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Synthesis of 2-(1-alkyl(aryl)-4-oxo-5,6,7,8-tetrafluoro-1, 4-dihydroquinolin-3-yl)glyoxylic acid derivatives

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Abstract

Methods for synthesis of previously unknown 2-(1-alkyl(aryl)-4-oxo-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-3-yl)glyoxylic acids and their esters from the copper chelate of ethyl pentafluorobenzoylpyruvate were developed. 1-Aryl(alkyl)-3-ethoxalyl-5,6,7,8-tetrafluoro-quinolin-4-ones react with *o*-phenylenediamine and *o*-aminophenol to give the corresponding quinolin-3-ylquinoxalones and quinolin-3-ylbenzoxazines. The same heterocycles act with *o*-aminothiophenol to yield ethyl-2-(7-(2-aminophenylthio)-1-aryl-5,6,8-trifluoro-quinolon-3-yl)-2-(2-mercaptophenylimino)glioxylates. Interaction of 1-aryl-3-ethoxalyl-(heteryl)-5,6,7,8-tetrafluoroquinolones with morpholine gives 7-mono- and 5,7-disubstituted products depending on the reaction conditions.

Keywords: Ethyl pentafluorobenzoylpyruvate; 3-Ethoxalyl-5,6,7,8-tetrafluoroquinolin-4-ones; 2-(1-Alkyl(aryl)-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)glyoxylic acids; *o*-Phenylenediamine; *o*-Aminophenol; *o*-Aminothiophenol; Morpholine

1. Introduction

The substituted fluoroquinolone-3-carboxylic acids have attracted considerable attention in recent years [1–4]. This is mainly due to the fact that compounds of this class have been used as antibacterial agents in medicine for example ciprofloxacin, oflofloxacin, pefloxacin. In this context, development of modification paths of a fluoroquinolone structure is of considerable interest for investigating new effective drugs.

In the present paper, 2-(1-alkyl(aryl)-5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)glyoxylic acids and their esters were obtained. The reactions of derivatives of these compounds with nucleophiles are described.

2. Results and discussion

2.1. Synthesis of derivatives of 2-(1-alkyl(aryl)-4-oxo-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-3-yl)glyoxylic acids

One of known methods for synthesis of fluorine-containing 1-alkyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acids is transformation of fluorobenzoylacetic acids by the Gould–Jacobs reaction [1–3].

The copper chelate of ethyl pentafluorobenzoylpyruvate **1** was used as the starting compound for synthesis of fluoroquinolone-3-glyoxylic acid. Decomposition of chelate **1** by dry gaseous hydrogen chloride in anhydrous ether yields ethyl pentafluorobenzoylpyruvate **2**. The latter without additional purification was treated with triethylorthoformate in the presence of acetic anhydride to form α-ethoxymethylenesubstituted ethyl pentafluorobenzoylpyruvate **3** (Scheme 1). Use of copper chelate **1** as the starting material instead of free ligand **2** is because of conversion of the latter into 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone [5].

In contrast to its fluorobenzoylacetic analogs [5], the ethoxymethylene derivative **3** is readily hydrolyzed to give the starting ethyl pentafluorobenzoylpyruvate **2**, which converted into stable 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone under the reaction conditions. In order to reduce the formation of by-products and to increase yields of end compounds, unstable ethers **2** and **3** were not isolated from the reaction.

Interaction of compound **3** with various amines (ammonia, methylamine, ethylamine, cyclopropylamine, *n*-hexylamine and *o*-toluidine) results in the formation of acyclic precursors of quinolones — ethyl-4-alkyl(aryl)amino-2-oxo-3-pentafluorobenzoylbut-3-enoates **4a–f** (Scheme 1).

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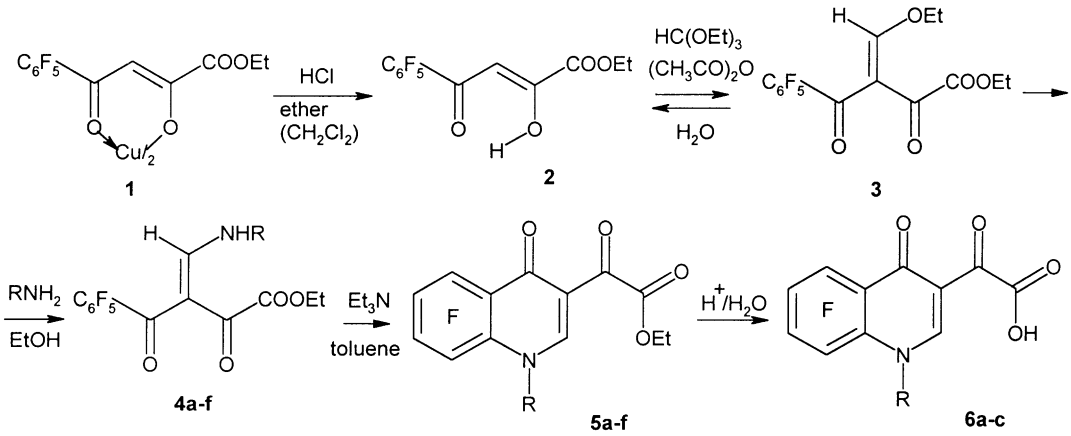


R= Et (a), *cyclo*-Pr (b), *o*-MeC_6H_4 (c), H (d), Me (e), C_6H_{13} (f)

Scheme 1.

There are quite stable compounds. The compounds **4a–f** in the presence of triethylamine upon heating in a dry aprotic solvent (toluene, chloroform) undergo intramolecular cyclization to form the corresponding 3-ethoxalyl-5,6,7,8-tetrafluoroquinolones **5a–f** (Scheme 1). The cyclization proceeds through intramolecular substitution of the *o*-fluorine atom in the pentafluorophenyl substituent by the amino group.

The products **4a–f** exist as a mixture of *Z*- and *E*-isomers showing two sets of identical signals in the ^1H and ^{19}F NMR spectra and thus the presence of two isomers in all cases.

When ethers **5a–c** were heated with a boiling mixture of concentrated acetic and hydrochloric acids, quinolone-3-glyoxylic acids **6a–c** were obtained (Scheme 1).

