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CASCADE THREE-COMPONENT SYNTHESIS OF 2-AMINO-4-(FLUOROALKYL)-4,5-DIHYDROPYRANO[3,2-B]INDOLE-3-CARBONITRILES WITH THE INVOLVEMENT OF ALIPHATIC FLUOROCARBONYL COMPOUNDS

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Abstract: A three-component cascade synthesis (3CCS) of 5-acetyl-2-amino-4-(fluoroalkyl)-4,5-dihydropyrano[3,2-b]indole-3-carbonitriles **1a-e** based on aliphatic fluorocarbonyl compounds **2a-e** with N-acetylindoxyl and malonitrile was carried out. The yields of 3CC synthesis of **1a-e** are 51-76% when carried out at room temperature in the presence of a catalytic amount of organic base. Removal of N-acetyl protection group in **1a-e** leads to the formation of indolepyrans **4a-e** with high yields of 84-88%. The structure of the compounds was confirmed by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, mass spectrometry, and elemental analysis data.

Keywords: 2-(2,2,2-trifluoroethylidene)malonitrile, fluoro-substituted dicyanoethylenes, three-component cascade synthesis, C^{2}-alkylation, aliphatic fluorocarbonyl compounds, N-acetylindoxyl, malonitrile.

Introduction

Currently, almost 25% of the known biologically active compounds used in pharmaceuticals contain a fluorine atom [1-3]. Organofluorine compounds have been widely used as medicines, and herbicides, plant growth stimulants and antidotes to sulfonylureas in agrochemistry [4, 5].

For the construction of polycyclic heteroatomic structures with biological activity, multicomponent reactions involving such compounds are very attractive, in which, after passing the key stage of the formation of a C-C bond according to the type of Michael reaction, the following reaction could take place, for example, the formation of a pyran cycle. Such multicomponent reactions are commonly called cascade reactions [6].

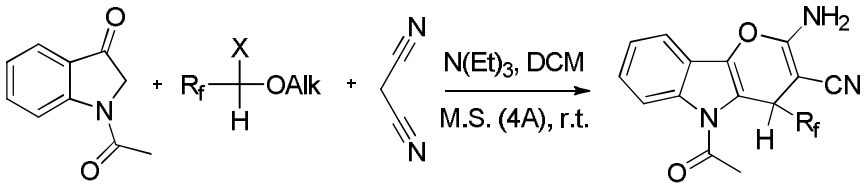
To date, cascade multicomponent reactions have reached the level of highly effective synthetic methods, the search and development of which is stimulated by the principles of waste-free chemical production, that is, the principles of "green" chemistry [7, 8]. In this case, the application of the multicomponent synthesis procedure avoids the stage of preparation, purification and use of fluorinated cyanoethylenes, known for their high reactivity and toxicity [11].

Earlier we reported about a three-component reaction involving derivatives of indole, pyrrole, trifluoroacetaldehyde ethyl semiacetal **2a** and malonitrile in the presence of an organic base. Nitriles of 3-(1*H*-indole-3-yl)-2-cyano-4,4,4-trifluorobutanoic acid are formed with good yields [9, 10]. Further studying of multicomponent reactions involving fluorinated carbonyl compounds, we introduced N-acetylindoxyl into them.

In this work, a cascade three-component synthesis of fluorinated derivatives of indolepyranes **1a-e** was carried out with the participation of N-acetylindoxyl, malonitrile and aliphatic fluorocarbonyl compounds **2a-e**.

Results and discussion

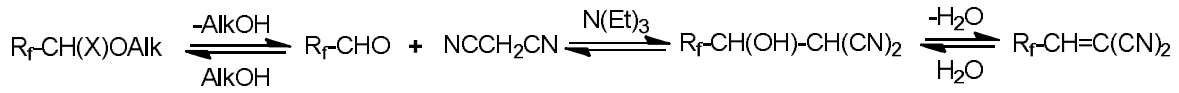
Three-component cascade synthesis of indolepyranes **1a-e** was carried out according to Scheme 1. All reagents were introduced into the reaction sequentially in equimolar amounts: fluorocarbonyl compound **2a-e**, malonitrile, N-acetylindoxyl, molecular sieves and a catalytic amount of organic base – $N(Et)_3$. 3CC synthesis was carried out in a DCM solution at room temperature for 16 hours. The completion of 3CC synthesis was controlled by TLC method.



