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SYNTHESIS OF FLUOROALKYLATED DIHYDROAZOLO[1,5-*a*]PYRIMIDINES AND THEIR RING-CHAIN ISOMERISM

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Abstract – Cyclisation of ethyl 2-ethoxymethylidene-3-polyfluoroalkyl-3-oxo-propionates with 3-amino-1*H*-[1,2,4]triazole, 3-amino-5-methylpyrazole, ethyl 3-aminopyrazole-4-carboxylate and ethyl 5-aminoimidazole-4-carboxylate hydrochloride results in the formation of polyfluoroalkylated dihydroazolo[1,5-*a*]pyrimidines. The latter are subject to ring-chain isomerisation in solutions depending on the solvent and the “length” of the fluoroalkyl substituent to yield ethyl 3-polyfluoroalkyl-3-oxo-2-[(azol-3-yl)aminomethylidene]propionates *via* opening of the heterocycle at the C-N bond. Dehydration of dihydroazolo[1,5-*a*]pyrimidine were realized.

INTRODUCTION

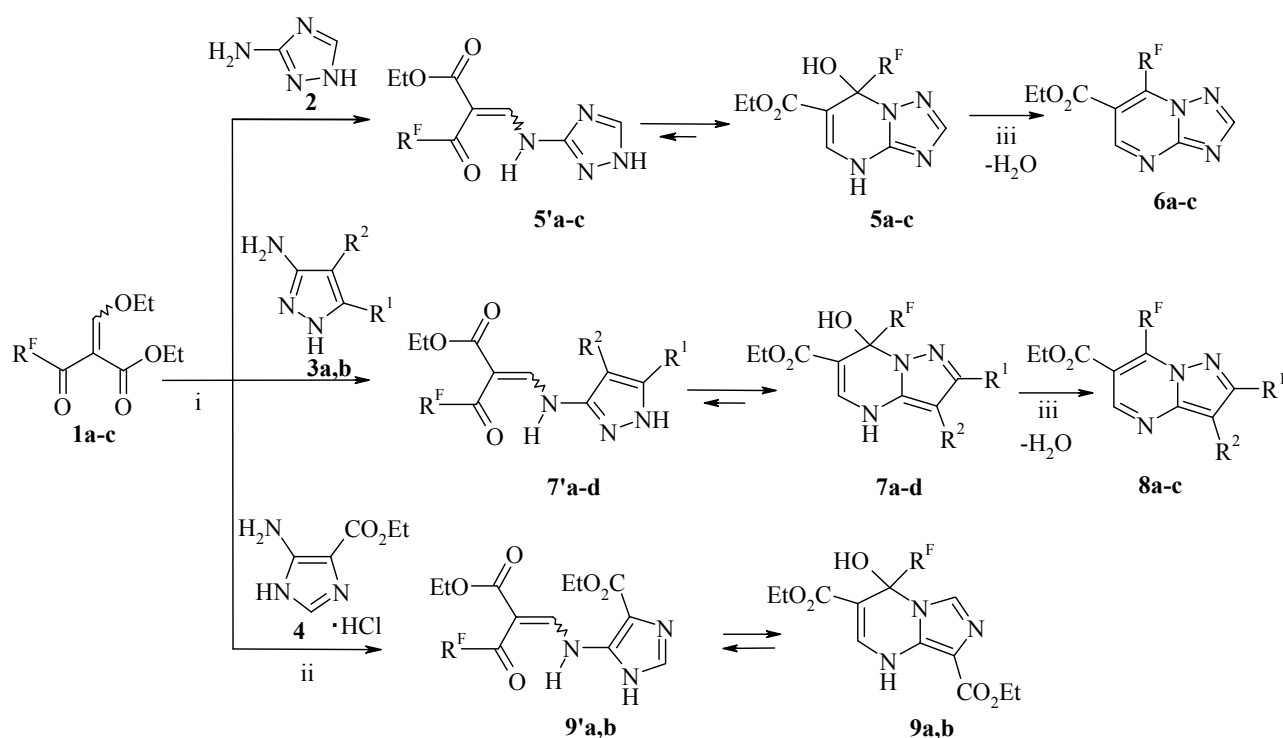
Azolo[*a*]pyrimidines containing a bridging nitrogen atom are structural analogues (isosteres) of purine bases and can therefore disturb the metabolism and hinder the protein biosynthesis.¹ New families of antiviral compounds have been found among these compounds.² Syntheses of such azolopyrimidines widely employ condensations of 1,3-dielectrophiles with aminoazoles that contain an NH group at the α -position. Convenient 1,3-dielectrophiles include 1,3-dicarbonyl compounds³ and unsaturated ketones.⁴ It is most promising to synthesise azolo[*a*]pyrimidines with functional groups that are capable of various conversions. Compounds suitable for this purpose include 1,3-dicarbonyl compounds functionalised at position 2. In fact, 2-arylmethylidene-⁵ and 2-ethoxymethylidene-3-oxoesters⁶ are suitable for building azolo[1,5-*a*]pyrimidines containing an alkoxycarbonyl fragment. A distinctive feature of

polyfluoroalkylated derivatives of 3-oxoesters in these syntheses is that they can form stable tetrahydroazolo[1,5-*a*]pyrimidines with a *gem*-aminoalcohol fragment at the polyfluoroalkyl substituent.^{4a,5d}

RESULTS AND DISCUSSION

In this work, aimed at the synthesis of potential biologically-active compounds, we have studied the reactions of ethyl 2-ethoxymethylidene-3-oxo-3-polyfluoroalkylpropionates **1a-c** with aminoazoles (3-amino-1*H*-[1,2,4]triazole **2**, 3-amino-5-methylpyrazole **3a**, ethyl 3-aminopyrazole-4-carboxylate **3b** and ethyl 5-aminoimidazole-4-carboxylate hydrochloride **4**).

It has been found that esters **1a-c** on refluxing in 1,4-dioxane with aminoazoles **2**, **3a,b**, **4** undergo conjugate substitution - addition at the ethoxymethylidene - fluoroacyl fragment to give dihydroazolo[1,5-*a*]pyrimidines **5a-c**, **7a-d**, **9a,b** (Scheme 1). The reaction could not be repeated by heating to reflux in ethanol or by heating in DMF at ~ 80 °C.



1: $R^F = CF_3$ (**a**), $(CF_2)_2H$ (**b**), C_3F_7 (**c**); **3:** $R^1 = Me$, $R^2 = H$ (**a**); $R^1 = H$, $R^2 = CO_2Et$ (**b**); **5, 6:** $R^F = CF_3$ (**a**), $(CF_2)_2H$ (**b**), C_3F_7 (**c**); **7:** $R^F = CF_3$, $R^1 = Me$, $R^2 = H$ (**a**); $R^F = C_3F_7$, $R^1 = Me$, $R^2 = H$ (**b**); $R^F = CF_3$, $R^1 = H$, $R^2 = CO_2Et$ (**c**); $R^F = (CF_2)_2H$, $R^1 = H$, $R^2 = CO_2Et$ (**d**); **8:** $R^F = CF_3$, $R^1 = Me$, $R^2 = H$ (**a**); $R^F = CF_3$, $R^1 = H$, $R^2 = CO_2Et$ (**b**); $R^F = CF_3$, $R^1 = H$, $R^2 = CO_2Et$; **9:** $R^F = CF_3$ (**a**), $(CF_2)_2H$ (**b**).