2.2. Reactions of 2-(1-alkyl(aryl)-3-ethoxycarbonyl-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-4-ones) with dinucleophiles

The quinolones **5** have great synthetic possibilities for the further modification due to the presence of an α-dicarbonyl fragment, including the creation of new heterocyclic compounds. Interaction with nucleophilic reagents can proceed both at one carbonyl group and at the α-dicarbonyl fragment. Moreover, aromatic nucleophilic substitution of fluorine atoms is typical for these heterocycles.

In the present work, the reactions of quinolones **5** with aromatic dinucleophiles: *o*-phenylenediamine, *o*-aminophenol, *o*-aminothiophenol were studied. It has been found that quinolones **5b,c** upon refluxing in alcohol with the double excess of *o*-phenylenediamine and *o*-aminophenol afford the corresponding quinolonylquinoxalones **7a,b** and quinolonylbenzoxazinones **8a,b** (Scheme 2).

In contrast to *o*-phenylenediamine and *o*-aminophenol, *o*-aminothiophenol reacts with heterocycle **5c** to form the product **9** (Scheme 2). The structure of the latter is the result of two parallel processes: the addition of one molecule of *o*-aminothiophenol at the α-carbonyl and the nucleophilic substitution of an aromatic fluorine atom at position C-7 by the 2-aminophenylthiogroup of the second molecule of the dinucleophile. The possibility of nucleophilic substitution in this case may be caused by high nucleophility of the sulfur atom of this reagent. Further this reaction demonstrates the preferred attack of nucleophile at α-carbonyl rather an ester group.

Attempts to subject product **9** to further cyclization into quinolonylbenzothiazinone upon refluxing toluene or *n*-butanol failed.

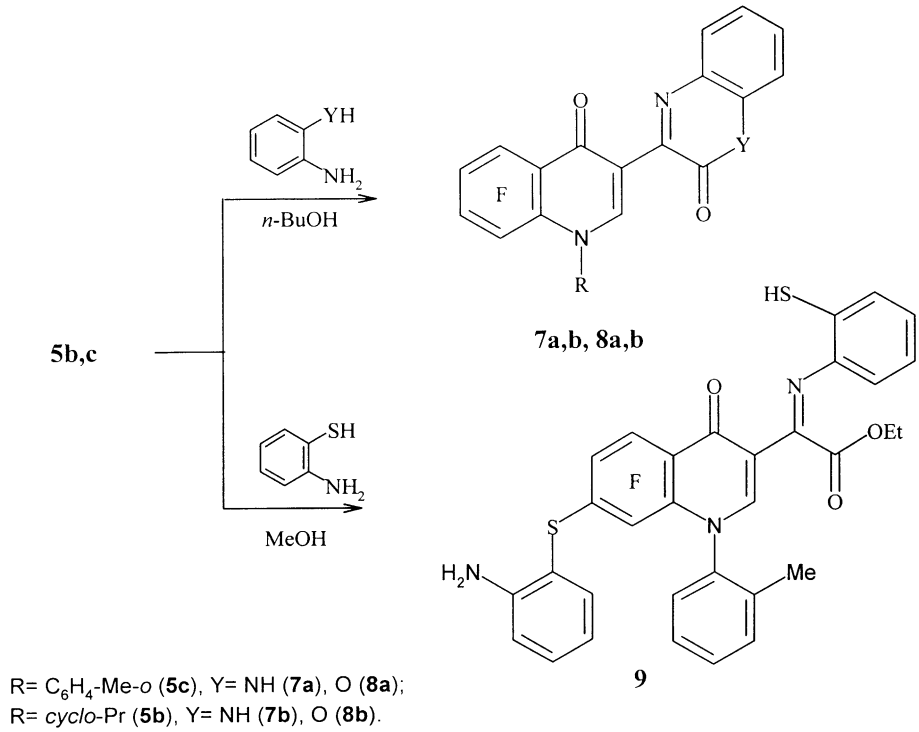
2.3. Reactions of derivatives of 2-(1-alkyl(aryl)-4-oxo-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-3-yl)glyoxylic acids with morpholine

Interaction of 3-ethoxalylsubstituted quinolone **5c** with an excess of morpholine in DMSO at the room temperature gives product **10** as the result of mono-substitution of fluorine at position C-7. When the quinolone **5c** was refluxed in pyrydine with an excess of morpholine, the product of 5,7-disubstitution **11** was obtained (Scheme 3).

Replacement of the ethoxalyl group by the heterocyclic quinoxalonyl fragment in quinolones does not change the direction of their reactions with morpholine. Thus, 7-monosubstituted product **12** was derived from 3-quinolonylquinoxaline **7a** in DMSO at room temperature. Boiling compound **7a** in pyridine affords 5,7-disubstituted heterocycle **13** (Scheme 4).

Thus, using DMSO as the solvent promotes the selective substitution of fluorine atom at position C-7 of the quinolones while boiling in pyridine leads to formation of 5,7-disubstituted products.

In conclusion, new 1-aryl(alkyl)-3-ethoxalyl-5,6,7,8-tetrafluoroquinolin-4-ones prepared in the present work have the reactivity of α-dicarbonyl compounds in interaction with dinucleophiles giving quinoxalinone and benzoxazinone derivatives. Moreover, the aromatic nucleophilic



Scheme 2.

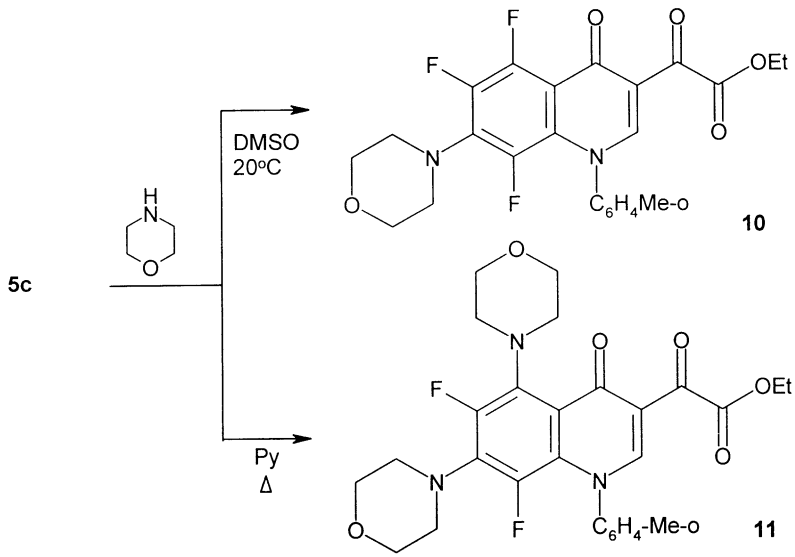
substitution of fluorine atoms is also characteristic for these heterocycles.