2a-e **1a-e**

Scheme 1. *Cascade three-component synthesis of indolepyranes **1a-e**.*
a) *R_f= CF_3, X= OH, Alk= Et;* ***b)*** *R_f= C_2F_5, X= OH, Alk= Me;* ***c)*** *C_3F_7, X= OH, Alk= H;*
d) *C_4F_9, X= OH, Alk= H;* ***e)*** *R_f= $CHF_2(CF_2)_5$, X= O, OAlk is absent.*

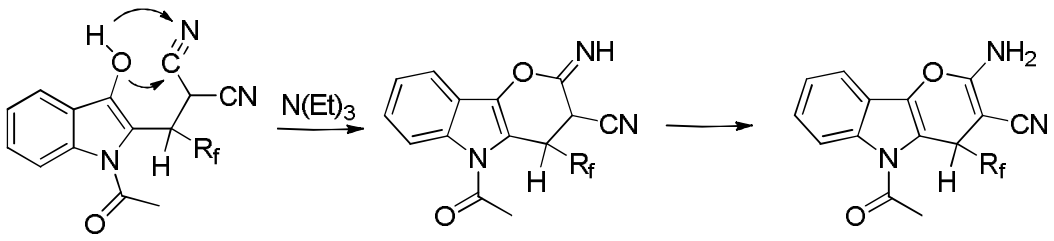
The key step of synthesis **1** is the C^2-alkylation of N-acetylindoxyl by reactive alkenes – 2-(fluoroalkylidene)malonitriles **3a-e**, i.e. the formation of a C-C bond by the Michael reaction. The corresponding alkenes **3** are formed *in situ* by the interaction of fluorocarbonyl compounds **2a-e** and malononitrile in the presence of a catalytic amount of base (Scheme 2).



2a **3a-e**

Scheme 2. *Formation of 2-(fluoroalkylidene)malonitriles **3a-e** in the reaction mass in situ.*
a) *R_f= CF_3, X= OH, Alk= Et;* ***b)*** *R_f= C_2F_5, X= OH, Alk= Me;* ***c)*** *C_3F_7, X= OH, Alk= H;*
d) *C_4F_9, X= OH, Alk= H;* ***e)*** *R_f= $CHF_2(CF_2)_5$, X= O, OAlk is absent.*

The resulting C^2-alkylation adducts under the conditions of a three-component reaction undergoes a "cascade" transformation with the formation of a 1,4-dihydropyrane cycle in the final compounds **1** (Scheme 3).



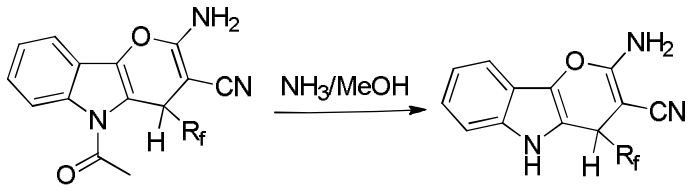
1

Scheme 3. *Probable mechanism of cascade cyclization with the formation of 1,4-dihydropyrane cycle in **1**.*

In the ^{1}H NMR spectra of **1a-e**, there are signals of protons located at the sp^3-hybridized carbon atom at position 4 of the pyrane ring. These signals have a characteristic detection interval at 5.2-5.7 ppm (DMSO-d_6, $CDCl_3$) with a multiplicity of doublets of doublets and have SSCC equal to 5-6 and 15-18 Hz.

Experimental data show that with an increase in the chain length of the fluorine-containing fragment $CF_3 \rightarrow C_6F_{12}$, the yields of compounds **1a-e** increase. It is possible that with the growth of the chain of the fluorine-containing fragment, higher synthons **3** become less reactive due to the steric factor and react more selectively [14].

