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Synthesis of *gem*-difluorinated 1,6-naphthyridine-5,7-diones

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ABSTRACT

A synthetic route toward new 8,8-difluoro-1,6-naphthyridine-5,7-diones, which are of interest as new building blocks in pharmaceutical chemistry, is described. The key steps include a copper-mediated cross-coupling of ethyl bromodifluoroacetate and 2-bromo-3-cyanopyridine, followed by hydrolysis of the nitrile function and subsequent cyclization.

1. Introduction

Site-selective fluorination has become an important strategy for developing new bioactive compounds, which is reflected by the numerous papers in the area of organofluorine chemistry in the last decade.[1] The intensified research dealing with the synthesis of new fluorinated organic compounds has resulted in numerous new commercial applications in pharmaceutical chemistry and agrochemistry.[2] In particular, heterocycles containing a *gem*-difluoromethylene group in their ring structure or bearing an exocyclic difluoromethylenated substituent, have been the subject of intense research for developing new bioactive compounds.[3] Due to the high electronegativity of the fluorine atom, the introduction of a CF_2-group can strongly influence the electronic nature of the molecule and therefore alter its bioactivity. Furthermore, CF_2/CH_2 transposition has been recognised as a valuable tool in blocking metabolic oxidation.[4] For example, this strategy of replacing a methylene by a difluoromethylene group has been successfully applied to synthesize antifungal agents, such as 1,2,4-triazoles **1**[5] and thrombin inhibitors (e.g., **2**, Fig. 1).[6] Moreover, several *gem*-difluorinated bicyclic heterocycles are known as compounds with interesting bioactive properties. Isoquinoline-1,3-dione **3** possesses nitric oxide synthase (NOS) inhibiting activity and is promising for treating diabetes,[7] while compounds **4** are recognised as HSP90 inhibitors, which are useful in the treatment of diseases of the cardiovascular and central nervous system.[8]

Despite these interesting properties, *gem*-difluorinated bicyclic azaheterocycles are scarcely described in literature. To the best of our knowledge, compounds containing the 8,8-difluoro-1,6-naphthyridine moiety **5** are even unknown in literature. In this paper, we describe the successful preparation of 8,8-difluoro-1,6-naphthyridine-5,7-diones **5** (X, Y: C=O), which are of specific interest in medicinal chemistry.

2. Results and discussion

Among the variety of methods available to introduce a CF_2-group in organic compounds,[4] the copper-mediated coupling reaction of ethyl bromodifluoroacetate and halogenated heteroaromatics is well-established and has resulted in useful heterocycles bearing an exocyclic difluoromethylene susbstituent.[5,9] In this respect, it was believed that this strategy could be suitable for synthesizing new *gem*-difluorinated bicyclic compounds. In a first attempt to reach precursors for the construction of the envisaged bicyclic ring structures, 2-chloro-3-cyanopyridine **6** was stirred in the presence of copper and ethyl bromodifluoroacetate in DMSO at 50 °C (Scheme 1). After reaction for 15 h, the obtained mixture contained only 50% of ethyl pyridin-2-yldifluoroacetate **8**, which was accompanied by starting material and decomposition products of the in situ generated organocopper reagent. Because the obtained pyridine **8** was isolated from the mixture in a disappointing 12% yield, and because 2-bromopyridines are known to be more reactive substrates for the cross-coupling reactions as compared to 2-chloropyridines,[9,10] the corresponding 2-bromopyridine **7** was evaluated as a substrate for the reaction with ethyl bromodifluoroacetate in the presence of copper. 2-Chloropyridine **6** was treated with bromotrimethylsilane to give 2-bromo-3-cyanopyridine **7** in excellent yield.[11] Subsequently, the copper-mediated cross-coupling of 2-bromo-3-cyanopyridine **7** and ethyl bromodifluoroacetate proceeded smoothly, affording ethyl (3-cyanopyridin-2-yl)difluoroacetate **8** in 83% yield.