3. Experimental details

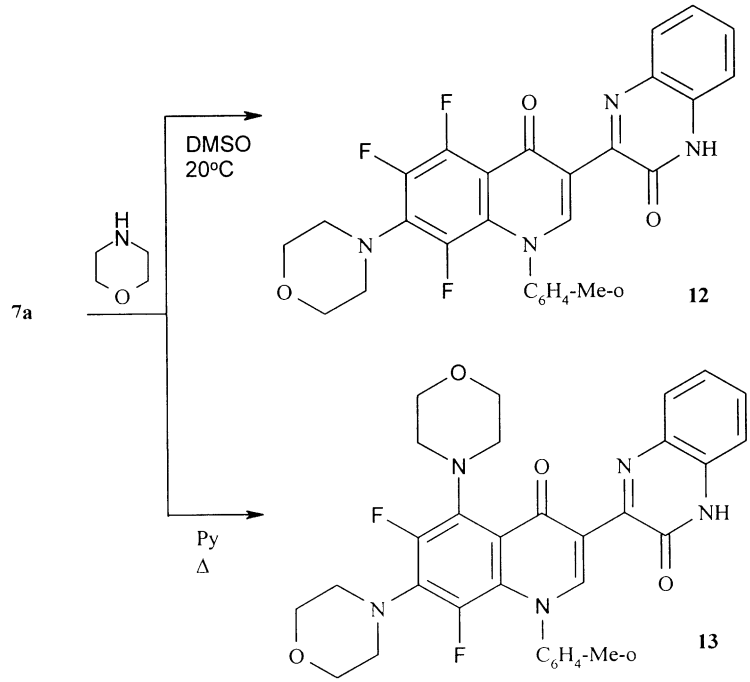
Melting points were measured in open capillaries and are reported uncorrected. Infrared spectra were recorded on a Specord 75 IR spectrometer. ^{1}H- and ^{19}F-NMR spectra were recorded on a Tesla BS-587A instrument (^{1}H: 80 MHz, using TMS as internal standard, ^{19}F: 75 MHz, using C_6F_6 as internal standard). Microanalyses were performed with a Carlo Erba CHNS-O EA 1108 elemental analyzer.

3.1. Materials

The copper chelate of ethyl pentafluorobenzoylpyruvate **1** was prepared by the method described previously [6].



Scheme 3.



Scheme 4.

3.2. Synthesis of derivatives of 2-(1-alkyl(aryl)-4-oxo-5,6,7,8-tetrafluoro-1,4-dihydroquinolon-3-yl)glyoxylic acids

3.2.1. Synthesis of ethyl-4-alkylamino-2-oxo-3-pentafluorobenzoylbut-3-enoates (**4a,d,e**) (nc)

Anhydrous gaseous hydrogen chloride was passed through a solution of chelate **1** (10 g, 29.3 mmol) in 100 ml of dry ether for 2 h. Ether was removed in vacuum at 20°C. Acetic anhydride (6.64 ml, 78.2 mmol) and triethylorthoformate (7.32 ml, 43.8 mmol) were added. The reaction mixture was refluxed for 2 h. Excess of reagents was removed in vacuum. The residue was dissolved in 100 ml of anhydrous ethanol. The corresponding gaseous amine was passed through the solution for 10 min. The resulting precipitate was filtered and recrystallized from methanol to give product **4**.

*3.2.1.1. Compound **4a***. Yield, 4.82 g, 45%; m.p. 158–159°C. ^{1}H-NMR ($CDCl_3$, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 1.26–1.55 (6H, m, CH_3); 3.32–4.10 (2H, m, CH_2); 4.23, 4.27 (2H, 2q, CH_2); 7.61 (0.5H, d.t, =CH, $J_{(H-H)} = 13.8$, $J_{(H-F)} = 1.5$ Hz, *Z*-isomer), 8.28 (0.5H, d, CH, $J_{(H-H)} = 13.8$ Hz, *E*-isomer); 10.86, 11.23 (1H, 2d, NH, $J_{(H-H)} = 13.8$ Hz) ppm. ^{19}F-NMR ($CDCl_3$, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 0.09, 2.12 (2F, 2m); 7.94, 10.84 (1F, 2m); 18.69, 21.84 (2F, 2m) ppm. IR: 3200 (NH); 1730 (CO_2Et); 1650 (C=O); 1620 (C_6F_5C=O); 1590 (C=C) cm^{-1}. Analysis: found: C, 49.21; H, 3.39; F, 25.99; N, 3.91. Calculated for $C_{15}H_{12}F_5NO_4$: C, 49.31; H, 3.31; F, 26.00; N, 3.83%.

*3.2.1.2. Compound **4d***. Yield, 3.16 g, 32%; m.p. 197°C. ^{1}H-NMR ($CDCl_3$, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 1.32, 1.35 (3H, 2t, $2CH_3$, $J_{(H-H)} = 7.0$ Hz); 4.19, 4.30 (2H, 2q, $2CH_2$, $J_{(H-H)} = 7.0$ Hz); 7.38 (1H, br.s, NH); 7.67, 7.76 (1H, 2d, =CH, $J_{(H-H)} = 14.1$ Hz,); 9.97, 10.09 (1H, 2d, NH, $J_{(H-H)} = 13.8$ Hz) ppm. ^{19}F-NMR ($CDCl_3$, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 0.04, 2.32 (2F, 2m); 8.42, 11.32 (1F, 2m); 18.56, 21.62 (2F, 2m) ppm. IR: 3380, 3255 (NH); 1720 (CO_2Et); 1660 (C=O); 1625 (C_6F_5C=O); 1610 (C=C) cm^{-1}. Analysis: found: C, 46.44; H, 2.39; F, 28.31; N, 4.16. Calculated for $C_{13}H_8F_5NO_4$: C, 46.30; H, 2.39; F, 28.17; N, 4.15%.