Scheme 1. Conditions: i, 1,4-dioxane, Δ ; ii, NaOAc; iii, AcOH, Δ

Condensation of 2-ethoxymethylidene-substituted acetoacetic ester with 3-amino-1*H*-[1,2,4]triazole and 3-aminopyrazoles is known to give 6-ethoxycarbonylazolo[1,5-*a*]pyrimidines.^{6b}

X-Ray diffraction analysis of crystalline compound **5b** (Figure 1) reveals that it is ethyl 7-hydroxy-7-tetrafluoroethyl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate, in which XRD

data show the existence of an O(1)...H(1) intramolecular hydrogen bond (IMHB). The IMHB parameters for compound **5b** are as follows: the intramolecular distance O(1)...H(1) is 1.89(0) Å; the O(1) – H(1)...O(3) and C(8) – O(1)...H(1) angles are 148.28° and 99.03°. The existence of an IMHB in triazolopyrimidine **5b** is also supported by its IR spectrum where a low-frequency shift of the ethoxycarbonyl group's stretching vibration absorption band (1682 cm⁻¹) is observed in comparison with the values of C=O groups in α,β -unsaturated esters (1730-1710 cm⁻¹).⁷

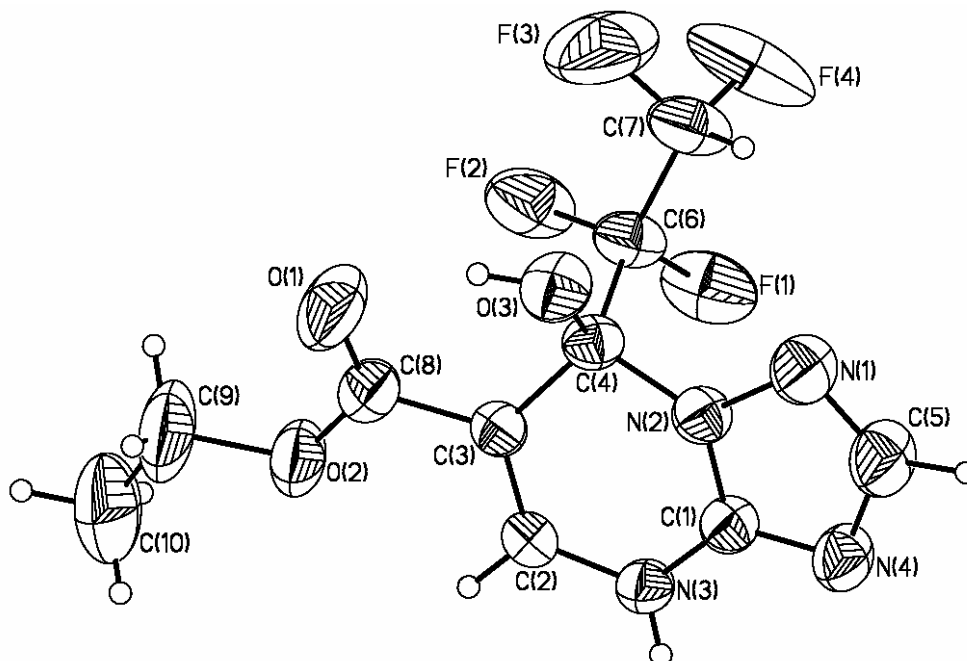


Figure 1. The general view of compound **5b**

A comparison of the IR spectra of compounds **5a,c** in nujol did not reveal considerable differences in their features.

The IR spectra of compounds **7a,b** in nujol contain one intense ethoxycarbonyl group's absorption band at 1680-1670 cm⁻¹. In the IR spectra of products **7c,d**, **9a,b**, having two ethoxycarbonyl groups, two absorption bands at 1673-1672 and 1690-1689 cm⁻¹ are observed.

Based on the above data, it is believed that the compounds **5a-c**, **7a-d**, **9a,b** in the solid state exist as cyclic form of dihydroazolo[1,5-*a*]pyrimidines.

The structure of products **5a-c**, **7a-d**, **9a,b** in solutions was studied by NMR spectroscopy.

The ¹H NMR spectra of compounds **5a-c**, recorded in (CD₃)₂SO, contain signals of ethoxy-group protons, singlet signals of two methine protons (H(2), H(5)) and broadened low-field singlet signals of NH and OH protons. These signals should be assigned to the resonance absorption of protons in bicyclic form **5**. The ¹⁹F NMR spectrum of product **5a** contains a singlet signal of the fluorine atoms at the trifluoromethyl group at $\delta \sim 83.94$ ppm, which is typical for the CF₃ group at the sp³-hybridized carbon atom in form **5**.^{5d} However, the ¹H and ¹⁹F NMR spectra of compound **5c**, recorded in (CD₃)₂SO, as well as containing the set of signals belonging to cyclic form **5** (80 %), is also two additional sets of signals corresponding to the

(*Z*)-**5'** (11 %) and (*E*)-**5'** (9%) isomers. Ethyl-2-(het)arylmethylidene-3-oxo-3-fluoroalkylpropionates have previously discovered to exist in a mixture of *Z,E*-isomeric forms.⁸

Furthermore the ¹³C NMR spectrum **5c** in (CD₃)₂SO confirms the presence of the bicyclic form **5** and the (*Z*)-**5'** and (*E*)-**5'** open-chain isomers. In this spectrum, the signals of carbon atoms at the heptafluoropropyl substituent are significant; they have the shape of a triplet due to interactions with the nearby fluorine atoms of the α-CF₂ group. The two low-field triplet signals (δ 179.43 and 180.74 ppm) are due to the resonance absorption of the C(3) carbonyl atoms of the (*Z*)-**5'** and (*E*)-**5'** forms, whereas a triplet signal of resonance absorption of the C(7) atom of the predominant cyclic form **5** is observed at 86.53 ppm, which is characteristic of the sp³-hybridised carbon atom.^{5d}

Earlier⁸, assignment of signals of C(1) and C(3) atoms for the (*Z*)-**5'** and (*E*)-**5'** isomers was performed. Thus the signal of the C(1) atom in the ethoxycarbonyl of the (*Z*)-**5'** form is observed in lower field (165.09 ppm) in comparison with the corresponding signal of the (*E*)-**5'** form (164.11 ppm), whereas the signals of the C(3) carbonyl atom at the polyfluoroacyl fragment of isomeric forms (*Z*)-**5'** and (*E*)-**5'** are arranged in the opposite order.⁸

In the ¹H and ¹⁹F NMR spectra of trifluoromethylated compounds **7a,c** in (CD₃)₂SO are observed signals corresponding to the only cyclic form **7**. However the ¹H and ¹⁹F NMR spectra of compounds **7b,d** having longer fluoroalkyl substituents (R^F = (CF₂)₂H, C₃F₇) contain in addition to the signals of cyclic form **7**, the signals of the (*Z*)-**7'** and (*E*)-**7'** isomers of open forms.