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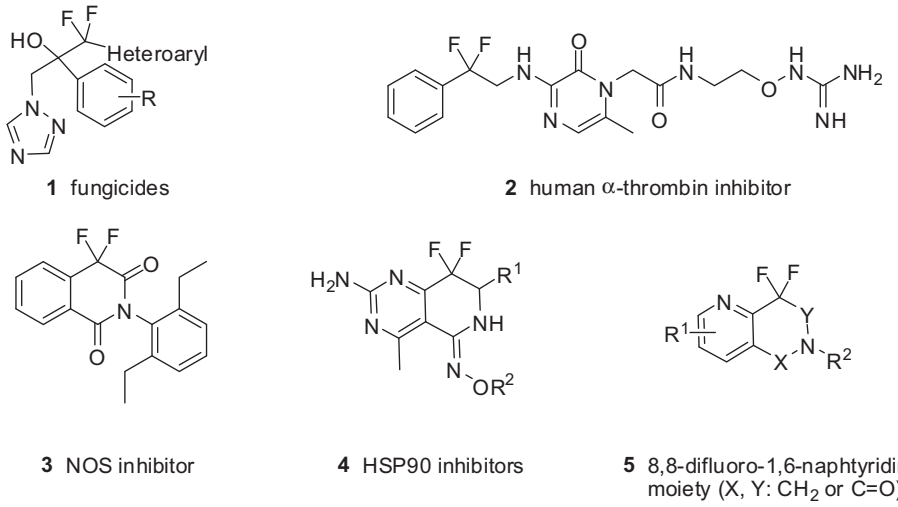
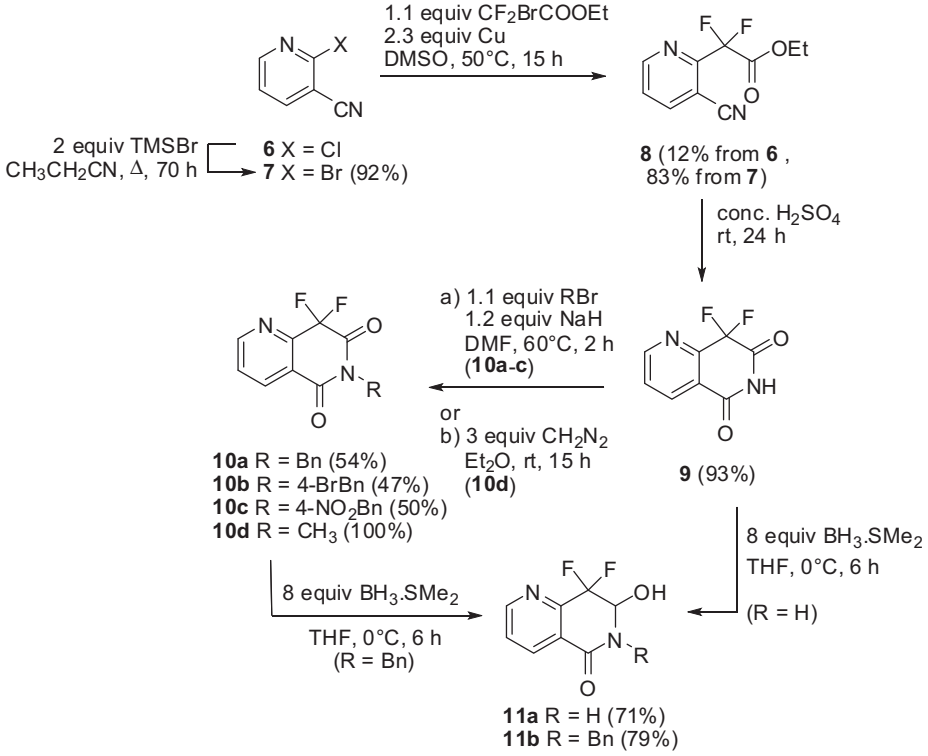


Fig. 1. Examples of *gem*-difluorinated bioactive compounds.



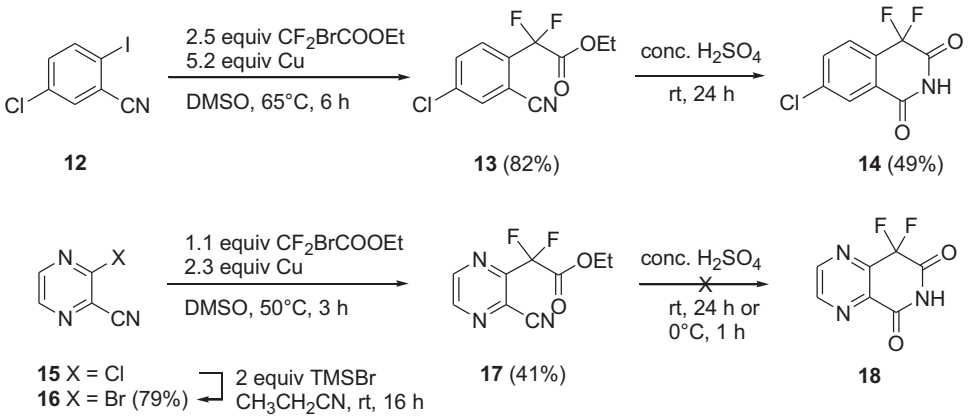
Scheme 1.