*3.2.1.3. Compound **4e***. 1.85 g, 18%; m.p. 224°C. ^{1}H-NMR ($CDCl_3$, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 1.34 (3H, br.t, $2CH_3$, $J_{(H-H)} = 7.3$ Hz); 3.29 (3H, 2d, CH_3, $J_{(H-H)} = 5.2$ Hz); 4.20, 4.27 (2H, 2q, $2CH_2$, $J_{(H-H)} = 7.3$ Hz); 7.54 (0.5H, d.t, =CH, $J_{(H-H)} = 14.3$, $J_{(H-F)} = 1.5$ Hz, *Z*-isomer), 8.25 (0.5H, d, CH, $J_{(H-H)} = 14.3$ Hz, *E*-isomer); 10.75, 11.13 (1H, 2br.s, NH) ppm. ^{19}F-NMR ($CDCl_3$, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 0.07, 2.16 (2F, 2m); 7.97, 10.85 (1F, 2m); 18.64, 21.8 (2F, 2m) ppm. IR: 3200 (NH); 1735, 1720 (CO_2Et); 1660, 1650 (C=O); 1610 (C6F5C=O); 1595 (C=C) cm^{-1}. Analysis: found: C, 48.01; H, 2.81; F, 27.16; N, 3.89. Calculated for $C_{14}H_{10}F_5NO_4$: C, 47.88; H, 2.87; F, 27.05; N, 3.99%.

3.2.2. Synthesis of ethyl-4-alkyl(aryl)amino-2-oxo-3-pentafluorobenzoylbut-3-enoates (**4b,c,f**) (nc)

Anhydrous gaseous hydrogen chloride was passed through a solution of chelate **1** (10 g, 29.3 mmol) in

100 ml of dry ether to brown color of the reaction mass. Ether was removed in vacuum at 20°C. Acetic anhydride (6.64 ml, 78.2 mmol) and triethylorthoformate (7.32 ml, 43.8 mmol) were added. The reaction mixture was refluxed for 2 h. Excess of reagents was removed in vacuum. The residue was dissolved in 60 ml of anhydrous methanol. To the solution, the corresponding amines (29.3 mmol) in 20 ml of anhydrous methanol was added. The reaction mixture was refluxed for 10 min. After cooling, the resulting precipitate was filtered and recrystallized from methanol to give compound **4**.

*3.2.2.1. Compound **4b***. Yield, 4.32 g, 39%; m.p. 143°C. ^{1}H-NMR ($CDCl_3$, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 0.78–1.08 (4H, m, CH_2); 1.34 (3H, t, CH_3, $J_{(H-H)} = 7.3$ Hz); 2.86–3.25 (1H, m, CH); 4.24, 4.28 (2H, 2q, CH_2, $J_{(H-H)} = 7.3$ Hz); 7.68 (0.5H, d.t, =CH, $J_{(H-H)} = 14.1$, $J_{(H-F)} = 1.5$ Hz, *Z*-isomer), 8.37 (0.5H, d, CH, $J_{(H-H)} = 14.1$ Hz, *E*-isomer); 10.84, 11.26 (1H, 2br.d, NH, $J_{(H-H)} = 14.1$ Hz) ppm. ^{19}F-NMR ($CDCl_3$, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 0.09, 2.21 (2F, 2m); 8.01, 11.13 (1F, 2m); 18.63, 21.87 (2F, 2m) ppm. IR: 3170 (NH); 1730 (CO_2Et); 1650 (C=O); 1610 (C_6F_5C=O); 1590 (C=C) cm^{-1}. Analysis: found: C, 51.15; H, 3.19; F, 25.09; N, 3.83. Calculated for $C_{16}H_{12}F_5NO_4$: C, 50.94; H, 3.25; F, 25.18; N, 3.71%.

*3.2.2.2. Compound **4c***. Yield, 1.85 g, 18%; m.p. 224°C. ^{1}H-NMR ($CDCl_3$, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 1.36, 1.38 (3H, 2t, $2CH_3$, $J_{(H-H)} = 7.1$ Hz); 2.42, 2.48 (3H, 2s, CH_3); 4.26, 4.32 (2H, 2q, $2CH_2$, $J_{(H-H)} = 7.1$ Hz); 7.03–7.40 (4H, m, C_6H_4); 7.66 (0.5H, d.t, =CH, $J_{(H-H)} = 13.6$, $J_{(H-F)} = 1.5$ Hz, *Z*-isomer), 8.46 (0.5H, d, CH, $J_{(H-H)} = 13.6$ Hz, *E*-isomer); 12.65, 13.51 (1H, 2br.d, NH, $J_{(H-H)} = 13.6$ Hz) ppm. ^{19}F-NMR ($CDCl_3$, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 0.36, 2.44 (2F, 2m); 8.77, 11.67 (1F, 2m); 19.41, 22.39 (2F, 2m) ppm. IR: 3380 (NH); 1735 (CO_2Et); 1640 (C=O); 1615 (C_6F_5C=O); 1590 (C=C) cm^{-1}. Analysis: found: C, 56.11; H, 3.07; F, 22.26; N, 3.39. Calculated for $C_{20}H_{14}F_5NO_4$: C, 56.21; H, 3.30; F, 22.23; N, 3.28%.