According to the data of the ¹H and ¹⁹F NMR spectroscopy in (CD₃)₂SO the compounds **9a,b** exist as a mixture of (*Z*)-**9'** and (*E*)-**9'** isomers of open forms ((2-[(imidazolyl)aminomethylidene]-3-oxo-3-polyfluoroalkylpropionates)) and cyclic (1,4-dihydroimidazo[1,5-*a*]pyrimidine) form **9**.

The discovery of the ability of heterocycles **5c**, **7b**, **7d**, **9a,b** to undergo open-chain isomerism in (CD₃)SO prompted us to study the ¹H and ¹⁹F NMR spectra of compounds **5**, **7**, **9** in various solvents. The result of this study is depicted in Table, where the existence of compounds **5**, **7**, **9** depends on the NMR solvent used.

It is found that the ¹H NMR spectra of compounds **5b,c**, **7b,d** and **9a** in (CD₃)₂CO contain, in addition to the signals corresponding to cyclic form, also signals of the *Z*- and *E*-isomers of open form **5'**, **7'**, **9'**. In contrast, the ¹H NMR spectra of compounds **5a**, **7a,c** in (CD₃)₂CO show that only cyclic form are present. However, the ¹H NMR spectra of compounds recorded in CD₃CN show that the cyclic form and the *Z*- and *E*-isomers are presented not only for compounds **5b,c**, **7b,d**, **9a** but for the product **5a** as well (Table 1).

¹H NMR spectra of compound **9b** in (CD₃)₂CO and CD₃CN contain non-cyclic form (*Z*)-**9'b** and (*E*)-**9'b** (Table 1).

The signals of the cyclic form are found in the ¹H NMR spectra of compounds **5a-c**, **7a-d** measuring in

CD₃OD (Table 1). The compounds **7d** and **9a,b** in CD₃OD exist as a mixture of the open and cyclic forms. The heterocycles **5a-c**, **7a-d**, **9a,b** are insoluble in CDCl₃.

Table 1. Cyclic and open-chain forms ratios according to the NMR data

compounds	R ^F	solvent			
		(CD ₃) ₂ SO	CD ₃ CN	(CD ₃) ₂ CO	CD ₃ OD
5a	CF ₃	5a , 100 %	5a , 92 % (<i>Z</i>)- 5'a , 3 % (<i>E</i>)- 5'a , 5 %	5a , 100 %	5a , 100 %
5b	(CF ₂) ₂ H	5b , 100 %	5b , 68 % (<i>Z</i>)- 5'b , 11 % (<i>E</i>)- 5'b , 21 %	5b , 59 % (<i>Z</i>)- 5'b , 15 % (<i>E</i>)- 5'b , 26 %	5b , 100 %
5c	C ₃ F ₇	5c , 80 % (<i>Z</i>)- 5'c , 11 % (<i>E</i>)- 5'c , 9 %	5c , 41 % (<i>Z</i>)- 5'c , 32 % (<i>E</i>)- 5'c , 27 %	5c , 28 % (<i>Z</i>)- 5'c , 41 % (<i>E</i>)- 5'c , 31 %	5c , 100 %
7a	CF ₃	7a , 100 %	7a , 100 %	7a , 100 %	7a , 100 %
7b	C ₃ F ₇	7b , 40 % (<i>Z</i>)- 7'b , 26 % (<i>E</i>)- 7'b , 33 %	7b , 19% (<i>Z</i>)- 7'b , 35 % (<i>E</i>)- 7'b , 46 %	7b , 3 % (<i>Z</i>)- 7'b , 44 % (<i>E</i>)- 7'b , 53 %	7b , 100 %
7c	CF ₃	7c , 100 %	7c , 100 %	7c , 100 %	7c , 100 %
7d	(CF ₂) ₂ H	7d , 81 % (<i>Z</i>)- 7'd , 7 % (<i>E</i>)- 7'd , 12 %	7d , 60 % (<i>Z</i>)- 7'd , 13 % (<i>E</i>)- 7'd , 27 %	7d , 45 % (<i>Z</i>)- 7'd , 19 % (<i>E</i>)- 7'd , 36 %	7d , 3 % (<i>Z</i>)- 7'd , 19 % (<i>E</i>)- 7'd , 7 %
9a	CF ₃	9a , 72 % (<i>Z</i>)- 9'a , 10 % (<i>E</i>)- 9'a , 18 %	9a , 32 % (<i>Z</i>)- 9'a , 26 % (<i>E</i>)- 9'a , 42 %	9a , 22 % (<i>Z</i>)- 9'a , 31 % (<i>E</i>)- 9'a , 47 %	9a , 69 % (<i>Z</i>)- 9'a , 10 % (<i>E</i>)- 9'a , 21 %
9b	(CF ₂) ₂ H	9b , 19 % (<i>Z</i>)- 9'b , 27 % (<i>E</i>)- 9'b , 54 %	(<i>Z</i>)- 9'b , 27 % (<i>E</i>)- 9'b , 73 %	(<i>Z</i>)- 9'b , 31 % (<i>E</i>)- 9'b , 69 %	9b , 11 % (<i>Z</i>)- 9'b , 25 % (<i>E</i>)- 9'b , 64 %

A specific feature of signals of the open-chain isomers **5'**, **7'**, **9'** in the ¹H NMR spectrum is the character of resonance absorption of the =CH and NH protons of their aminomethylidene fragment that are observed as low-field doublets with a coupling constant of ~ 14 Hz, which is evidence of their *trans*-configuration.⁹ The signals of fluorine atoms of the CF₃ and α-CF₂ groups of open form **5'c**, **7'b,d** and **9'a,b** in the ¹⁹F NMR spectra in (CD₃)₂SO are characterised by a downfield shift (δ_{CF₃} 90.83-91.82,

$\delta_{\alpha\text{-CF}_2((\text{CF}_2)_2\text{H})}$ 42.98-43.11, $\delta_{\alpha\text{-CF}_2(\text{C}_3\text{F}_7)}$ 49.61-50.23 ppm) with respect to the corresponding signals of fluorine atoms in cyclic form **9a**, **5b** (δ_{CF_3} 81.38, $\delta_{\alpha\text{-CF}_2((\text{CF}_2)_2\text{H})}$ 32.29-41.79, $\delta_{\alpha\text{-CF}_2(\text{C}_3\text{F}_7)}$ 46.13-46.26 ppm). Assignment of the *Z*- and *E*-isomers of open form in the ^1H NMR spectra was made using the regularities that we revealed previously for 2-alkyl(aryl)aminomethylidene-3-fluoroalkyl-3-oxopropionates, according to which the protons of the $=\text{CH}$ and NH groups of the *E*-isomer are observed in weaker field than the corresponding protons of the *Z*-isomer.⁸

Dehydration of 4,7-dihydrotriazolo[1,5-*a*]pyrimidines **5a-c** is hindered. In fact, prolonged refluxing (~60 h) in acetic acid is necessary to obtain ethyl 7-polyfluoroalkyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylates **6a-c**.