In a next step toward the desired 1,6-naphtyridines, it was attempted to reduce the nitrile function of pyridine **8** via catalytic hydrogenation over Pd/C, PtO_2 or Raney nickel, via borane reduction or via $LiAlH_4$ reduction. Unfortunately, the corresponding 3-aminomethylpyridine could not be obtained. Therefore, it was decided to hydrolyze the cyano group as an alternative strategy. Treatment of ethyl (3-cyanopyridin-2-yl)difluoroacetate **8** with an excess of sulfuric acid at room temperature for 24 h nicely gave rise to 8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione **9** in 93% yield (100 mg scale). It should be noted that applying this method on a larger scale (0.50 g), somewhat lower yields of 65–80% were obtained. Nevertheless, 8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione **9** could be used as a starting material for further *N*-functionalization. The reaction of **9** with (substituted) benzyl bromides resulted in new *N*-substituted imides **10a**–**c** in moderate yields, while treating the *N*-unsubstituted imide with an ethereal diazomethane solution afforded the *N*-methylated derivative **10d** quantitatively.

As fused bicyclic piperidines are known to possess interesting bioactivities,[12] the reduction of both carbonyl functions of the imide moiety of compounds **9** and **10a** using borane, $LiAlH_4$ or monochloroalane (AlH_2Cl) was evaluated. In contrast to the complex reaction mixtures obtained by using $LiAlH_4$ or monochloroalane (AlH_2Cl), the reaction of imides **9** and **10a** with 8 equiv of $BH_3.SMe_2$ in tetrahydrofuran for 6 h at 0 °C gave rise to stable hemiaminals **11a** and **11b**. Increasing the temperature or using more equivalents

of the borane reagent in order to obtain full reduction of the carbonyl group resulted in decomposition of the product. Indeed, it is known that a hydroxyl group at β-position of a CF_2-group is quite stable and generally difficult to reduce.[13]

Having in hand a straightforward method for the synthesis of imide **9**, the above described methodology was extended toward the synthesis of other fluorinated bicyclic aromatics. Based on known cross-coupling procedures of ethyl bromodifluoroacetate and aryl iodides,[13,14] commercially available 5-chloro-2-iodobenzonitrile **12** was treated with 2.5 equiv of ethyl bromodifluoroacetate and 5.2 equiv of copper in DMSO at 65 °C for 6 h afforded the cross-coupled product **13** in 82% yield after chromatographic purification on silica gel (Scheme 2). The use of less



Scheme 2.

equivalents of copper and ethyl bromodifluoroacetate resulted in an incomplete conversion, while applying more equivalents (3 equiv $CF_2BrCOOEt$, 6.6 equiv Cu) considerably increased the formation of unidentified side products. Stirring the difluorinated ester **13** in sulfuric acid for 24 h at room temperature subsequently gave rise to the desired 7-chloro-4,4-difluoroisoquinoline-1,3(2*H*,4*H*)-dione **14** in moderate yield. It should be noted that due to the presence of the CF_2-moiety, the acidity of the imidic proton of *N*-unsubstituted isoquinoline-1,3-diones, such as **14**, is significantly increased (typically pK_a 4–5), which makes this type of compounds of interest as carboxylic acid bioisosteres.[15] In addition, the developed cyclization methodology was also applied using a suitably substituted pyrazine **17**, which was obtained in 41% yield from 2-bromo-3-cyanopyrazine **16**. However, in this case, the hydrolysis of the nitrile function proved to be much more difficult, since only decomposition products were obtained after treatment with sulfuric acid.