*3.2.2.3. Compound **4f***. Yield, 4.57 g, 37%; m.p. 104–106°C. ^{1}H-NMR ($CDCl_3$, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 0.85–1.00 (2H, m, CH_2); 1.23–1.89 (9H, m, CH_3, CH_2); 3.32–3.62 (2H, m, CH_2); 4.25 (2H, 2q, $2CH_2$, $J_{(H-H)} = 8.2$ Hz); 7.55 (0.5H, d.t, =CH, $J_{(H-H)} = 13.3$, $J_{(H-F)} = 1.5$ Hz, *Z*-isomer), 8.25 (0.5H, d, CH, $J_{(H-H)} = 13.3$ Hz, *E*-isomer); 10.87, 11.20 (1H, 2br.d, NH, $J_{(H-H)} = 13.3$ Hz) ppm. ^{19}F-NMR ($CDCl_3$, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 0.05, 2.08 (2F, 2m); 7.92, 10.81 (1F, 2m); 18.75, 21.88 (2F, 2m) ppm. IR: 3200 (NH); 1740 (CO2Et); 1650 (C=O); 1610 (C_6F_5C=O); 1600 (C=C) cm^{-1}. Analysis: found: C, 54.13; H, 4.75; F, 22.67; N, 3.49. Calculated for $C_{19}H_{20}F_5NO_4$: C, 54.16; H, 4.78; F, 22.54; N, 3.32%.

*3.2.3. Synthesis of 1-alkyl(aryl)-3-ethoxalyl-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-4-ones (**5a–f**) (nc)*

To a solution of compound **4** (5.0 mmol) in 30 ml of dry toluene, triethylamine (2.53 g, 15.0 mmol) was added. The reaction mixture was refluxed for 15 min. After cooling, the solution was washed with 5% HCl and water to pH ~ 7, dried over $MgSO_4$. The solvent was removed in vacuum. The product **5** was obtained by recrystallization from methanol.

*3.2.3.1. Compound **5a***. Yield, 1.57 g, 91%; m.p. 168–170°C. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, CH_3, $J_{(H-H)} = 7.3$ Hz); 1.57 (3H, d.t, CH_3, $J_{(H-H)} = 7.0$ Hz); 4.31–4.58 (2H, m, CH_2); 8.28 (1H, s, =CH) ppm. ^{19}F-NMR ($CDCl_3$) δ: 2.67 (1F, m); 14.31 (2F, m); 20.45 (1F, m) ppm. IR: 3045 (CH); 1735 (CO_2Et); 1660, 1640 (C=O); 1610 (C=C) cm^{-1}. Analysis: found: C, 52.28; H, 3.06; F, 21.65; N, 3.94. Calculated for $C_{15}H_{11}F_4NO_4$: C, 52.18; H, 3.21; F, 21.65; N, 4.06%.

*3.2.3.2. Compound **5b***. Yield, 1.32 g, 74%; m.p. 209–210°C. ^{1}H-NMR ($CDCl_3$) δ: 0.78–0.93 (7H, m, CH_3, CH_2); 4.07–4.27 (1H, m, CH); 4.38 (2H, q, CH_2, $J_{(H-H)} = 7.0$ Hz); 8.44 (1H, s, =CH) ppm. ^{19}F-NMR ($CDCl_3$) δ: 4.57 (1F, m); 15.61 (1F, m); 17.50 (1F, m); 22.44 (1F, m) ppm. IR: 3030 (CH); 1730 (CO_2Et); 1665, 1635 (C=O); 1605 (C=C) cm^{-1}. Analysis: found: C, 53.81; H, 3.10; F, 21.40; N, 3.78. Calculated for $C_{16}H_{11}F_4NO_4$: C, 53.79; H, 3.10; F, 21.27; N, 3.92%.

*3.2.3.3. Compound **5c***. Yield, 1.53 g, 75%; m.p. 197°C. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, CH_3, $J_{(H-H)} = 7.4$ Hz); 2.15 (3H, s, CH_3); 4.34 (2H, q, CH_2, $J_{(H-H)} = 7.4$ Hz); 7.32–7.74 (4H, m, C_6H_4); 8.34 (1H, s, =CH) ppm. ^{19}F-NMR ($CDCl_3$) δ: 6.34 (1F, m); 29.23–29.89 (2F, m); 40.74 (1F, m) ppm. IR: 3045 (CH); 1740 (CO_2Et); 1650, 1640 (C=O); 1600 (C=C) cm^{-1}. Analysis: found: C, 58.75; H, 3.19; F, 18.75; N, 3.30. Calculated for $C_{20}H_{13}F_4NO_4$: C, 58.98; H, 3.22; F, 18.66; N, 3.44%.

*3.2.3.4. Compound **5d***. Yield, 1.0 g, 63%; m.p. 197°C. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, CH_3, $J_{(H-H)} = 7.0$ Hz); 4.31 (2H, q, CH_2, $J_{(H-H)} = 7.0$ Hz); 8.44 (1H, s, =CH); 13.24 (1H, br.s, NH) ppm. ^{19}F-NMR ($CDCl_3$) δ: 1.17 (1F, m); 9.27 (1F, m); 12.61 (1F, m); 19.63 (1F, m) ppm. IR: 3395 (NH); 3060, 3040 (CH); 1735 (CO_2Et); 1660, 1635 (C=O); 1600 (C=C) cm^{-1}. Analysis: found: C, 49.35; H, 2.06; F, 23.84; N, 4.19. Calculated for $C_{13}H_7F_4NO_4$: C, 49.23; H, 2.22; F, 23.96; N, 4.42%.

*3.2.3.5. Compound **5e***. Yield, 1.19 g, 75%; m.p. 173–175°C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, CH_3, $J_{(H-H)} = 7.0$ Hz); 4.25 (3H, d, CH_3); 4.44 (2H, q, CH_2, $J_{(H-H)} = 7.0$ Hz); 8.21 (1H, s, =CH) ppm. ^{19}F-NMR ($CDCl_3$) δ: 5.05 (1F, m); 13.53 (1F, m); 15.69 (1F, m); 23.24 (1F, m) ppm. IR: 3030 (CH); 1725 (CO_2Et); 1665, 1635 (C=O); 1605 (C=C) cm^{-1}. Analysis: found: C, 50.89;

H, 2.91; F, 22.80; N, 4.48. Calculated for $C_{14}H_9F_4NO_4$: C, 50.77; H, 2.74; F, 22.94; N, 4.23%.