Dehydration of 4,7-dihydropyrazolo[1,5-*a*]pyrimidine **7a,b,d** in boiling acetic acid proceeds easily to give ethyl-7-(fluoroalkyl)pyrazolo[1,5-*a*]pyrimidine-6-carboxylates **8a-c**.

An attempts to dehydrate dihydroimidazo[1,5-*a*]pyrimidine **9a,b** under similar conditions were unsuccessful because of their resinification.

To summarize the obtained data, it can be concluded that fluoroalkyl-containing dihydroazolo[1,5-*a*]pyrimidines **5**, **7**, **9** can undergo ring-chain isomerism. Thus, they have cyclic structures in the solid state, whereas in solution, depending on the solvent and the “length” of the fluoroalkyl substituent, they may also exist in open-chain form **5'**, **7'**, **9'**. It should be noted that this kind of isomerism is not typical for their non-fluorinated analogues, *viz*, 2-azolylaminomethylidene-3-oxoalkanoates. The latter compounds are only capable of irreversible intramolecular condensation to give azolopyrimidines.^{6b} Ring-chain isomerism becomes possible owing to the presence of an electron-withdrawing polyfluoroalkyl substituent that prevents easy elimination of a water molecule and the formation of azolopyrimidines **6**, **8**, on the one hand, and facilitates the addition of an amine to give dihydroazolopyrimidines **5**, **7**, **9** that are stabilized due to formation of the strong IMHBs, on the other hand.

EXPERIMENTAL

Melting points were measured in open capillaries by apparatus “Stuart SMP3”. The infrared spectra were recorded on Perkin Elmer Spectrum One FT-IR and Thermo Nicolet 6700 FT-IR spectrometers at 4000-400 cm^{-1} in Nujol mulls. The ^1H and ^{13}C NMR spectra were measured on a Bruker DRX-400 spectrometer (^1H , 400; ^{13}C , 100.6 MHz) relative to SiMe_4 . The ^{19}F NMR spectra were obtained on a Bruker DRX-400 spectrometer (^{19}F , 376 MHz) using C_6F_6 as an internal standard. The microanalyses were carried out on a Perkin Elmer PE 2400 series II elemental analyzer.

Ethyl 2-ethoxymethylidene-3-polyfluoroalkyl-3-oxopropionates **1a-c** were prepared according to a reported procedure,⁸ ethyl 5-aminoimidazole-4-carboxylate hydrochloride **4** – procedure.¹¹

3-Amino-1*H*-[1,2,4]triazole **2**, 3-amino-5-methylpyrazole **3a**, ethyl 3-aminopyrazole-4-carboxylate **3b** are commercial compounds.

Crystallographic data for **5b**: at 295 K, C₁₀H₁₀F₄N₄O₃ (*M* = 310.22) are monoclinic, space group P2₁/c, *a* = 16.737(2) Å, *b* = 8.7692(10) Å, *c* = 8.8892(10) Å, β = 100.022(10) °, *V* = 1284.7(3) Å³, *Z* = 4, *d*_{calc} = 1.604 g/cm⁻³, μ (Mo-Kα) = 0.157 cm⁻¹, F(000) = 632. The intensities of 14817 were measured with a Xcalibur 3 at 295 K (ω/2θ-scans, Mo-Kα, graphite monochromator, CCD-detector) and 3963 independent reflection (*R*_{int} = 0.0211) were used in further refinement. The structure was solved by the direct methods with the set programs SHELXL-97¹⁰ and refined by full-matrix least-squares method. The refinement converged to *wR*₂ = 0.1885 and GOF = 1.000 for all independent reflections (*R*_i = 0.0633 for 2225 reflection with *F*_o > 4σ(*F*_o)). CCDC 646963 contains the supplementary crystallographic data for this compound.¹

General procedure A: A mixture of ester **1** (3 mmol) and aminoazole **2**, **3a,b** (3 mmol) in 1,4-dioxane (20 mL) was refluxed for 16-18 h. The reaction mixture was poured into water. The resulting precipitate was filtered off and recrystallized from EtOH.

General procedure B: The solution of pyrimidine **5**, **7** (1 mmol) in glacial acetic acid was refluxed for 6-60 h. The reaction mixture was poured into water and was reduced to pH 7. The resulting precipitate was filtered off and recrystallized from hexane.

General procedure C: A mixture of ester **1a,b** (3 mmol), ethyl 5-aminoimidazole-4-carboxylate hydrochloride (0.575 g, 3 mmol) and NaOAc·3H₂O (0.408 g, 3 mmol) in 1,4-dioxane (20 mL) was refluxed for 12-14 h. The reaction mixture was poured into water. The resulting precipitate was filtered off and recrystallized from EtOH.

Ethyl 7-hydroxy-7-(trifluoromethyl)-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (5a).

The ester **1a** (0.720 g, 3 mmol) gave by procedure A 0.601 g (72 %) of product **5a**, mp 184-186 °C. Anal. Calcd for C₉H₉F₃N₄O₃: C, 38.86; H, 3.26; F, 20.49; N, 20.14. Found: C, 38.86; H, 3.11; F, 20.47; N, 20.27 %. IR: ν 3200, 3114, (NH, OH), 2923 (C-H), 1678 (CO₂Et), 1599, 1521 (C=C, C=N), 1267-1158 (C-F) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.23 (t, *J* 7.0 Hz, 3H, OCH₂CH₃), 4.15 (m, AB-system, Δ_{AB} 0.05 ppm, *J*_{AB} 10.8, *J* 7.0 Hz, 2H, OCH₂CH₃), 7.88, 7.91 (both s, 1H each, H(2), H(5)), 8.48 (s, 1H, NH), 11.77 (br.s, 1H, OH) ppm. ¹⁹F NMR (DMSO-*d*₆): δ 83.94 (s, CF₃) ppm.

Ethyl 7-hydroxy-7-(1,1,2,2-tetrafluoroethyl)-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (5b).

The ester **1b** (0.817 g, 3 mmol) gave by procedure A 0.633 g (68 %) of product **5b**, mp 155-157 °C. Anal.