It should be noted that a competing reaction C^2-hydroxyalkylation of N-acetylindoxyl by fluorine carbonyl compounds **2a-e** with the formation of secondary alcohols is not observed in this 3CC synthesis [10].



1a-e **4a-e**

Scheme 4. *Removal of the N-acetyl group.*
a) *R_f= CF_3;* ***b)*** *R_f= C_2F_5;* ***c)*** *C_3F_7;* ***d)*** *C_4F_9;* ***e)*** *R_f= $CHF_2(CF_2)_5$.*

The removal of N-acetyl protection group proceeds smoothly in a solution of MeOH saturated with ammonia. Indolepyranes **4a-e** are formed with high yields of 84-87% (Scheme 4).

In the ^{1}H NMR spectra of compounds **4a-e**, the absence of the N-acetyl group causes a shift of their signals into a strong field by ~0.5 ppm, compared with compounds **1**. The signal of such a proton is detected in the region of 5 ppm (DMSO-d_6, $CDCl_3$) with a multiplicity of triplet and has SSCC equal to 5-6 Hz.

Our indolepyranes **1** and **4** have a carbon skeleton similar to the compounds described in [12, 13] as having anti-tuberculosis activity. The described compounds were obtained on the basis of aromatic and heterocyclic aldehydes derivatives according to the traditional step-by-step method [12].

Conclusions

Thus, not only trifluoroacetaldehyde takes part in the three-component cascade synthesis of indolepyranes **1a-e**, but also higher aliphatic fluorocarbonyl compounds, both in the form of free aldehydes and in the form of their less reactive derivatives - semi-acetals and hydrates with good yields of 51-76%. Aliphatic fluorocarbonyl compounds **2** allow for 3CC synthesis of indolepyranes **1** at room temperature in the presence of a catalytic amount of organic base in an inert solvent. Increasing the chain length of the fluorinated fragment increases the yields of compounds **1a-e**. The removal of N-acetyl protection group by the action of ammonia in MeOH effectively proceeds at -30°C with the formation of indolepyranes **4a-e** with high yields of 84-88%. Heterocyclic compounds **4a-e**, apparently, may be of interest as potential anti-tuberculosis agents.

Experimental part

All starting compounds were purchased from Merck, Sigma-Aldrich and used without purification. All solvents: petroleum ether T_{bp}= 40-70°C (PE), EtOAc (EA), DCM and triethylamine were purified by distillation before use. Merck Kieselgel 60 F254 TLC plates were used to monitor the reaction and detect substances. The products were purified by column chromatography using Merck Kieselgel 60 silica gel (0.06-0.20 mm). The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a

Bruker Avance 400 spectrometer with an operating frequency of 400, 100 and 376 MHz, respectively. Chemical shifts of ^{1}H and ^{13}C nuclei were determined relative to the residual $CDCl_3$ and DMSO-d_6 signals (7.26, 2.50 and 77.16, 39.52 ppm, respectively) and recalculated to the $SiMe_4$ signal. The signals of ^{13}C atoms containing an odd and even number of protons have the opposite polarity in the *J*MODECHO mode. The ^{19}F nuclei spectra were recorded both with and without suppression of the H-F spin-spin coupling. Chemical shifts of ^{19}F atoms are determined relative to $CFCl_3$ as an external standard. The mass spectra were recorded on a FINNIGAN MAT INCOS 50 quadrupole mass spectrometer, direct sample input, ionization energy - 70 eV. The melting points of the obtained compounds have values above 235°C.

General 3CC method of synthesis of 5-acetyl-2-amino-4-(fluoroalkyl)-4,5-dihydropyrano[3,2-b]indole-3-carbonitriles 1a-e.