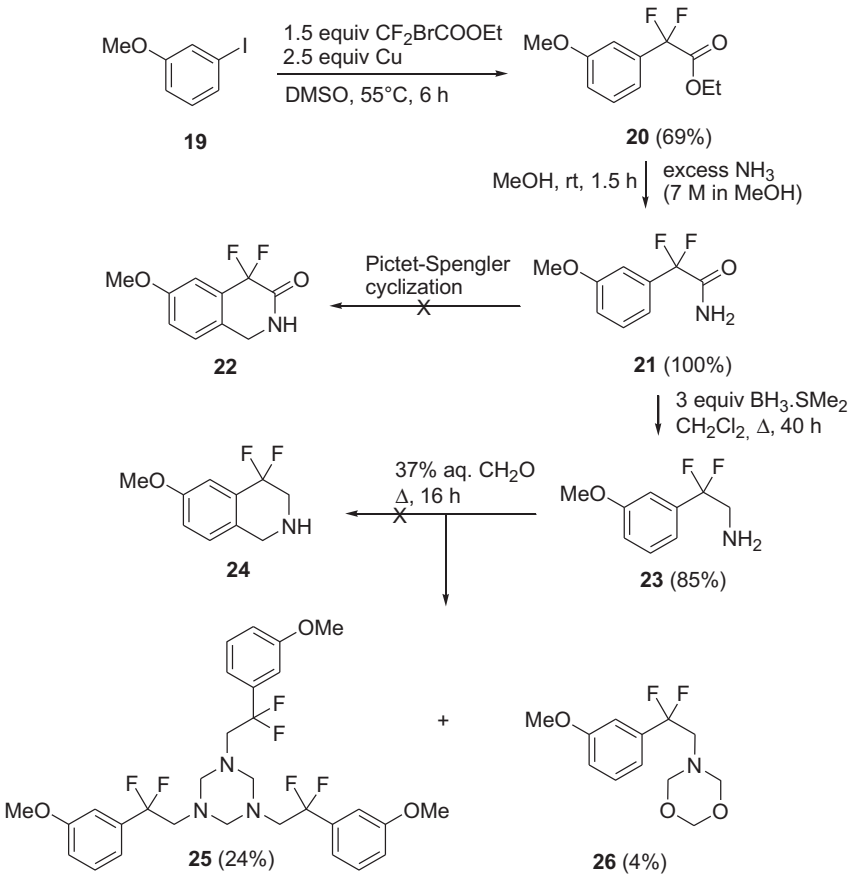
In an alternative strategy toward interesting fluorinated isoquinolines or tetrahydroisoquinolines, a Pictet–Spengler reaction of suitable fluorinated amines or amides was evaluated. Toward this end, 1-iodo-3-methoxybenzene **19** was cross-coupled with ethyl bromodifluoroacetate, affording ethyl 2,2-difluoro-2-(3-methoxyphenyl)acetate **20** (Scheme 3). The latter was treated with ammonia in methanol to obtain quantitatively the corresponding amide **21**, which was subsequently reduced using borane to yield 2,2-difluoro-2-(3-methoxyphenyl)ethylamine **23**. Finally, the transformation of amide **21** and amine **23** into 1,4-dihydroisoquinoline-3-one **22** and 1,2,3,4-tetrahydroisoquinoline **24**, respectively, via a Pictet–Spengler reaction was assessed. This type of reaction is an important tool for creating tetrahydroisoquinoline ring systems,[16] which are the core structural units of many organic compounds with interesting pharmacological activities.[17] Although a plethora of reaction conditions was evaluated in order to obtain the ring-closed products (e.g., (para)formaldehyde in the presence of HCl, AcOH, H_2SO_4, TFA, pyrophosphoric acid or Lewis acids, in a broad range of solvents, including CH_2Cl_2, $ClCH_2CH_2Cl$, benzene, toluene or xylenes), the bicyclic compounds **22** and **24** were never detected. In this respect, it should be mentioned that treatment of amine **23** with an aqueous solution of formaldehyde (37%) for 16 h under reflux afforded 1,3,5-triazinane **25** (24%) and dioxazinane **26** (4%). Although it is known that compounds bearing an aromatic ring, which is activated by electron-donating substituents, easily undergo Pictet–Spengler cyclization reactions, compounds **21** and **23** proved to be unsuitable substrates for cyclization, most probably due to the strong electron-withdrawing effect of the CF_2-substituent.

In conclusion, a straightforward synthetic pathway toward new bicyclic difluorinated azaheterocyclic compounds was developed. A copper-mediated cross-coupling of ethyl bromodifluoroacetate and (hetero)aryl halides, followed by hydrolysis of the nitrile group and subsequent ring closure were the key steps in the synthesis of new 8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-diones **9**, **10** and 7-chloro-4,4-difluoroisoquinoline-1,3-(2*H*,4*H*)-dione **14**, which are of interest as new building blocks for medicinal chemistry purposes.

3. Experimental part

3.1. General

^1H NMR spectra were recorded at 300 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{19}F NMR spectra were recorded at 282 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and $CFCl_3$ as internal standard. Electron spray (ES) mass spectra were obtained with an Agilent 1100 Series MS (ES, 4000 V) mass spectrometer. Electron impact (EI) mass spectra were recorded by using a HP 6890 GC coupled to a HP 5973 MSD (mass selective detector). IR spectra were measured with a Spectrum One FTIR spectrophotometer. Elemental analysis of new compounds was performed using a CHN-elemental analyser (tin combustion capsules were used for both solids and sticky oils). Diethyl ether and tetrahydrofuran were dried over sodium benzophenone ketyl. Other solvents were used as received from the supplier. Melting points of crystalline compounds were measured with a Buchi 540 apparatus.



Scheme 3.