¹ These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Calcd for $C_{10}H_{10}F_4N_4O_3$: C, 38.72; H, 3.25; F, 24.50; N, 18.06. Found: C, 38.96; H, 3.20; F, 24.52; N, 18.03 %. IR: ν 3220, 3108, (NH, OH), 2930 (C-H), 1682 (CO₂Et), 1614, 1529 (C=C, C=N), 1206-1078 (C-F) cm^{-1} . 1H NMR (DMSO- d_6): δ 1.24 (t, J 7.0 Hz, 3H, OCH₂CH₃), 4.16 (m, AB-system, Δ_{AB} 0.03 ppm, J_{AB} 10.7, J 7.0 Hz, 2H, OCH₂CH₃), 6.70 (d.d.d.d, $J_{H,F}$ 53.2, 51.3, 10.5, 2.4 Hz, 1H, (CF₂)₂H), 7.86, 7.91 (both s, 1H each, H(2), H(5)), 8.36 (s, 1H, NH), 11.68 (br.s, 1H, OH) ppm. 1H NMR ((CD₃)₂CO): δ **5b** (59 %) 1.24 (t, J 7.1 Hz, 3H, OCH₂CH₃), 4.29 (q, J 7.1 Hz, 2H, OCH₂CH₃), 6.73 (d.d.d.d, $J_{H,F}$ 52.1, 53.0, 10.4, 2.3 Hz, 1H, (CF₂)₂H), 7.34 (br.s, 1H, NH), 7.85, 8.09 (both s, 1H each, H(2), H(5)), 10.69 (s, 1H, OH); (**Z**)-**5b'** (15 %) 1.35 (t, J 7.0 Hz, 3H, OCH₂CH₃), 4.29 (q, J 7.0 Hz, 2H, OCH₂CH₃), 6.66 (t.t, $J_{H,F}$ 52.7, 5.9 Hz, 1H, (CF₂)₂H), 8.48 (br.s, 1H, H(5')), 8.79 (d, J 13.5 Hz, 1H, CH), 11.08 (br.d, J 13.5 Hz, 1H, NH), 13.20 (br.s, 1H, NH(1')); (**E**)-**5b'** (26 %) 1.34 (t, J 7.0 Hz, 3H, OCH₂CH₃), 4.36 (q, J 7.0 Hz, 2H, OCH₂CH₃), 6.95 (t.t, $J_{H,F}$ 53.4, 5.8 Hz, 1H, (CF₂)₂H), 8.52 (br.s, 1H, H(5')), 8.98 (d, J 13.5 Hz, 1H, CH), 10.69 (br.d, J 13.5 Hz, 1H, NH), 13.27 (br.s, 1H, NH(1')) ppm. ^{19}F NMR (DMSO- d_6): δ : 26.04 (t.d.d, $J_{F,F}$ 293.71, 9.6, $J_{F,H}$ 53.2 Hz, 1F, CF₂H), 31.02 (d.d.d.d, $J_{F,F}$ 293.7, 10.6, 1.4, $J_{F,H}$ 51.3 Hz, 1F, CF₂H), 32.97 (d.d.d, $J_{F,F}$ 261.2, 19.6, $J_{F,H}$ 10.5 Hz, 1F, CF₂), 41.66 (d.d.d, $J_{F,F}$ 261.2, 10.6, $J_{F,H}$ 2.4 Hz, 1F, CF₂) ppm.

Ethyl 7-(1,1,2,2,3,3,3-heptafluoropropyl)-7-hydroxy-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (5c**).**

The ester **1c** (1.021 g, 3 mmol) gave by procedure A 0.681 g (60 %) of product **5c**, mp 136-138 °C. Anal. Calcd for $C_{11}H_9F_7N_4O_3$: C, 34.93; H, 2.40; F, 35.16; N, 14.81. Found: C, 34.94; H, 2.11; F, 35.25; N, 14.81 %. IR: ν 3200, 3115 (NH, OH), 3015, 2924 (C-H), 1693 (CO₂Et), 1602, 1599 (C=C, C=N), 1220-1119 (C-F) cm^{-1} . 1H NMR (DMSO- d_6): δ **5c** (80 %) 1.25 (t, J 7.2 Hz, 3H, OCH₂CH₃), 4.18 (m, AB-system, Δ_{AB} 0.04 ppm, J_{AB} 10.8, J 7.2 Hz, 2H, OCH₂CH₃), 7.89, 7.92 (both s, 1H each, H(2), H(5)), 8.56 (s, 1H, NH), 11.81 (br.s, 1H, OH); (**Z**)-**5c'** (11 %) 1.25 (t, J 7.1 Hz, 3H, OCH₂CH₃), 4.27 (q, J 7.1 Hz, 2H, OCH₂CH₃), 8.56 (s, 1H, H(5')), 8.60 (d, J 13.9 Hz, 1H, CH), 11.29 (d, J 13.9 Hz, 1H, NH), 14.13 (br.s, 1H, NH(1')); (**E**)-**5c'** (9 %) 1.25 (t, J 7.1 Hz, 3H, OCH₂CH₃), 4.26 (q, J 7.1 Hz, 2H, OCH₂CH₃), 8.58 (s, 1H, H(5')), 8.77 (d, J 13.9 Hz, 1H, CH), 11.81 (d, J 13.9 Hz, 1H, NH), 14.22 (br.s, 1H, NH(1')) ppm. ^{19}F NMR (DMSO- d_6): δ **2c** (80 %) 37.44 (m, AB-system, Δ_{AB} 1.40 ppm, J_{AB} 290.0 Hz, 2F, β -CF₂), 46.26 (m, 2F, α -CF₂), 82.34 (t, $J_{F,F}$ 11.6 Hz, 3F, CF₃); (**Z**)-**2c'** (11%) 38.43 (m, 2F, β -CF₂), 49.96 (m, 2F, α -CF₂), 82.94 (t, $J_{F,F}$ 9.3 Hz, 3F, CF₃); (**E**)-**5c'** (9 %) 39.64 (m, 2F, β -CF₂), 49.61 (m, 2F, α -CF₂), 82.92 (t, $J_{F,F}$ 9.3 Hz, 3F, CF₃) ppm. ^{13}C NMR (DMSO- d_6): δ 105.81-121.88 (m, C₃F₇ ((**E**)-**5c'**, (**Z**)-**5c'**, **5c**); **5c** (80%) 14.03 (CH₃), 59.89 (OCH₂), 86.53 (t, $J_{C,F}$ 27.2 Hz, C(7)), 96.86 (C(6)), 139.09 (C(5)), 147.19 (C(3a)), 150.56 (C(2)), 163.98 (C(9)); (**Z**)-**5c'** (11 %) 13.74 (CH₃), 60.86 (OCH₂), 101.77 (C(2)), 144.52 (C(5')), 151.52 (C(4')), 157.15 (C(3')), 165.09 (C(1)), 179.43 (br.t, $J_{C,F}$ 25.4 Hz, C(3)); (**E**)-**5c'** (9 %) 13.85 (CH₃), 60.69 (OCH₂), 100.63 (C(2)), 144.73 (C(5')), 154.90 (C(4)), 156.69 (C(3')), 164.11 (C(1)), 180.74 (br.t, $J_{C,F}$ 25.0 Hz, C(3)) ppm.

Ethyl 7-(trifluoromethyl)-5H-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (6a).

Pyrimidine **5a** (0.278 g, 1 mmol) gave by procedure B 0.247 g (95 %) of product **6a**, mp 77-78 °C. Anal. Calcd for C₉H₇F₃N₄O₂: C, 41.55; H, 2.71; F, 21.91; N, 21.53. Found: C, 41.69; H, 2.80; F, 21.78; N, 21.69 %. IR: ν 3069, 3018 (C-H), 1719 (CO₂Et), 1627, 1511 (C=C, C=N), 1191-1129 (C-F) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.37 (t, *J* 7.2 Hz, 3H, OCH₂CH₃), 4.41 (q, *J* 7.2 Hz, 2H, OCH₂CH₃), 9.05 (s, 1H, H(5)), 10.16 (s, 1H, H(2)) ppm. ¹⁹F NMR (DMSO-*d*₆): δ 98.46 (s, CF₃) ppm.

