (s, 1 H, 3-H), 7. 97 (s, 1 H, 8-H), 7.13 (s, 1 H, 5-H), 9.75 and 10.30 (b, 2x1 H, 6-OH and 7-OH); ir: 3450 b, m, 3083 m, 1649 m, 1590 m cm^{-1}; uv (DMSO): λ_{max} (nm) = 384; (water): 354. MS: m/z (%) = 259 (39) [M], 255 (16). *Anal.* Calcd. for $C_{11}H_8F_3NO_3$ (259.19): C, 50.98; H, 3.11; N, 5.40. Found: C, 51.24; H, 3.02; N, 5.67.

Ethyl (7-Methoxy-1-methyl-2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-yloxy)acetate (8). A mixture of 6-hydroxyquinolone **6a** (273 mg, 1 mmol) and potassium carbonate (200 mg, 14 mmol) in dry dimethylformamide (5 mL) was stirred for 35 min at room temperature. Then ethyl bromoacetate (167 mg, 1 mmol) was added dropwise and the reaction mixture was heated to 35 °C for 4 hours. The mixture was then poured into water (50 mL) and stirred for 1 hour. The solid was filtered by suction and washed with water which afforded 296 mg (83%) of colorless needles, mp 133-134 °C (ethanol); ^1H nmr ($CDCl_3$): δ 1.31 (t, J =7.07 Hz, 3 H, ester-Me), 3.76 (s, 3 H, NMe), 4.05 (s, 3 H, 7-OMe), 4.29 (q, J =7.04 Hz, 2 H, ester-CH_2), 4.74 (s, 2 H, 6-OCH_2), 6.86 (s, 1 H, 3-H), 7.00 (s, 1 H, 8-H), 7.27 (s, 1 H, 5-H); ir: 3450 b, 2983 s, 1757 s, 1662 s, 1624 w, 1603 m, 1561 w cm^{-1}; uv (DMSO): λ_{max} (nm) = 365; (water): 354. *Anal.* Calcd. for $C_{16}H_{16}F_3NO_5$ (359.30): C, 53.49; H, 4.49; N, 3.90. Found: C, 53.54; H, 4.46; N, 3.90.

(7-Methoxy-1-methyl-2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-yloxy)acetic acid (9). To a solution of 6-quinolinyloxyacetate **8** (343 mg, 1 mmol) in dry tetrahydrofurane (7 mL), 1 *M* aq. sodium hydroxide (4 mL) was added and the mixture stirred at room temperature for 5 hours. Then the solvent was removed *i. vac.*, the residue dissolved in ice/water (50 mL) and neutralized with conc. hydrochloric acid to pH = 6. The solid was filtered by suction and washed with water to afford 200 mg (60%) of colorless prisms, mp 255-256 °C (acetonitrile); ^1H nmr (DMSO-d_6): δ 3.70 (s, 3 H, NMe), 4.00 (s, 3 H, 7-OMe), 4.73 (s, 2 H, 6-OCH_2), 6.91 (s, 1 H, 3-H), 7.04 (s, 1 H, 8-H), 7.12 (s, 1 H, 5-H); ir: 3450 b, 2929 b, 1724 s, 1650 s, 1626 w, 1575 s, 1529 m cm^{-1}; uv (DMSO): λ_{max} (nm) = 380; (water): 360. *Anal.* Calcd. for $C_{14}H_{12}F_3NO_5$ (331.25): C, 50.76; H, 3.65; N, 4.23. Found: C, 50.72; H, 3.54; N, 4.20.

7-Methoxy-1-methyl-2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-yl acetate (10). A mixture of 6-hydroxyquinolone **6a** (273 mg, 1 mmol) and potassium carbonate (200 mg, 14 mmol) in dry DMF (6 mL) was stirred at room temperature for 35 min. Then acetylchloride (39 mg, 0.5 mmol) was added and the reaction mixture stirred at room temperature for 5 hours. Then the mixture was poured into water (50 mL) and stirred for 1 hour. The solid was then filtered by suction and washed with water which afforded 83 mg (52%) of colorless needles, mp 174-175 °C (methanol); ^1H nmr ($CDCl_3$): δ 2.36 (s, 3 H, Me of acetyl), 3.76 (s, 3 H, NMe), 3.99 (s, 3 H, 7-OMe), 6.87 (s, 1 H, 3-H), 7.00 (s, 1 H, 8-H), 7.51 (s, 1 H, 5-H); ir: 3455 b, 1764 s, 1676 s, 1627 sh, 1616 m, 1603 m, 1560 w, 1528 m cm^{-1}; uv (DMSO): λ_{max} (nm) = 350, 311; (water): 345. *Anal.* Calcd. for $C_{14}H_{12}F_3NO_4$ (315.25): C, 53.34; H, 3.84; N, 4.44. Found: C, 53.44; H, 3.48; N, 4.36.