*3.2.3.6. Compound **5f***. 1.71 g, 85%; m.p. 175°C. ^{1}H-NMR ($CDCl_3$) δ: 0.82–1.05 (2H, m, CH_2); 1.09–1.65 (9H, m, CH_3, $2CH_2$); 1.75–2.02 (2H, m, CH_2); 4.27–4.52 (2H, m, CH_2); 8.25 (1H, s, =CH) ppm. ^{19}F-NMR ($CDCl_3$) δ: 4.37 (1F, m); 13.25 (1F, m); 15.69 (1F, m); 23.13 (1F, m) ppm. IR: 3050 (CH); 1735 (CO_2Et); 1660, 1645 (C=O); 1605 (C=C) cm^{-1}. Analysis: found: C, 56.92; H, 4.79; F, 18.84; N, 3.20. Calculated for $C_{19}H_{19}F_4NO_4$: C, 56.86; H, 4.77; F, 18.93; N, 3.49%.

*3.2.4. Synthesis of 2-(1-alkkyl(aryl)-4-oxo-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-3-yl)glyoxylic acids (**6a–c**) (nc)*

A mixture of water (3.5 ml), acetic (4.6 ml) and conc. sulfuric (0.6 ml) acids was added to compound 5 (0.69 g, 2.0 mmol). The solution was refluxed for 30 min. After cooling, 10 ml of water was added. The resulting precipitate was filtered and washed with methanol to give compound **6**.

*3.2.4.1. Compound **6***. 0.46 g, 95%; m.p. 168–170°C. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, CH_3, $J_{(H-H)} = 7.0$ Hz); 1.29 (1H, s, OH); 4.51 (2H, q, CH_2, $J_{(H-H)} = 7.0$ Hz); 8.68 (1H, s, =CH) ppm. ^{19}F-NMR ($CDCl_3$) δ: 2.67 (1F, m); 13.85–14.77 (2F, m); 20.45 (1F, m) ppm. IR: 1735 (CO_2H); 1670, 1620 (C=O); 1590 (C=C) cm^{-1}. Analysis: found: C, 49.18; H, 2.05; F, 24.02; N, 4.23. Calculated for $C_{13}H_7F_4NO_4$: C, 49.23; H, 2.22; F, 23.97; N, 4.41%.

*3.2.4.2. Compound **6b***. 0.62 g, 94%; m.p. 240°C. ^{1}H-NMR ($CDCl_3$) δ: 1.14–1.21 (4H, m, CH_2); 1.29 (1H, s, OH); 2.94–3.12 (1H, m, CH); 8.50 (1H, s, =CH) ppm. ^{19}F-NMR ($CDCl_3$) δ: 2.70 (1F, m); 13.85 (1F, m); 18.88–19.84 (2F, m) ppm. IR: 1740 (CO_2H); 1680, 1620 (C=O); 1590 (C=C) cm^{-1}. Analysis: found: C, 51.21; H, 2.13; F, 23.17; N, 4.21. Calculated for $C_{14}H_7F_4NO_4$: C, 51.08; H, 2.14; F, 23.08; N, 4.25%.

*3.2.4.3. Compound **6c***. 0.71 g, 93%; m.p. 230–232°C. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s, CH_3); 4.07 (1H, br.s, OH); 7.48 (4H, br.s, C_6H_4); 8.27 (1H, s, =CH) ppm. ^{19}F-NMR ($CDCl_3$) δ: 2.88 (1F, m); 14.61 (2F, m); 20.30 (1F, m) ppm. IR: 1710 (CO_2H); 1690, 1640 (C=O); 1590 (C=C) cm^{-1}. Analysis: found: C, 57.22; H, 2.31; F, 19.89; N, 3.91. Calculated for $C_{18}H_9F_4NO_4$: C, 57.01; H, 2.39; F, 20.04; N, 3.69%.

3.3. Reactions of 1-alkyl(aryl)-3-ethoxycarbonyl-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-4-ones with dinucleophiles

*3.3.1. 3-(1-(2-Methylphenyl)-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-4-on-3-yl)-1,2-dihydroquinoxalin-2-one (**7a**) (nc)*

To a solution of compound **5c** (0.41 g, 1.0 mmol) in 5 ml of methanol, *o*-phenylenediamine (0.22 g, 2.0 mmol) in 5 ml of methanol was added. The mixture was refluxed for 2 h. The resulting precipitate was filtered and washed with methanol to give product **7a** (0.37 g, 64%) as yellow crystals (m.p. 255°C). ^{1}H-NMR (DMSO-d_6) δ: 2.29 (3H, s, CH_3); 7.20–7.83 (8H, br.s, $2C_6H_4$); 8.09 (1H, s, =CH); 12.43 (1H, s, NH) ppm. ^{19}F-NMR (DMSO-d_6) δ: −0.41 (1F, m); 11.73–12.96 (2F, m); 18.48–19.03 (1F, m) ppm. IR: 3320, 2780, 2720 (NH); 3040 (CH); 1670 (CONH), 1635 (C=O); 1610 (C=N) cm^{-1}. Analysis: found: C, 63.74; H, 2.86; F, 16.87; N, 9.27. Calculated for $C_{24}H_{13}F_4N_3O_2$: C, 63.86; H, 2.90; F, 16.84; N, 9.31%.

*3.3.2. 3-(1-Cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-4-on-3-yl)-1,2-dihydroquinoxalin-2-one (**7b**) (nc)*

Similarly product **7b** (0.29 g, 73%) was obtained from compound **5b** (0.22 g, 2.0 mmol) and *o*-phenylenediamine (0.22 g, 2.0 mmol) as yellow crystals (m.p. >300°C). ^{1}H-NMR (DMSO-d_6) δ: 1.12–1.19 (4H, m, CH_2); 3.83–4.16 (1H, m, CH); 7.11–7.83 (4H, m, C_6H_4); 8.26 (1H, s, =CH); 12.41 (1H, br.s, NH) ppm. ^{19}F-NMR (DMSO-d_6) δ: −0.66 (1F, m); 11.33 (1F, m); 16.47 (1F, m); 18.38 (1F, m) ppm. IR: 3290, 3060, 2760, 2700 (NH); 3045 (CH); 1675 (CONH); 1640 (C=O); 1595 (C=N) cm^{-1}. Analysis: found: C, 59.85; H, 2.78; F, 18.62; N, 10.32. Calculated for $C_{20}H_{11}F_4N_3O_2$: C, 59.86; H, 2.76; F, 18.94; N, 10.47%.