Ethyl 7-(1,1,2,2-tetrafluoroethyl)-5H-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (6b).

Pyrimidine **5b** (0.310 g, 1 mmol) gave by procedure B 0.228 g (78 %) of product **6b**, mp 93-95 °C. Anal. Calcd for C₁₀H₈F₄N₄O₂: C, 41.11; H, 2.76; F, 26.01; N, 19.17. Found: C, 41.25; H, 2.81; F, 25.89; N, 18.95 %. IR: ν 3118, 3079, 3029 (C-H), 1707 (CO₂Et), 1620, 1506 (C=C, C=N), 1164-1071 (C-F) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.36 (t, *J* 7.1 Hz, 3H, OCH₂CH₃), 4.41 (q, *J* 7.1 Hz, 2H, OCH₂CH₃), 7.19 (t.t, *J*_{H,F} 51.8, 6.0 Hz, 1H, (CF₂)₂H), 9.02 (s, 1H, H(5)), 10.12 (s, 1H, H(2)) ppm. ¹⁹F NMR (DMSO-*d*₆): δ : 24.69 (d.m, *J*_{F,H} 51.8 Hz, 2F, CF₂H), 48.38 (m, 2F, CF₂) ppm.

Ethyl 7-(1,1,2,2,3,3,3-heptafluoropropyl)-5H-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (6c).

Pyrimidine **5c** (0.378 g, 1 mmol) gave by procedure B 0.234 g (65 %) of product **6c**, mp 125-126 °C. Anal. Calcd for C₁₁H₇F₇N₄O₂: C, 36.68; H, 1.96; F, 36.92; N, 15.55. Found: C, 36.36; H, 2.00; F, 36.94; N, 15.28 %. IR: ν 3049, 3104 (C-H), 1727 (CO₂Et), 1622, 1502 (C=C, C=N), 1236-1124 (C-F) cm⁻¹. ¹H NMR (CDCl₃): δ 1.43 (t, *J* 7.2 Hz, 3H, OCH₂CH₃), 4.49 (q, *J* 7.2 Hz, 2H, OCH₂CH₃), 8.78 (s, 1H, H(5)), 9.39 (s, 1H, H(2)) ppm. ¹⁹F NMR (CDCl₃): δ 39.12 (m, 2F, β -CF₂), 54.73 (m, 2F, α -CF₂), 81.86 (t, *J*_{F,F} 10.0 Hz, 3F, CF₃) ppm.

Ethyl 7-hydroxy-2-methyl-7-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxylate (7a).

The ester **1a** (0.720 g, 3 mmol) gave by procedure A 0.664 g (76 %) of product **7a**, mp 193-195 °C. Anal. Calcd for C₁₁H₁₂F₃N₃O₃: C, 45.37; H, 4.15; F, 19.57; N, 14.43. Found: C, 45.41; H, 4.08; F, 19.49; N, 14.46 %. IR: ν 3300, 3119 (NH, OH), 3007, 2961 (C-H), 1669 (CO₂Et), 1628, 1601 (C=C, C=N), 1200-1080 (C-F) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.22 (t, *J* 7.0 Hz, 3H, OCH₂CH₃), 2.14 (s, 3H, CH₃), 4.13 (m, AB-system, Δ_{AB} 0.05 ppm, *J*_{AB} 10.8, *J* 7.0 Hz, 2H, OCH₂CH₃), 5.64 (s, 1H, H(3)), 7.83 (c, 1H, H(5)), 7.85 (br.s, 1H, OH), 10.82 (br.s, 1H, NH(4)) ppm. ¹⁹F NMR (DMSO-*d*₆): δ : 84.24 (s, CF₃) ppm.

Ethyl 7-(1,1,2,2,3,3,3-heptafluoropropyl)-7-hydroxy-2-methyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxylate (7b).

The ester **1c** (1.021 g, 3 mmol) gave by procedure A 0.822 g (70 %) of product **5c**, mp 128-130 °C. Anal. Calcd for C₁₃H₁₂F₇N₃O₃: C, 39.91; H, 3.09; F, 33.99; N, 10.74. Found: C, 40.11; H, 3.21; F, 34.07; N, 10.72 %. IR: ν 3241, 3212, 3133 (NH, OH), 3077, 2990 (C-H), 1682 (CO₂Et), 1637, 1606 (C=C, C=N), 1265-1088 (C-F) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ **7b** (40 %) 1.22 (t, *J* 7.1 Hz, 3H, OCH₂CH₃), 4.13 (m,

AB-system, Δ_{AB} 0.03 ppm, J_{AB} 10.8, J 7.1 Hz, 2H, OCH_2CH_3), 5.66 (s, 1H, H(3)), 7.85 (d, J 5.0 Hz, 1H, H(5)), 7.94 (s, 1H, OH), 10.90 (d, J 5.0 Hz, 1H, NH(4)); (**Z**)-**7'b** (26 %) 1.25 (t, J 7.0 Hz, 3H, OCH_2CH_3), 4.25 (q, J 7.0 Hz, 2H, OCH_2CH_3), 6.12 (s, 1H, H(4')), 8.49 (d, J 14.3 Hz, 1H, CH); 11.10 (d, J 14.3 Hz, 1H, NH), 12.48 (s, 1H, NH(1')); (**E**)-**7'b** (34 %) 1.24 (t, J 7.0 Hz, 3H, OCH_2CH_3), 4.18 (q, J 7.0 Hz, 2H, OCH_2CH_3), 6.20 (s, 1H, H(4')), 8.66 (d, J 14.5 Hz, 1H, CH), 11.87 (d, J 14.5 Hz, 1H, NH), 12.55 (s, 1H, NH(1')) ppm. ^{19}F NMR (DMSO- d_6): δ **7b** (40 %) 37.14 (m, AB-system, Δ_{AB} 1.10 ppm, J_{AB} 288.5 Hz, 2F, β -CF₂), 46.13 (m, AB-system, Δ_{AB} 1.36 ppm, J_{AB} 278.6 Hz, 2F, α -CF₂), 82.33 (t, $J_{F,F}$ 11.5 Hz, 3F, CF₃); (**Z**)-**7'b** (26 %) 38.73 (m, 2F, β -CF₂), 50.23 (m, 2F, α -CF₂), 83.00 (t, $J_{F,F}$ 9.2 Hz, 3F, CF₃); (**E**)-**7'b** (34 %) 39.59 (m, 2F, β -CF₂), 49.79 (m, 2F, α -CF₂), 82.93 (t, $J_{F,F}$ 9.2 Hz, 3F, CF₃) ppm.

Diethyl 7-hydroxy-7-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate (7c).