Into a round-bottomed single-necked flask equipped with a magnetic stirrer, fluorine carbonyl compound **2a-e** (1 mmol), malonitrile (0.066 g, 1 mmol), N-acetylindoxyl (0.175 g, 1 mmol), freshly distilled DCM (5 ml), 5-7 granules of dried molecular sieves with a pore size of 4A are loaded. The flask is closed with a septa, vacuumed, filled with argon, cooled to +5°C, triethylamine (0.05 g) is injected with a syringe. The reaction mass is kept at room temperature for 16 hours. The completion of the 3CC reaction is controlled by the TLC method. 10 ml of a mixture of DCM and EA (8 and 2 ml) is added to the contents of the flask and transferred to a chromatographic column containing 20 ml of silica gel. The reaction mass is eluted with the same mixture of solvents and, if necessary, the gradient of the eluent is increased by adding EA. Solutions of purified products **1a-e** are evaporated at reduced pressure and re-evaporated with 20 ml of DCM.

General method of synthesis of 4a-e, removal of N-acetyl protection in 1a-e.

Into a round-bottomed single-necked flask equipped with a magnetic stirrer **1a-e** (1 equivalent), MeOH (1 ml) are loaded, a septa is closed, vacuumed, filled with argon, cooled to -30 °C and an ammonia-saturated MeOH (~15% by weight, 2 ml) is injected into the flask with a syringe cooled to -30 °C. The reaction mass is kept at a temperature of -30 °C for 16 hours. The completion of the reaction is controlled by TLC. The contents of the flask are diluted with DCM (10 ml) and transferred to a glass filter containing 10 ml of silica gel. Indolepyrans **4a-e** are eluted with a mixture of solvents DCM and EA (4/1). Solutions **4a-e** are evaporated at reduced pressure and re-evaporated with 20 ml of DCM.

(1a) 5-acetyl-2-amino-4-(trifluoromethyl)-4,5-dihydropyrano[3,2-b]indole-3-carbonitrile, $C_{15}H_{10}F_3N_3O_2$, MM: 321.

Yield 51% (0.165 g), light beige powder, R_f= 0.2 (PE+EA, 8+2).

^{1}H NMR (DMSO-d_6, δ, ppm., *J*/Hz): 2.81 (3H, s, CH_3); 5.25 (1H, q, 6.3 Hz, $CHCF_3$); 7.40 (1H, t, 7.4 Hz, Ar); 7.50 (1H, t, 7.7 Hz, Ar); 7.58 (1H, d, 7.7 Hz, Ar); 7.73 (2H, br. s, NH_2); 7.99 (1H, d, 8.5 Hz, Ar).

^{13}C NMR (DMSO-d_6, δ, ppm., *J*/Hz): 26.92 (CH_3); 38.62 (q, 30.3 Hz, $\underline{C}HCF_3$); 47.55 (q, 2.4 Hz); 110.68 (q, 1.7 Hz, CN); 115.63; 116.94; 118.64; 119.45; 124.01; 125.42 (q, 283.7 Hz, CF_3); 126.83; 133.67; 137.64; 163.39; 170.21.

^{19}F NMR (DMSO-d_6, δ, ppm., *J*/Hz): -72.08 (s, CF_3).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 322 $[M+H]^+$ (5.79); 252 $[M-CF_3]^+$ (17.57); 210 $[M-CF_3\text{-}Ac]^+$ (37.74).

Calculated: C, 56.08; H, 3.14; N, 13.08. **Found:** C, 56.04; H, 3.19, N, 13.05.

(4a) 2-amino-4-(trifluoromethyl)-4,5-dihydropyrano[3,2-b]indole-3-carbonitrile, $C_{13}H_8F_3N_3O$, MM: 279.

Yield: 84 % (0.11 g), light beige powder, R_f= 0.3 (PE+EA, 8+2).

^{1}H NMR (DMSO-d_6, δ, ppm., *J*/Hz): 4.83 (1H, q, 6.6 Hz, $CHCF_3$); 6.78 (2H, br. s, NH_2); 7.07 (1H, t, 7.4 Hz, Ar); 7.18 (1H, t, 7.6 Hz, Ar); 7.40 (1H, d, 8.3 Hz, Ar); 7.49 (1H, d, 7.8 Hz, Ar); 11.12 (1H, br. s, NH).