1-(7-Methoxy-1-methyl-2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-yloxy)acetyloxypyrrolidine-2,5-dione (11). *N*-Hydroxysuccinimide (58 mg, 0.5 mmol) was added slowly whilst stirring to a solution of 6-quinolinyloxyacetic acid **9** (165 mg, 0.5 mmol) in dry tetrahydrofurane (20 mL) at 0 °C. Then 1,3-diisopropylcarbodiimide (63 mg, 0.5 mmol) was added dropwise at 0-5 °C and the mixture then stirred for 8 hours. The formed solid was separated by suction filtration, washed well

with dry tetrahydrofurane and stirred in dry ethanol (10 mL) at 20 °C for 30 min to remove *N,N'*-diisopropylurea formed as by-product during the reaction. Suction filtration afforded 130 mg (61%) of colorless prisms, mp 212-213 °C (ethanol); ^{1}H nmr ($CDCl_3$): δ 2.88 (s, 4 H, 2 CH_2 of succinimide), 3.76 (s, 3 H, NMe), 4.06 (s, 3 H, 7-OMe), 5.06 (s, 2 H, 6-OCH_2), 6.86 (s, 1 H, 3-H), 7.00 (s, 1 H, 8-H), 7.46 (s, 1 H, 5-H); ir: 3537 m, 3454 m, 1813 w, 1783 w, 1738 s, 1652 m, 1625 w, 1585 m, 1528 m cm^{-1}; uv (DMSO): λ_{max} (nm) = 376, 307; (water): 356. MS: m/z (%) = 429 (28), 428 (62) [M], 345 (100). *Anal.* Calcd. for $C_{18}H_{15}F_3N_2O_7$ (428.32): C, 50.48; H, 3.53; N, 6.54. Found: C, 50.37; H, 3.43; N, 6.18.

Ethyl 2-[2-(7-Methoxy-1-methyl-2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-yloxy)-acetylamino]-3-phenylpropionate (13a). Method A: A solution of OSu-ester **11** (53 mg, 0.125 mmol) in dimethylformamide (1 mL) was added dropwise to a solution of ethyl 2-amino-3-phenylpropanoate (**12a**) (24 mg, 0.125 mmol) in dimethylformamide (1 mL), and then N-methylmorpholine (0.01 mL) was added. The reaction mixture was stirred at 20 °C for 14 hours and poured into water (10 mL), filtered and washed with water to afford 31 mg (49%) of colorless prisms, mp 145-146 °C (ethyl acetate). Method B: A solution of OSu-ester **11** (53 mg, 0.125 mmol) in aq. dimethylsulfoxide (90%, 2 mL) was added dropwise to a solution of (D,L)-phenylalanine (**12a**) (24 mg, 0.125 mmol) in aq. dimethylsulfoxide (90%, 2 mL). Then pH7 buffer (1 mL) was added, the reaction mixture stirred at 20 °C for 14 h, poured into water (20 mL) and acidified with a few drops of conc. hydrochloric acid. The solid was filtered and washed with water, then dried and washed again with ethyl acetate to afford 39 mg (62%) of colorless prisms ; ^{1}H nmr ($CDCl_3$): δ 1.26 (t, J = 6.83 Hz, 3 H, ester-CH_3), 3.17 (d, J = 5.6 Hz, 2 H, Ph-CH_2), 3.77 (s, 3 H, NMe), 3.91 (s, 3 H, 7-OCH_3), 4.20 (q, J = 7.2 Hz, 2 H, ester-CH_2), 4.59 (s, 2 H, 6-OCH_2), 4.97 (dd, J = 5.1 and 5.3 Hz, 1 H, NCH), 6.80 (s, 1 H, 3-H), 7.01 (s, 1 H, 8-H), 7.13 (m, 2 H, 5-H and Ph-H), 7.22 (s, 4 H, PhH), 7.49 (d, J = 7.7 Hz, 1 H, NH); ir: 3411 m, 1730 m, 1672 s, 1611 w, 1530 m cm^{-1}; uv (DMSO): λ_{max} (nm) = 366; (water): 354. *Anal.* Calcd. for $C_{25}H_{25}F_3N_2O_6$ (506.48): C, 59.29; H, 4.98; N, 5.53. Found: C, 59.24; H, 4.86; N, 5.48.