*3.3.3. 3-(1-(2-Methylphenyl)-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-4-on-3-yl)-1,2-dihydrobenzoxazin-2-one (**8a**) (nc)*

To a solution of compound **5c** (0.41 g, 1.0 mmol) in 20 ml of *n*-butanol, *o*-aminophenol (0.22 g, 2.0 mmol) in 20 ml of *n*-butanol was added. The mixture was refluxed for 1 h. After cooling, the reaction mixture was poured into water (30 ml). The resulting was filtered and recrystallized from *n*-butanol to give product **8a** (0.29 g, 82%) as yellow crystals (m.p. 240°C). ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s, CH_3); 7.40–7.84 (8H, m, $2C_6H_4$); 8.08 (1H, s, =CH) ppm. ^{19}F-NMR (DMSO-d_6) δ: −0.41 (1F, m); 11.73–12.96 (2F, m); 18.48–19.03 (1F, m) ppm. IR: 3055 (CH); 1765 (CO_2); 1645 (C=O); 1610 (C=N); 1590, 1580, 1520, 1510, 1500, 1490 (C=C) cm^{-1}. Analysis: found: C, 63.75; H, 2.69; F, 16.75; N, 6.21. Calculated for $C_{24}H_{12}F_4N_2O_3$: C, 63.72; H, 2.69; F, 16.80; N, 6.19%.

*3.3.4. 3-(1-Cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-4-on-3-yl)-1,2-dihydrobenzoxazin-2-one (**8b**) (nc)*

Similarly, product **8b** (0.33 g, 83%) was obtained from compound **5b** (0.36 g, 1.0 mmol) and *o*-aminophenol (0.22 g, 2.0 mmol) for 10 h as yellow crystals (m.p. 125–127°C). ^{1}H-NMR (DMSO-d_6) δ: 1.13–1.30 (4H, m, CH_2); 3.74–4.20 (1H, m, CH); 7.41–7.89 (4H, m, C_6H_4); 8.30 (1H, s, =CH) ppm. ^{19}F-NMR (DMSO-d_6) δ: 0.18 (1F, m); 12.01 (1F, m); 17.07 (1F, m); 18.57 (1F, m) ppm. IR: 3040 (CH); 1765 (CO_2); 1640 (C=O); 1600 (C=C) cm^{-1}. Analysis:

found: C, 59.47; H, 2.60; F, 18.44; N, 6.87. Calculated for $C_{20}H_{10}F_4N_2O_3$: C, 59.71; H, 59.71; F, 18.98; N, 6.96%.

*3.3.5. Ethyl-2-(7-(2-aminophenylthio)-1-(2-methylphenyl)-5,6,8-trifluoro-1,4-dihydroquinolin-4-on-3-yl)-2-(2-mercaptophenylimino)glyoxylate (**9**) (nc)*

To a solution of compound **5c** (0.85 g, 2.1 mmol) in 20 ml of methanol, *o*-aminothiophenol (0.674 ml, 6.3 mmol) was added. The mixture was refluxed for 10 h. After cooling, the reaction mass was poured into water (30 ml). The resulting precipitate was filtered and recrystallized from *n*-butanol to give product **9** (0.33 g, 82%) as yellow crystals (m.p. 125–127°C). ^{1}H-NMR (DMSO-d_6, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 1.11, 1.13 (3H, 2t, OCH_2CH_3, $J_{(H-H)} = 7.1$ Hz); 1.88, 1.96 (3H, 2s, CH_3); 4.10, 4.12 (2H, 2q, OCH_2CH_3, $J_{(H-H)} = 7.1$ Hz); 5.28 (2H, br.s, NH_2); 6.40–7.41 (12H, m, $3C_6H_4$,); 7.34 (1H, br.s, SH); 7.72, 7.74 (1H, 2s, CH) ppm. ^{19}F-NMR (DMSO-d_6, a mixture of *Z* and *E* isomers, ratio 1:1) δ: 16.73, 17.02 (1F, 2d.d, F-5, $J_{(5-8)} = 17.1$ Hz; $J_{(5-6)} = 22.0$ Hz); 24.63, 24.66 (1F, 2d, F-6, $J_{(6-5)} = 22.0$ Hz, $J_{(6-8)} = 0$ Hz); 46.18, 46.47 (1F, 2d, F-8, $J_{(8-5)} = 17.1$ Hz; $J_{(8-6)} = 0$ Hz) ppm. IR: 3450, 3340 (NH); 3050 (CH); 1740 (CO_2Et); 1630 (C=O); 1610, 1580 (C=N, C=C); 1590, 1580, 1520, 1510, 1500, 1490 (C=C) cm^{-1}. Analysis: found: C, 61.75; H, 3.80; F, 9.05; N, 6.76. Calculated for $C_{32}H_{24}F_3N_3O_3S_2$: C, 62.02; H, 3.90; F, 9.20; N, 6.19%.

3.4. Reactions of 1-alkyl(aryl)-3-ethoxalyl(heteryl)-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-4-ones with morpholine

*3.4.1. 3-Ethoxalyl-1-(2-methylphenyl)-7-(morpholin-1-yl)-5,6,8-trifluoro-1,4-dihydroquinolin-4-one (**10**) (nc)*

To a solution of compound **5c** (0.41 g, 1 mmol) in 30 ml of dry DMSO, morpholine (0.43 g, 5.0 mmol) was added. The mixture was stored at 20°C for 96 h and than poured into 50 ml of 5% hydrochloric acid. The resulting precipitate was filtered, washed with water and recrystallized from isopropyl alcohol to give product 10 (0.31 g, 69%) as yellow crystals (m.p. 226–228°C). ^{1}H-NMR (DMSO-d_6) δ: 1.31 (3H, t, CH_3, $J_{(H-H)} = 7.1$ Hz); 2.14 (3H, s, CH_3); 3.03–3.85 (8H, m, CH_2); 4.33 (2H, q, CH_2, $J_{(H-H)} = 7.1$ Hz); 7.26–7.58 (4H, m, C_6H_4); 8.17 (1H, s, =CH) ppm. ^{19}F-NMR (DMSO-d_6) δ: 14.74 (1F, d.d, F-6, $J_{(6-5)} = 19.5$ Hz, $J_{(6-8)} = 5.4$ Hz); 18.24 (1F, d.d, F-5, $J_{(5-6)} = 19.5$ Hz, $J_{(5-8)} = 12.2$ Hz); 26.92 (1F, d.d, F-8, $J_{(8-5)} = 12.2$ Hz, $J_{(8-6)} = 5.4$ Hz) ppm. IR: 3045 (CH); 1735 (CO_2Et); 1665, 1640 (C=O); 1620 (C=N); 1585 (C=C) cm^{-1}. Analysis: found: C, 60.79; H, 4.51; F, 12.12; N, 5.93. Calculated for $C_{24}H_{21}F_3N_2O_5$: C, 60.76; H, 4.46; F, 12.01; N, 5.91%.