^{13}C NMR (DMSO-d_6, δ, ppm., *J*/Hz): 38.17 (q, 30.1 Hz, $\underline{C}HCF_3$); 47.21; 110.34 (CN); 115.65; 116.73; 118.31; 119.96; 124.11; 125.11 (q, 282.1 Hz, CF_3); 126.;53 133.15; 137.94; 163.77.

^{19}F NMR (DMSO-d_6, δ, ppm., *J*/Hz): -71.55 (d, 6.4 Hz, CF_3).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 279 $[M]^+$ (12.77); 210 $[M-CF_3]^+$ (75.63).

Calculated: C, 55.92; H, 2.89; N, 15.05. **Found:** C, 55.87; H, 2.94; N, 15.01.

(1b) 5-acetyl-2-amino-4-(perfluoroethyl)-4,5-dihydropyrano[3,2-b]indole-3-carbonitrile, $C_{16}H_{10}F_5N_3O_2$, MM: 371.

Yield: 63 % (0.235 g), light beige powder, R_f= 0.2 (PE+EA, 8+2).

^{1}H NMR (DMSO-d_6, δ, ppm., *J*/Hz): 2.82 (3H, s, CH_3); 5.40 (1H, dd, 6.6 Hz, 15.3 Hz, $CHCF_2$); 7.40 (1H, t, 7.5 Hz, Ar); 7.50 (1H, t, 7.8 Hz, Ar); 7.58 (1H, d, 7.7 Hz, Ar); 7.83 (2H, br. s, NH_2); 7.97 (1H, d, 8.5 Hz, Ar).

^{13}C NMR (DMSO-d_6, δ, ppm., *J*/Hz): 26.91 (CH_3); 37.43 (t, 23.2 Hz, $\underline{C}HCF_2$); 47.13 (t, 4.6 Hz); 110.89 (t, 1.0 Hz, CN); 114.57 (tq, 257.5 Hz, 35.3 Hz, CF_2); 115.55; 116.93; 118.68; 118.75 (qt, 287.4 Hz, 36.6 Hz, CF_3); 119.54; 123.71; 126.60; 133.64; 138.29; 164.33; 170.41.

^{19}F NMR (DMSO-d_6, δ, ppm., *J*/Hz): -77.22 (3F, s, CF_3); -112.70 (1F, d, 266.4 Hz, CF_2); -116.60 (1F, d, 266.0 Hz, CF_2).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 371 $[M]^+$ (1.1); 252 $[M- C_2F_5]^+$ (30.68); 210 $[M- C_2F_5\text{-}Ac]^+$ (44.63).

Calculated: C, 51.76; H, 2.71; N, 11.32. **Found:** C, 51.70; H, 2.77; N, 11.28.

(4b) 2-amino-4-(perfluoroethyl)-4,5-dihydropyrano[3,2-b]indole-3-carbonitrile, $C_{14}H_8F_5N_3O$, MM: 329.

Yield: 85 % (0.12 g), light beige powder, R_f= 0.3 (PE+EA, 8+2).

^{1}H NMR (DMSO-d_6, δ, ppm., *J*/Hz): 5.01 (1H, t, 9.9 Hz, $CHCF_2$); 7.08 (1H, t, 7.5 Hz, Ar); 7.19 (1H, t, 7.6 Hz, Ar); 7.42 (1H, d, 8.3 Hz, Ar); 7.47 (1H, d, 8.4 Hz, Ar); 7.49 (2H, br. s, NH_2); 11.26 (1H, s, NH).

^{13}C NMR (DMSO-d_6, δ, ppm., *J*/Hz): 36.97 (t, 24.9 Hz, $\underline{C}HCF_2$); 46.09 (t, 5.0, Hz); 109.61 (t, 4.4 Hz, CN); 112.35; 113.31 (tq, 257.4 Hz, 33.9 Hz, CF_2); 115.19; 115.93; 119.32 (qt, 288.1 Hz, 36.7 Hz, CF_3); 119.70; 120.27; 122.91; 130.98; 133.94; 164.49.