3.2. Ethyl (3-cyanopyridin-2-yl)difluoroacetate 8

To a solution of 4.52 g (22.25 mmol, 1.1 equiv) of ethyl bromodifluoroacetate and 3.70 g (20.23 mmol, 1 equiv) of 2-bromo-3-cyanopyridine **7** in DMSO (40 mL) was added 2.95 g (46.53 mmol, 2.3 equiv) of copper powder, and the resulting mixture was stirred at 50 °C for 15 h. Afterward, the reaction mixture was cooled to room temperature, diluted with EtOAc (40 mL) and poured in an aqueous solution of 1.27 M KH_2PO_4 (60 mL). After 30 min of stirring, the resulting suspension was filtered through a pad of Celite®, after which the copper salts were washed with EtOAc (40 mL). Subsequently, the organic phase of the filtrate was washed with water (2×40 mL), dried ($MgSO_4$), concentrated and purified by flash chromatography (hexane/EtOAc 4:1, R_f=0.07) to afford 3.79 g (16.79 mmol, 83% yield) of ethyl (3-cyanopyridin-2-yl)difluoroacetate **8** as orange crystals (mp=41.6 °C). ^{1}H NMR ($CDCl_3$): δ 1.37 (3H, t, J=7.2 Hz, CH_3); 4.44 (2H, q, J=7.2 Hz, OCH_2); 7.61 (1H, dd, J=8.0 Hz, 4.7 Hz, NCHC*H*CH); 8.19 (1H, dd, J=8.0 Hz, 1.4 Hz, NCHCHC*H*); 8.82 (1H, dd, J=4.7 Hz, 1.4 Hz, NC*H*CHCH). ^{19}F NMR ($CDCl_3$): δ −101.7 (2F, s, CF_2). ^{13}C NMR ($CDCl_3$): δ 13.8 (CH_3); 63.6 (OCH_2); 107.9 (C_{ar}CN); 111.9 (t, J=255.0 Hz, CF_2); 113.9 (CN); 125.4 (NCHCHCH); 142.5 (NCHCHCH); 151.6 (NCHCHCH); 153.2 (t, J=28.3 Hz, $NC_{q,ar}$); 162.0 (t, J=31.2 Hz, C=O). IR (ATR, cm^{-1}): ν=2237 (CN); 1771 (C=O); 1585; 1468; 1444; 1393; 1373; 1316; 1285; 1270; 1236; 1181; 1132; 1106; 1058; 1015; 845; 813; 782; 722; 662. MS (ES+) m/z (%): 227 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_8F_2N_2O_2$: C, 53.10; H, 3.57; N, 12.39. Found: C, 53.28; H, 3.65; N, 12.36.

3.3. 8,8-Difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione 9

In a flask of 10 mL, 185 mg (0.817 mmol, 1 equiv) of ethyl (3-cyanopyridin-2-yl)difluoroacetate **8** was dissolved in 0.5 mL of sulfuric acid. After stirring vigorously for 24 h at room temperature, the mixture was poured onto 1 g of ice and the product was extracted with EtOAc (4×5 mL). Drying ($MgSO_4$) of the organic phases, evaporation of the solvent and recrystallisation from methanol, afforded 150 mg (0.757 mmol, 93% yield) of 8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione **9** as white crystals (mp=257 °C). ^{1}H NMR (acetone-*d*6): δ 7.92 (1H, dd, J=8.0 Hz, 4.8 Hz, NCHC*H*CH); 8.57 (1H, dd, J=8.0 Hz, 1.5 Hz, NCHCHC*H*); 9.07 (1H, dd, J=4.8 Hz, 1.5 Hz, NC*H*CHCH); 11.17 (1H, s(broad), NH). ^{19}F NMR (acetone-*d*6): δ −101.0 (2F, s, CF_2). ^{13}C NMR (acetone-*d*6): δ 104.2 (t, J=243.5 Hz, CF_2); 122.7 (t, J=4.6 Hz, C_{ar}CO); 127.4 (NCHCHCH); 136.5 (NCHCHCH); 149.0 (t, J=21.9 Hz, $C_{ar}CF_2$); 155.3 (NCHCHCH); 161.3 ($C_{ar}C$=O); 162.3 (t, J=29.4 Hz, CF_2C=O). IR (ATR, cm^{-1}): ν=3442 (NH); 3168; 3032; 2923; 2829; 1745 (C=O); 1720 (C=O); 1597; 1450; 1377; 1301; 1269; 1160; 1133; 1087; 1069; 1051; 1014; 863; 834; 794; 710; 667. MS (ES+) m/z (%): 217 ($M+H_3O^+$, 100). GC–MS (EI) m/z (%): 198 (M^+, 11); 179 (M^+-F, 1); 155 (M^+-CONH, 100); 127 ($M^+-CONHCO$, 97). Anal. Calcd for $C_8H_4F_2N_2O_2$: C, 48.50; H, 2.03; N, 14.14. Found: C, 48.25; H, 2.13; N, 13.98.