*3.4.2. 6,8-Difluoro-5,7-di(morpholin-1-yl)-3-ethoxalyl-1-(2-methylphenyl)-1,4-dihydro-quinolin-4-one (**11**) (nc)*

To a solution of compound **5c** (0.41 g, 1.0 mmol) in 30 ml of dry pyrydine, morpholine (0.43 g, 5.0 mmol) was added. The mixture was refluxed for 3 h. The solvent was removed in vacuum. The residue was dissolved in 50 ml of chloroform and washed with 100 ml of 5% hydrochloric acid and water to pH = 7. Chloroform layer was separated and dried over $MgSO_4$. The solvent was removed in vacuum. The residue was recrystallized from methanol to give product **11** (0.38 g, 75%) as yellow crystals (m.p. 197–200°C). ^{1}H-NMR (DMSO-d_6) δ: 1.33 (3H, t, CH_3, $J_{(H-H)} = 7.1$ Hz); 2.11 (3H, s, CH_3); 2.96–3.81 (16H, m, $8CH_2$); 4.33 (2H, q, CH_2, $J_{(H-H)} = 7.1$ Hz); 7.26–7.58 (4H, m, C_6H_4); 8.17 (1H, s, =CH) ppm. ^{19}F-NMR (DMSO-d_6) δ: 29.57 (1F, s); 29.83 (1F, s) ppm. IR: 3050 (CH); 1735 (CO_2Et); 1665, 1630 (C=O); 1595 (C=N, C=C) cm^{-1}. Analysis: found: C, 62.18; H, 5.36; F, 6.98; N, 7.79. Calculated for $C_{28}H_{29}F_2N_3O_6$: C, 62.10; H, 5.40; F, 7.02; N, 7.76%.

*3.4.3. 3-(1-(2-Methylphenyl)-7-(morpholin-1-yl)-5,6,8-trifluoro-1,4-dihydroquinolin-4-on-3-yl)-1,2-dihydroquinoxalin-2-one (**12**) (nc)*

To a solution of compound **7a** (0.45 g, 1.0 mmol) in 10 ml of DMSO, a mixture of triethylamine (0.28 ml, 2.0 mmol) and morpholine (0.09 g, 1.0 mmol) was added. The reaction mixture was stored at 20°C for 190 h, than poured into 100 ml of 5% hydrochloric acid. The resulting precipitate was filtered and washed with water. Recrystallization from isopropyl alcohol gave product **12** (0.46 g, 88%) as yellow crystals (m.p. 328–330°C). ^{1}H-NMR (DMSO-d_6) δ: 2.21 (3H, s, CH_3); 3.03–3.71 (8H, m, $4CH_2$); 7.21–7.64 (8H, m, $2C_6H_4$); 7.75 (1H, s, =CH); 12.28 (1H, br.s, NH) ppm. ^{19}F-NMR (DMSO-d_6) δ: 11.42 (1F, d, F-6, $J_{(6-5)} = 18.8$ Hz, $J_{(6-8)} = 0$ Hz); 17.11 (1F, d.d, F-5, $J_{(5-6)} = 18.8$ Hz, $J_{(5-8)} = 13.3$ Hz); 25.25 (1F, d, F-8, $J_{(8-5)} = 13.3$ Hz, $J_{(8-6)} = 0$ Hz) ppm. IR: 3150 (NH); 1685 (CO_2N); 1620 (C=O); 1590 (C=N, C=C); 1585 (C=C) cm^{-1}. Analysis: found: C, 64.89; H, 4.05; F, 10.70; N, 10.89. Calculated for $C_{28}H_{21}F_3N_4O_3$: C, 64.86; H, 4.08; F, 10.99; N, 10.81%.

*3.4.4. 6,8-Difluoro-3-(5,7-di(morpholin-1-yl)-1-(2-methylphenyl)-1,4-dihydroquinolin-4-on-3-yl)-1,2-dihydroquinoxalin-2-one (**13**) (nc)*

To a solution of compound **7a** (0.7 g, 1.6 mmol) in 20 ml of dry pyridine, morpholine (1.37 ml, 10.0 mmol) was added. The mixture was refluxed for 10 h. The solvent was removed in vacuum. The residue was dissolved in 70 ml of chloroform. The chloroform layer was separated, washed with 100 ml of 5% hydrochloric acid and water to pH = 7, dried under $MgSO_4$. The solvent was removed. The residue was recrystallized from isopropyl alcohol to give product **13** (0.83 g, 89%) as yellow crystals (m.p. 318–320°C). ^{1}H-NMR (DMSO-d_6) δ: 2.22 (3H, s, CH_3); 3.05–3.71 (16H, m, $4CH_2$); 7.44–7.71 (8H, m, $2C_6H_4$); 7.89 (1H, s, =CH); 12.28 (1H, br.s, NH) ppm. ^{19}F-NMR (DMSO-d_6) δ: 29.76 (1F, s); 29.86 (1F, s) ppm. IR: 1660 (CO_2N); 1625 (C=O); 1610, 1595 (C=N, C=C) cm^{-1}. Analysis: found: C, 65.33; H, 5.07; F, 6.42; N, 11.72. Calculated for $C_{32}H_{29}F_2N_5O_4$: C, 65.66; H, 4.99; F, 6.49; N, 11.96%.

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