^{19}F NMR (DMSO-d_6, δ, ppm., *J*/Hz): -79.98 (3F, s, CF_3); -114.76 (2F, d, 24.4 Hz, CF_2).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 329 $[M]^+$ (100); 210 $[M\text{-}C_2F_5]^+$ (77.54).

Calculated: C, 51.07; H, 2.45; N, 12.76. **Found:** C, 51.02; H, 2.51; N, 12.73.

***(1c) 5-acetyl-2-amino-4-(perfluoropropyl)-4,5-dihydropyrano[3,2-b]indole-3-carbonitrile, $C_{17}H_{10}F_7N_3O_2$,* MM: 421.**

Yield: 64 % (0.27 g), light beige powder, R_f= 0.2 (PE+EA, 8+2).

^{1}H NMR (DMSO-d_6, δ, ppm., *J*/Hz): 2.82 (3H, s, CH_3); 5.52 (1H, dd, 4.1 Hz, 18.6 Hz, $CHCF_2$); 7.41 (1H, t, 7.5 Hz, Ar); 7.51 (1H, t, 7.9 Hz, Ar); 7.59 (1H, d, 7.8 Hz, Ar); 7.83 (2H, br. s, NH_2); 7.97 (1H, d, 8.6 Hz, Ar).

^{13}C NMR (DMSO-d_6, δ, ppm., *J*/Hz): 26.95 (CH_3); 37.83 (t, 22.9 Hz, $\underline{C}HCF_2$); 47.32 (dd, 3.5 Hz, 5.7 Hz); 108-118 (multiplets family of C_3F_7); 111.00 ($\underline{C}N$); 115.59; 116.93; 118.75; 119.58; 123.72; 126.60; 133.66; 138.50; 164.68; 170.43.

^{19}F NMR (DMSO-d_6, δ, ppm., *J*/Hz): -80.23 (3F, t, 10.3 Hz, CF_3); -113.77 (1F, m, CF_2); -118.24 (1F, dd, 6.3 Hz, 271.6 Hz, CF_2); -125.15 (1F, dd, 4.8 Hz, 8.4 Hz, CF_2); -125.34 (1F, d, 9.5 Hz, CF_2).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 421 $[M]^+$ (1.31); 252 $[M\text{-}C_3F_7]^+$ (25.58); 210 $[M\text{-}C_3F_7\text{-}Ac]^+$ (35.16).

Calculated: C, 48.47; H, 2.39; N, 9.97. **Found:** C, 48.53; H, 2.33; N, 9.92.

(4c) 2-amino-4-(perfluoropropyl)-4,5-dihydropyrano[3,2-b]indole-3-carbonitrile, $C_{15}H_8F_7N_3O$, MM: 379.

Yield 85 % (0.1 g), light beige powder, R_f= 0.4 (PE+EA, 8+2).

^{1}H NMR (DMSO-d_6, δ, ppm., *J*/Hz): 5.07 (1H, t, 10.8 Hz, $CHCF_2$); 7.08 (1H, t, 7.3 Hz, Ar); 7.19 (1H, t, 7.4 Hz, Ar); 7.43 (1H, d, 8.2 Hz, Ar); 7.47 (1H, d, 7.9 Hz, Ar); 7.51 (2H, br. s, NH_2); 11.24 (1H, s, NH).

^{13}C NMR (DMSO-d_6, δ, ppm., *J*/Hz): 37.60 (t, 24.9 Hz, $\underline{C}HCF_2$); 46.10 (t, 5.1 Hz); 107-118 (multiplets family of C_3F_7); 109.69 ($\underline{C}N$); 112.35; 115.19; 115.89; 119.67; 120.34; 122.88; 131.20; 133.92; 164.75.

^{19}F NMR (DMSO-d_6, δ, ppm., *J*/Hz): -80.40 (3F, t, 10.4 Hz, CF_3); -112.27 (2F, s, CF_2); -124.94 (2F, s, CF_2).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 379 $[M]^+$ (16.21); 210 $[M\text{-}C_3F_7]^+$ (100).