2-[2-(7-Methoxy-1-methyl-2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-yloxy)-acetylamino]-3-phenylpropionic acid (13b). Method A: OSu-ester **11** (53 mg, 0.125 mmol) and (D,L)-phenylalanine (**12b**) (21 mg, 0.125 mmol) were brought to reaction and worked up as described for **13a** (method A) to afford 35 mg (58%) of colorless prisms, mp 232-233 °C (ethyl acetate). Method B: OSu-ester **11** (53 mg, 0.125 mmol) and (D,L)-phenylalanine (**12b**) (21 mg, 0.125 mmol) were brought to reaction and worked up as described for **13a** (method B) to afford 45 mg (75%) of **13b**; ^{1}H nmr (CF_3COOD): δ 3.75-3.82 (m, 2 H, Ph-CH_2), 4.53 (s, 3 H, NMe), 4.70 (s, 3 H, 7-OMe), 5.32 (s, 2 H, 6-OCH_2), 5.60 (m, 1 H, NCH), 7.69 (s, 5 H, PhH), 7.85 (s, 1 H, 3-H), 8.03 (s, 1 H, 8-H), 8.08 (s, 1 H, 5-H); ir: 3408 b, 3291 w, 2922 w, 1657s, 1570 m, 1526 s cm^{-1}; uv (DMSO): λ_{max} (nm) = 366, 310; (water): 354; MS: m/z (%) = 478 (27) [M], 382 (48), 377 (25) 376 (100). *Anal.* Calcd. for $C_{23}H_{21}F_3N_2O_6$ (478.43): C, 57.74; H, 4.42; N, 5.86. Found: C, 57.48; H, 4.12; N, 5.48.

(2-{2-[2-(7-Methoxy-1-methyl-2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-yloxy)-acetylamino]-acetylamino}-acetylamino)-acetic acid (13c). Method A: OSu-ester **11** (53 mg, 0.125 mmol) and glycyl-glycyl-glycine (**12c**) (24 mg, 0.125 mmol) were brought to reaction and worked-up as described for **13a** (method A). The yield was 35 mg (56%) of colorless prisms, mp 238-239 °C (ethyl acetate). Method B: OSu-ester **11** (53 mg, 0.125 mmol) and glycyl-glycyl-glycine (**12c**) (24 mg, 0.125 mmol) were brought to reaction and worked-up as described for **13a** (method B). The yield was 33 mg (54%); ^{1}H nmr (DMSO-d_6): δ 3.70 (s, 3 H, NMe), 3.73-3.74 (d, J = 5.5 Hz, 4 H, 2 peptide-CH_2), 3.81-3.82 (d, J = 5.2 Hz, 2 H, peptide-CH_2), 4.01 (s, 3 H, 7-OMe), 4.59 (s, 2 H, 6-OCH_2), 6.91(s, 1H, 3-H), 7.13 (s,1 H, 8-H), 7.17 (s, 1 H, 5-H), 8.17 (t, J = 5.5 Hz, 1 H, NH), 8.26 (t, J = 5.7 Hz, 1 H, NH), 8.30 (t, J = 5.4 Hz, 1 H, NH); ir: 3378 w, 3357 w, 3299 w, 1655 s, 1529 m cm^{-1}; uv (DMSO): λ_{max} (nm) = 371, 309; (water): 365. *Anal.* Calcd. for $C_{20}H_{21}F_3N_4O_8$ (502.41): C, 47.81; H, 4.21; N, 11.15. Found: C, 48.01; H, 3.87; N, 11.10.

2-(7-Methoxy-1-methyl-2-oxo-4-trifluoromethyl-1,2-dihydroquinolin-6-yloxy)-*N*-(2,4,5-trihydroxy-6-hydroxymethyltetrahydropyran-3-yl)-acetamide (15): A solution of OSu-ester **11** (53 mg, 0.125 mmol) in dimethylformamide (2 mL) was added dropwise to a solution of D-glucosamine hydrochloride (**16**) (27 mg, 0.125 mmol) in dimethylformamide/water (9:1, 2 mL), and then *N*-methyl-morpholine (0.01 mL) was added. The reaction mixture was stirred at 20 °C for 14 hours and poured into water (25 mL), stirred for 1 hour at 20 °C, the solid filtered by suction and washed with water to afford 33 mg (54%) of colorless prisms, mp 260-261 °C; ^{1}H nmr (CF_3COOD): δ 4.66 (s, 3 H, NMe), 4.72 (s, 3 H, 7-OMe), 4.78 (m, 2 H, 7'-CH_2), 4.83-4.95 (m, 3 H, 4', 5', 6'-H), 5.41 (s, 2 H, 6-OCH_2), 5.69 (m, 1 H, 3'-H) 5.98 (d, *J* = 3.2 Hz, 1 H, α-H), 7.91 (s, 1 H, 3-H), 8.10 (s, 2 H, 5-H, 8-H); ir: 3536 w, 3484 w, 3350 w, 3305 m, 1663 s, 1597 m, 1530 m cm^{-1}; uv (DMSO): λ_{max} (nm) = 375, 309; (water): 355; MS: m/z (%) = 472 (47) [M], 416 (100), 349 (55). *Anal.* Calcd. for $C_{20}H_{23}F_3N_2O_9$ (492.41): C, 48.79; H, 4.71; N, 5.69. Found: C, 48.73; H, 4.59; N, 5.61.

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