3.4. 6-Benzyl-8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione 10a

To a solution of 1.00 g (5.05 mmol, 1 equiv) of 8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione **9** in DMF (10 mL) at 0 °C was added 0.24 g of sodium hydride (60% in mineral oil, 6.06 mmol,

1.2 equiv). After stirring for 20 min at 0 °C, 0.95 g (5.55 mmol, 1.1 equiv) of benzyl bromide was added dropwise at 0 °C, and the resulting mixture was stirred at 60 °C for 2 h. Subsequently, the reaction mixture was cooled to 0 °C and quenched with aq satd $NaHCO_3$ (5 mL), after which, water (10 mL) was added and the aqueous phase was extracted with EtOAc (4×20 mL). The combined organic phases were washed with brine (3×20 mL), dried ($MgSO_4$) and concentrated to afford the crude product, which was dissolved in CH_3CN and extracted with hexane to remove the residual mineral oil (from the used NaH dispersion). After evaporation of the CH_3CN in vacuo, the product was recrystallized from MeOH to afford 0.79 g (2.74 mmol, 54% yield) of 6-benzyl-8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione **10a** as white crystals (mp=145.5 °C). ^{1}H NMR ($CDCl_3$): δ 5.21 (2H, s, CH_2); 7.28–7.36 (3H, m, 3×CH_{benzyl}); 7.44–7.49 (2H, m, 2×CH_{benzyl}); 7.72 (1H, dd, *J*=8.0 Hz, 4.9 Hz, NCHC*H*CH); 8.56 (1H, dd, *J*=8.0 Hz, 1.7 Hz, NCHCHC*H*); 9.03 (1H, dd, *J*=4.9 Hz, 1.7 Hz, NC*H*CHCH). ^{19}F NMR ($CDCl_3$): δ −98.6 (2F, s, CF_2). ^{13}C NMR ($CDCl_3$): δ 44.4 (CH_2); 103.6 (t, *J*=245.2 Hz, CF_2); 122.1 (t, *J*=4.6 Hz, $C_{q,ar}CO$); 127.3 (NCH*C*HCH); 128.2 (CH_{benzyl}); 128.7 (2×CH_{benzyl}); 129.1 (2×CH_{benzyl}); 135.2 ($C_{q,benzyl}$); 137.3 (NCHCH*C*H); 148.0 (t, *J*=22.0 Hz, $C_{ar}CF_2$); 155.4 (NCHCHCH); 160.8 (C_{ar}C=O); 162.5 (t, *J*=29.4 Hz, CF_2*C*=O). IR (ATR, cm^{-1}): ν=2926; 1741 (C=O), 1693 (C=O), 1584, 1492; 1455; 1432; 1389; 1360; 1340; 1312; 1299; 1250; 1224; 1207; 1156; 1138; 1113; 1070; 1029; 954; 848; 824; 794; 759; 724,699; 666; 658; 620. GC–MS (EI) *m*/*z* (%): 288 (M^+, 100); 260 (11); 232 (20); 231 (10); 212 (14); 204 (18); 155 (11); 132 (10); 129 (99); 127 (33); 100 (12); 91 ($C_7H_7^+$, 29); 77 (13); 65 (12). Anal. Calcd for $C_{15}H_{10}F_2N_2O_2$: C, 62.50; H, 3.50; N, 9.72. Found: C, 62.02; H, 3.72; N, 9.48.

3.5. 6-(4-Bromobenzyl)-8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione 10b

The same procedure as described for the synthesis of 6-benzyl-8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione **10a** was applied. Since 4-bromobenzyl bromide is a solid, it was first dissolved in DMF and the solution was added dropwise to the reaction mixture.