Calculated: C, 47.51; H, 2.13; N, 11.08. **Found:** C, 47.47; H, 2.18, N, 11.04.

(1d) 5-acetyl-2-amino-4-(perfluorobutyl)-4,5-dihydropyrano[3,2-b]indole-3-carbonitrile, $C_{18}H_{10}F_9N_3O_2$, MM:471.

Yield 76 % (0.36 g), light beige powder, R_f= 0.2 (PE+EA, 8+2).

^{1}H NMR (DMSO-d_6, δ, ppm., *J*/Hz): 2.82 (3H, s, CH_3); 5.53 (1H, dd, 4.2 Hz, 18.7 Hz, $CHCF_2$); 7.41 (1H, t, 7.4 Hz, Ar); 7.50 (1H, t, 7.9 Hz, Ar); 7.59 (1H, d, 7.7 Hz, Ar); 7.83 (2H, br. s, NH_2); 7.97 (1H, d, 8.5 Hz, Ar).

^{13}C NMR (DMSO-d_6, δ, ppm., *J*/Hz): 26.93 (CH_3); 38.08 (t, 23.0 Hz, $\underline{C}HCF_2$); 47.44 (t, 8.5 Hz); 111.02 (CN); 112.07-119.46 (multiplets family of C_4F_9); 115.58; 116.94; 118.77; 119.61 123.71; 126.59; 133.68; 138.57; 164.74; 170.40.

^{19}F NMR (DMSO-d_6, δ, ppm., *J*/Hz): -80.45 (3F, s, CF_3); -113.44 (1F, d, 272.2 Hz); -117.47 (1F, dd, 273.3 Hz, 15.1 Hz, CF_2); -121.68 (2F, s, CF_2); -124.76 (1F, dd, 21.2 Hz, 291.1 Hz); -126.52 (1F, dt, 14.9 Hz, 30.3 Hz).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 471 $[M]^+$ (0.81); 428 $[M\text{-}Ac]^+$ (1.15); 252 $[M\text{-}C_4F_9]^+$ (65.66); 210 $[M\text{-}C_4F_9\text{-}Ac]^+$ (79.57).

Calculated: C, 45.87; H, 2.14; N, 8.92. **Found:** C, 45.92; H, 2.09; N, 8.88.

(4d) 2-amino-4-(perfluorobutyl)-4,5-dihydropyrano[3,2-b]indole-3-carbonitrile, $C_{16}H_8F_9N_3O$, MM:429.

Yield 88 % (0.12 g), light beige powder, R_f= 0.3 (PE+EA, 8+2).

^{1}H NMR (DMSO-d_6, δ, ppm., *J*/Hz): 5.07 (1H, t, 11.1 Hz, $CHCF_2$); 7.08 (1H, t, 7.5 Hz, Ar); 7.18 (1H, t, 7.6 Hz, Ar); 7.41 (1H, d, 8.3 Hz, Ar); 7.45 (1H, d, 8.1 Hz, Ar); 7.48 (2H, br. s, NH_2); 11.22 (1H, s, NH).

^{13}C NMR (DMSO-d_6, δ, ppm., *J*/Hz): 37.84 (t, 25.3 Hz, $\underline{C}HCF_2$); 46.15; 109.76 (CN); 111.71-118.34 (multiplets family of C_4F_9); 112.38; 115.21; 115.90; 119.69; 120.37; 122.89; 131.26; 133.93; 164.81.

^{19}F NMR (DMSO-d_6, δ, ppm., *J*/Hz): -80.38 (3F, s, CF_3); -112.03 (2F, s, CF_2); -121.67 (2F, s, CF_2); -125.83 (2F, d, 11.1 Hz).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 429 $[M]^+$ (15.64); 210 $[M\text{-}C_4F_9\text{-}Ac]^+$ (100).

Calculated: C, 44.77; H, 1.88; N, 9.79. **Found:** C, 44.81; H, 1.82; N, 9.73.