The ester **1a** (0.720 g, 3 mmol) gave by procedure A 0.702 g (67 %) of product **7a**, mp 216 – 218 °C. Anal. Calcd for C₁₃H₁₄F₃N₃O₅: C, 44.71; H, 4.04; F, 16.32; N, 12.03. Found: C, 44.73; H, 3.86; F, 15.99; N, 11.90 %. IR: ν 3287, 3133 (NH, OH), 2971 (C-H), 1690, 1672 (CO₂Et), 1607 (C=C, C=N), 1230-1104 (C-F). 1H NMR (DMSO- d_6): δ 1.24, 1.29 (both t, J 7.0 Hz, 3H each, 2 OCH_2CH_3), 4.18 (m, AB-system, Δ_{AB} 0.05 ppm, J_{AB} 10.8, J 7.0 Hz, 2H, OCH_2CH_3), 4.25 (q, J 7.0 Hz, 2H, OCH_2CH_3), 7.79 (d, J 5.1 Hz, 1H, H(5)), 7.92 (s, 1H, H(2)), 8.48 (d, $J_{H,F}$ 0.9 Hz, 1H, OH), 10.69 (d, J 5.1 Hz, 1H, NH(4)) ppm. ^{19}F NMR (DMSO- d_6): δ 84.01 (d, $J_{F,H}$ 0.9 Hz, CF₃) ppm.

Diethyl 7-hydroxy-7-(1,1,2,2-tetrafluoroethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate (7d).

The ester **1b** (0.817 g, 3 mmol) gave by procedure A 0.890 g (78 %) of product **7d**, mp 178-180 °C. Anal. Calcd for C₁₄H₁₅F₄N₃O₅: C, 44.10; H, 3.97; F, 19.93; N, 11.02. Found: C, 43.97; H, 3.82; F, 19.82; N, 11.16 %. IR: ν 3272, 3132 (NH, OH), 2998 (C-H), 1689, 1673 (CO₂Et), 1608 (C=C, C=N), 1229-1079 (C-F). 1H NMR (DMSO- d_6): **7d** (81 %) 1.24, 1.29 (both t, J 7.1 Hz, 3H each, 2 OCH_2CH_3), 4.16 (m, AB-system, Δ_{AB} 0.03 ppm, J_{AB} 10.8, J 7.1 Hz, 2H, OCH_2CH_3), 4.27 (m, AB-system, Δ_{AB} 0.02 ppm, J_{AB} 10.8, J 7.1 Hz, 2H, OCH_2CH_3), 6.68 (d.d.d.d, $J_{H,F}$ 53.5, 51.5, 10.9, 1.6 Hz, 1H, (CF₂)₂H), 7.76 (s, 1H, H(5)), 7.91 (d, J 6.3 Hz, 1H, H(2)), 8.33 (s, 1H, OH), 10.65 (br.s, 1H, NH(4)); (**Z**)-**7'd** (7 %) 1.26, 1.38 (both t, J 7.1 Hz, 3H each, 2 OCH_2CH_3), 4.30, 4.24 (both q, J 7.1 Hz, 2H each, 2 OCH_2CH_3), 6.68 (t.t, $J_{H,F}$ 51.5, 7.2 Hz, 1H, (CF₂)₂H), 8.39 (br.s, 1H, H(5')), 8.67 (br.d, J 13.7 Hz, 1H, CH), 11.84 (br.d, J 13.7 Hz, 1H, NH), 13.38 (br.s, 1H, NH(1')); (**E**)-**7'd** (12 %): 1.28, 1.34, (both t, J 7.1 Hz, 3H each, 2 OCH_2CH_3), 4.21, 4.32 (both q, J 7.1 Hz, 2H each, 2 OCH_2CH_3), 6.99 (t.t, $J_{H,F}$ 52.7, 7.3 Hz, 1H, (CF₂)₂H), 8.42 (br.s, 1H, H(5')), 8.83 (d, J 14.3 Hz, 1H, CH), 12.43 (d, J 14.3 Hz, 1H, NH), 13.49 (br.s, 1H, NH(1')) ppm. ^{19}F NMR (DMSO- d_6): δ **7d** (19 %) 26.01 (d.d.t, $J_{F,F}$ 293.4, 9.1, $J_{F,H}$ 53.5 Hz, 1F, CF₂H), 31.23 (d.d.d, $J_{F,F}$ 293.4, 10.7, $J_{F,H}$ 51.5 Hz, 1F, CF₂H), 32.29 (d.m, $J_{F,F}$ 260.8 Hz, 1F, CF₂), 41.79 (d.d, $J_{F,F}$ 260.8, 9.1 Hz, 1F, CF₂); (**Z**)-**7'd** (25 %) 23.90 (d.m, $J_{F,H}$ 51.5 Hz, 2F, CF₂H), 42.98 (m, 2F, CF₂); (**E**)-**7'd** (56 %)

25.17 (d.m, $J_{\text{F,H}}$ 52.7 Hz, 2F, CF₂H), 41.32 (m, 2F, CF₂) ppm.

Ethyl 2-methyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-6-carboxylate (8a).

Pyrimidine **7a** (0.291 g, 1 mmol) gave by procedure B 0.235 g (86 %) of product **8a**, mp 94-95 °C. Anal. Calcd for C₁₁H₁₀F₃N₃O₂: C, 48.36; H, 3.69; F, 20.86; N, 15.38. Found: C, 48.26; H, 3.53; F, 20.68; N, 15.68 %. IR: ν 3115, 3097 (C-H), 1717 (CO₂Et), 1618, 1553 (C=C, C=N), 1192-1116 (C-F) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.42 (t, J 7.1 Hz, 3H, OCH₂CH₃), 2.59 (s, 3H, CH₃), 4.44 (q, J 7.1 Hz, 2H, OCH₂CH₃), 6.75 (s, 1H, H(3)), 9.26 (s, 1H, H(5)) ppm. ¹⁹F NMR (DMSO-*d*₆): δ 96.73 (s, CF₃) ppm.

Diethyl 7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate (8b).

Pyrimidine **7c** (0.349 g, 1 mmol) gave by procedure B 0.298 g (90 %) of product **8b**, mp 95-97 °C. Anal. Calcd for C₁₃H₁₂F₃N₃O₄: C, 47.14; H, 3.65; F, 17.21; N, 12.69. Found: C, 47.11; H, 3.63; F, 17.18; N, 12.64 %. IR: ν 3062 (C-H), 1712 (CO₂Et), 1623, 1562 (C=C, C=N), 1219-1156 (C-F) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 1.34, 1.36 (both t, J 7.1 Hz, 3H each, 2 OCH₂CH₃), 4.34, 4.39 (both q, J 7.1 Hz, 2H each, 2 OCH₂CH₃), 8.96 (s, 1H, H(2)), 9.97 (s, 1H, H(5)) ppm. ¹⁹F NMR (DMSO-*d*₆): δ 98.52 (s, CF₃) ppm.

Diethyl 7-(1,1,2,2-tetrafluoroethyl)pyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate (8c).