Yield=47%. Mp=138.6 °C (methanol). White crystals. ^{1}H NMR ($CDCl_3$): δ 5.16 (2H, s, CH_2); 7.36 (2H, d, *J*=8.5 Hz, CHCH); 7.46 (2H, d, *J*=8.5 Hz, CHCH); 7.73 (1H, dd, *J*=8.0 Hz, 5.0 Hz, NCHC*H*CH); 8.56 (1H, dd, *J*=8.0 Hz, 1.7 Hz, NCHCHC*H*); 9.04 (1H, dd, *J*=5.0 Hz, 1.7 Hz, NC*H*CHCH). ^{19}F NMR ($CDCl_3$): δ −98.6 (2F, s, CF_2). ^{13}C NMR ($CDCl_3$): δ 43.9 (CH_2); 103.6 (t, *J*=245.8 Hz, CF_2); 122.1 (t, *J*=4.0 Hz, $C_{ar}CO$); 122.6 (CBr); 127.3 (NCH*C*HCH); 131.1 (2×$CH_{bromobenzyl}$); 132.0 (2×$CH_{bromobenzyl}$); 134.2 ($C_{q,\ bromobenzyl}$); 137.5 (NCHCH*C*H); 148.1 (t, *J*=22.5 Hz, $C_{ar}CF_2$); 155.7 (NCHCHCH); 160.9 (C_{ar}*C*=O); 162.6 (t, *J*=30.0 Hz, CF_2*C*=O). IR (ATR, cm^{-1}): ν=1740 (C=O); 1680 (C=O); 1593; 1488; 1434; 1394; 1340; 1314; 1302; 1252; 1222; 1146; 1088; 1070; 1057; 1032; 1014; 963; 830; 794; 728; 664; 635. GC–MS (EI) *m*/*z* (%): 366/368 (M^+, 26); 338/340 (3); 310/312 (4); 282/284 (7); 259 (6); 231 (5); 207(10); 184 (5); 169/171 (11); 155 (10); 129 (100); 127 (28); 109 (8); 100 (10); 90(16); 89 (19); 77 (9); 63 (7); 50 (7). Anal. Calcd for $C_{15}H_9BrF_2N_2O_2$: C, 49.07; H, 2.47; N, 7.63. Found: C, 49.05; H, 2.56; N, 7.54.

3.6. 8,8-Difluoro-6-(4-nitrobenzyl)-1,6-naphthyridine-5,7(6*H*,8*H*)-dione 10c

The same procedure as described for the synthesis of 6-(4-bromobenzyl)-8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione **10b** was applied.

Yield=50%. Mp=147.1 °C (ethanol). White crystals. ^{1}H NMR ($CDCl_3$): δ 5.30 (2H, s, CH_2); 7.64 (2H, d, *J*=8.3 Hz, CHCH); 7.76 (1H, dd, *J*=7.9 Hz, 4.7 Hz, NCHC*H*CH); 8.21 (2H, d, *J*=8.3 Hz, CHCH); 8.58 (1H, dd, *J*=7.9 Hz, 1.7 Hz, NCHCHC*H*); 9.07 (1H, dd, *J*=4.7 Hz, 1.7 Hz, NC*H*CHCH). ^{19}F NMR ($CDCl_3$): δ −98.5 (2F, s, CF_2). ^{13}C NMR ($CDCl_3$): δ 43.8 (CH_2); 103.7 (t, *J*=245.8 Hz, CF_2); 121.9 (t, *J*=4.0 Hz, $C_{ar}CO$); 124.0 (2×$CH_{nitrobenzyl}$); 127.5 (NCH*C*HCH); 130.1 (2×$CH_{nitrobenzyl}$); 137.6 (NCHCH*C*H); 142.2 ($C_{q,nitrobenzyl}$); 147.8 (CNO_2); 148.0 (t, *J*=21.9 Hz, $C_{ar}CF_2$); 155.9 (NCHCHCH); 160.9 (C_{ar}*C*=O); 162.7 (t, *J*=30.0 Hz, CF_2*C*=O). IR (ATR, cm^{-1}): ν=3069; 2359; 1743 (C=O); 1693 (C=O); 1613; 1598; 1545 (NO_2); 1428; 1383; 1349; 1335; 1309; 1291; 1250; 1226; 1162; 1145; 1111; 1090; 1076; 1060; 1030; 1014; 975; 958, 863; 846; 803; 796; 745; 738; 721; 696; 660. GC–MS (EI) *m*/*z* (%): 333 (M^+, 45); 305 (8); 277 (5); 258 (11); 249 (13); 207 (9); 155 (18); 129 (100); 127 (52); 100 (17); 89 (28); 77 (15); 63 (15); 51 (10); 50 (10). Anal. Calcd for $C_{15}H_9F_2N_3O_4$: C, 54.06; H, 2.72; N, 12.61. Found: C, 54.01; H, 2.69; N, 12.75.