(1e) 5-acetyl-2-amino-4-(1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexyl)-4,5-dihydropyrano[3,2-b]indole-3-carbonitrile, $C_{20}H_{11}F_{12}N_3O_2$, MM: 553.

Yield 71 % (0.39 g), light beige powder, R_f= 0.2 (PE+EA, 8+2).

^{1}H NMR (DMSO-d_6, δ, ppm., *J*/Hz): 2.80 (3H, s, CH_3); 5.67 (1H, dd, 4.6 Hz, 17.2 Hz, $CHCF_2$); 6.03 (1H, tt, 5.2 Hz, 51.9 Hz, CF_2H); 7.37 (1H, t, 7.6 Hz, Ar); 7.47 (1H, t, 7.8 Hz, Ar); 7.65 (1H, d, 7.6 Hz, Ar); 7.76 (1H, d, 8.4 Hz, Ar); 7.91 (2H, br. s, NH_2).

^{13}C NMR (DMSO-d_6, δ, ppm., *J*/Hz): 26.73; 38.12 (t, 25.2 Hz, $\underline{C}HCF_2$); 46.26 (t, 4.5 Hz); 108.07 (t, 30.9 Hz, CHF_2); 109.47 (t, 3.7 Hz, CN); 110.21-119.35 (multiplets family of C_6F_{12}); 112.79, 116.78, 116.54; 119.46; 120.49, 122.17; 131.95; 133.56; 164.63; 170.37.

^{19}F NMR (DMSO-d_6, δ, ppm., *J*/Hz): -111.87 (2F, s, CF_2); -120.75 (2F, s, CF_2); -121.92 (2F, s, CF_2); -123.17 (2F, s, CF_2); -129.05 (2F, s, CF_2); -138.44 (2F, s, CF_2).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 553 $[M]^+$ (0.97); 511 $[M\text{-}Ac]^+$ (5.41); 252 $[M\text{-}C_6F_{12}H]^+$ (85.04); 210 $[M\text{-}C_6F_{12}H\text{-}Ac]^+$ (100).

Calculated: C, 43.41; H, 2.00; N, 7.59. **Found:** C, 43.46, H, 1.96, N, 7.53.

(4e) 2-amino-4-(1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexyl)-4,5-dihydropyrano [3,2-b]indole-3-carbonitrile, $C_{18}H_9F_{12}N_3O$, MM: 511.

Yield 87 % (0.28 g), light beige powder, R_f= 0.3 (PE+EA, 8+2).

^{1}H NMR (DMSO-d_6, δ, ppm., *J*/Hz): 5.05 (1H, t, 11.0 Hz, $CHCF_2$); 7.08 (1H, t, 7.5 Hz, Ar); 7.15 (1H, tt, 5.3 Hz, 51.7 Hz, CF_2H, signals overlay); 7.19 (1H, t, 7.4 Hz, Ar); 7.40-7.48 (4H, Ar, NH_2, signals overlay); 11.22 (1H, br. s, NH).

^{13}C NMR (DMSO-d_6, δ, ppm., *J*/Hz): 38.04 (t, 25.1 Hz, $CHCF_2$); 46.38 (t, 4.8 Hz); 108.00 (t, 30.8 Hz, CHF_2); 109.95 (t, 3.9 Hz, CN); 110.18-119.05 (multiplets family of C_6F_{12}); 112.41, 115.28, 115.94; 119.70; 120.45, 122.89; 131.30; 133.97; 164.87.

^{19}F NMR (DMSO-d_6, δ, ppm., *J*/Hz): -111.94 (2F, s, CF_2); -120.77 (2F, s, CF_2); -121.98 (2F, s, CF_2); -123.23 (2F, s, CF_2); -129.19 (2F, s, CF_2); -138.52 (2F, d, 50.3 Hz, CF_2H).

MS (EI, 70 eV), *m/z* (I_{rel} (%)): 511 $[M]^+$ (2.80); 210 $[M\text{-}C_6F_{12}H]^+$ (100).

Calculated: C, 42.29; H, 1.77; N, 8.22. **Found:** C, 42.34, H, 1.73, N, 8.18.

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