Pyrimidine **7d** (0.381 g, 1 mmol) gave by procedure B 0.283 g (78 %) of product **8c**, mp 107-109 °C. Anal. Calcd for C₁₄H₁₃F₄N₃O₄: C, 46.13; H, 3.61; F, 20.92; N, 11.57. Found: C, 46.43; H, 3.61; F, 20.88; N, 11.59 %. IR: ν 2996 (C-H), 1727, 1719 (CO₂Et), 1624, 1598 (C=C, C=N), 1207-1092 (C-F) cm⁻¹. ¹H NMR (CDCl₃): δ 1.42, 1.43 (both t, J 7.1, 7.2 Hz, 3H each, 2 OCH₂CH₃), 4.47, 4.49 (both q, J 7.1, 7.2 Hz, 2H each, 2 OCH₂CH₃), 7.09 (t.t, $J_{\text{H,F}}$ 53.3, 5.8 Hz, 1H, (CF₂)₂H), 8.68 (s, 1H, H(5)), 8.84 (s, 1H, H(2)) ppm. ¹⁹F NMR (CDCl₃): δ 24.83 (d.m, $J_{\text{F-H}}$ 53.3 Hz, 2F, CF₂H), 44.49 (m, 2F, CF₂) ppm.

Diethyl 4-hydroxy-4-(trifluoromethyl)-1,4-dihydroimidazo[1,5-*a*]pyrimidine-3,8-dicarboxylate (9a).

The ester **1a** (0.720 g, 3 mmol) gave by procedure C 0.754 g (72 %) of product **9a**, mp 185-186 °C. Anal. Calcd for C₁₃H₁₄F₃N₃O₅: C, 44.71; H, 4.04; F, 13.32; N, 12.03. Found: C, 44.92; H, 3.90; F, 16.28; N, 11.91 %. IR: ν 3248 (NH, OH); 2999 (C-H), 1719, 1698 (CO₂Et), 1639, 1611 (C=C, C=N); 1194-1138 (C-F) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ **9a** (72 %) 1.24, 1.29 (both t, J 7.0 Hz, 3H each, 2 OCH₂CH₃), 4.16 (m, AB-system, Δ_{AB} 0.05 ppm, J_{AB} 10.8, J 7.0 Hz, 2H, OCH₂CH₃), 4.28 (q, J 7.0 Hz, 2H, OCH₂CH₃), 7.74 (s, 1H, H(6)), 7.78 (d, J 6.3 Hz, 1H, H(2)), 8.95 (s, 1H, OH), 10.62 (d, J 6.3 Hz, 1H, NH(1)); (**Z**)-**9'a** (10 %) 1.28, 1.38 (both t, J 7.0 Hz, 3H each, 2 OCH₂CH₃), 4.36, 4.12 (both q, J 7.0 Hz, 2H each, 2 OCH₂CH₃), 7.90 (br.s, 1H, H(2')), 8.83 (d, J 13.9 Hz, 1H, CH), 11.84 (d, J 13.9 Hz, 1H, NH), 13.47 (s, 1H, NH(1')); (**E**)-**9'a** (18 %): 1.27, 1.41 (both t, J 7.0 Hz, 3H each, 2 OCH₂CH₃), 5.89, 4.22 (both q, J 7.0 Hz, 2H each, 2 OCH₂CH₃), 7.94 (br.s, 1H, H(2')), 8.66 (d, J 13.7 Hz, 1H, CH), 12.51 (d, J 13.7 Hz, 1H, NH), 13.56 (s, 1H, NH(1')) ppm. ¹⁹F NMR (DMSO-*d*₆): δ **9a** (72 %) 81.38 (s, CF₃); (**Z**)-**9'a** (10 %) 91.82 (s, CF₃); (**E**)-**9'a** (18 %) 90.83 (s, CF₃) ppm.

Diethyl 4-hydroxy-4-(1,1,2,2-tetrafluoroethyl)-1,4-dihydroimidazo[1,5-*a*]pyrimidine-3,8-dicarboxy-

late (9b).

The ester **1b** (0.817 g, 0.003 mol) gave by procedure C 0.766 g (67 %) of product **9b**, mp 178–180 °C. Anal. Calcd for C₁₄H₁₅F₄N₃O₅: C, 44.10; H, 3.97; F, 19.93; N, 11.02. Found: C, 44.31; H, 3.83; F, 19.91; N, 10.96 %. IR: ν 3242 (NH), 3015 (C-H), 1724, 1674 (CO₂Et), 1634, 1609 (C=C, C=N), 1254–1114 (C-F) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ **9b** (19 %): 1.25, 1.30 (both t, *J* 7.1, 3H each, OCH₂CH₃), 4.16, 4.28 (both q, *J* 7.1 Hz, no 2H, OCH₂CH₃), 6.67 (d.d.d, *J*_{H,F} 52.0, 51.2, 8.5, 4.2 Hz, 1H, (CF₂)₂H), 7.67 (d, *J* 3.7 Hz, 1H, H(2)), 7.76 (s, 1H, H(6)), 8.82 (d, *J* 3.7 Hz, 1H, NH(1)), 10.55 (br.s, 1H, OH); (**Z**)-**9'b** (25 %) 1.29, 1.38 (both t, *J* 7.2, 7.0 Hz, 3H each, OCH₂CH₃), 4.29, 4.36 (both q, *J* 7.2, 7.0 Hz, 2H each, OCH₂CH₃), 6.67 (t.t, *J*_{H,F} 52.1, 5.9 Hz, 1H, (CF₂)₂H), 7.89 (c, 1H, CH(2')), 8.80 (d, *J* 13.7 Hz, 1H, CH), 11.69 (d, *J* 13.7 Hz, 1H, NH), 13.51 (br. s, 1H, NH(1')); (**E**)-**9'b** (56 %) 1.28, 1.40 (both t, *J* 7.2, 7.0 Hz, 3H each, OCH₂CH₃), 4.39, 4.23 (both q, *J* 7.0, 7.2 Hz, 2H each, OCH₂CH₃), 7.00 (t.t, *J*_{H,F} 52.3, 5.9 Hz, 1H, (CF₂)₂H), 7.93 (s, 1H, CH(2')), 8.93 (d, *J* 13.7 Hz, 1H, CH), 12.56 (d, *J* 13.7 Hz, 1H, NH), 13.51 (br.s, 1H, NH(1')) ppm. ¹⁹F NMR (DMSO-*d*₆): δ **9b** (19 %) 26.85 (d.d.m, *J*_{F,F} 296.6, *J*_{F,H} 52.0 Hz, 1F, CF₂H), 30.21, (d.d.m, *J*_{F,F} 296.6, *J*_{F,H} 51.2 Hz, 1F, CF₂H), 33.50 (d.m, *J*_{F,F} 262.0 Hz, 1F, CF₂), 38.16 (d.m, *J*_{F,F} 262.0 Hz, 1F, CF₂); (**Z**)-**9'b** (25 %) 23.80 (d.t, *J*_{F,H} 52.1, 8.2 Hz, 2F, CF₂H), 43.11 (m, 2F, CF₂); (**E**)-**9'b** (56 %) 25.27 (d.t, *J*_{F,H} 52.3, *J*_{F,F} 7.9 Hz, 2F, CF₂H), 41.43 (m, 2F, CF₂) ppm.

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