3.7. 8,8-Difluoro-6-methyl-1,6-naphthyridine-5,7(6*H*,8*H*)-dione 10d

To a solution of 30 mg (0.14 mmol, 1 equiv) of 8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione **9** in Et_2O (5 mL) was added 0.42 mmol (3 equiv) of a diazomethane solution in Et_2O (standard preparation according to literature procedures[18]). The resulting mixture was stirred at room temperature for 15 h, after which the solvent was evaporated in vacuo, yielding 32 mg (0.14 mmol, 100% yield) of 8,8-difluoro-6-methyl-1,6-naphthyridine-5,7(6*H*,8*H*)-dione **10d** as white crystals (mp=107.8 °C, Et_2O). ^{1}H NMR (acetone-*d*6): δ 3.38 (3H, s, CH_3); 7.91 (1H, dd, *J*=8.0 Hz, 4.6 Hz, NCHC*H*CH); 8.60 (1H, dd, *J*=8.0 Hz, 1.4 Hz, NCHCHC*H*); 9.05 (1H, dd, *J*=4.6 Hz, 1.4 Hz, NC*H*CHCH). ^{19}F NMR (acetone-*d*6): δ −99.5 (2F, s, CF_2). ^{13}C NMR (acetone-*d*6): δ 26.9 (CH_3); 104.0 (t, *J*=242.9 Hz, CF_2); 122.8 (t, *J*=4.6 Hz, $C_{ar}CO$); 127.6 (NCH*C*HCH); 136.8 (NCHCH*C*H); 148.1 (t, *J*=21.9 Hz, $C_{ar}CF_2$); 155.2 (NCHCHCH); 161.5 (C_{ar}C=O); 162.9 (t, *J*=29.4 Hz, CF_2*C*=O). IR (ATR, cm^{-1}): ν=3083; 2925; 1743 (C=O); 1678 (C=O); 1596; 1424; 1372; 1306; 1280; 1218; 1165; 1083; 1064; 1046; 952; 834; 795; 720. MS (ES+) *m*/*z* (%): 231 (M+H_3O^+, 100). Anal. Calcd for $C_9H_6F_2N_2O_2$: C, 50.95; H, 2.85; N, 13.20. Found: C, 50.85; H, 2.79; N, 13.28.

3.8. 8,8-Difluoro-7,8-dihydro-7-hydroxy-1,6-naphthyridine-5(6*H*)-one 11a

To a solution of 0.25 g (1.26 mmol, 1 equiv) of 8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione **9** in dry THF (4 mL) at 0 °C was added 0.77 g (0.96 ml, 10.09 mmol, 8 equiv) of $BH_3.SMe_2$ dropwise. After 6 h stirring at 0 °C, 5 mL of MeOH was slowly added at 0 °C, after which the solvents were evaporated in vacuo and the product was recrystallized from MeOH to afford 0.18 g (0.90 mmol, 71% yield) of 8,8-difluoro-7,8-dihydro-7-hydroxy-1,6-naphthyridine-5(6*H*)-one **11a** as gray crystals (mp=184.3 °C). ^{1}H NMR (acetone-*d*6): δ 5.38 (1H, s(broad), C*H*OH); 6.21 (1H, d, *J*=5.0 Hz, OH); 7.73–7.78 (1H, m, NCHC*H*CH); 8.39 (1H, dd, *J*=7.9 Hz, 1.7 Hz, NCHCHC*H*); 8.39 (1H, s(broad), NH); 8.89 (1H, dd, *J*=5.0 Hz, 1.7 Hz, NC*H*CHCH). ^{19}F NMR (acetone-*d*6): δ −99.9 (1F, dd, *J*=268.3 Hz, 6.6 Hz, CF_aF_b); −127.9 (1F, d, *J*=268.3 Hz, CF_aF_b). ^{13}C NMR (acetone-*d*6): δ 76.5 (dd, *J*=36.9 Hz, *J*=30.0 Hz, CHOH); 113.0 (dd, *J*=257.3 Hz, 233.1 Hz, CF_2); 124.5 (C_{ar}C=O); 126.7 (NCH*C*HCH); 136.1 (NCHCH*C*H); 149.0 (t, *J*=23.7 Hz, $C_{ar}CF_2$); 153.4 (NCHCHCH); 162.2 (C=O). IR (ATR, cm^{-1}): ν=3206; 3118; 2932; 1686 (C=O); 1592; 1491; 1469; 1455; 1432; 1393; 1356; 1315; 1257; 1228; 1197; 1160; 1128; 1094; 1080; 1061; 1017; 822; 788; 693; 636. MS (ES−) *m*/*z* (%): 199 ($M-H^-$, 100). Anal. Calcd for $C_8H_5F_2N_2O_2$: C, 48.01; H, 3.02; N, 14.00. Found: C, 47.93; H, 2.95; N, 14.11.

3.9. 6-Benzyl-8,8-difluoro-7,8-dihydro-7-hydroxy-1,6-naphthyridine-5(6*H*)-one 11b

To a solution of 0.20 g (0.69 mmol, 1 equiv) of 6-benzyl-8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione **10a** in dry THF

(4 mL) at 0 °C was added dropwise 0.42 g (0.52 ml, 5.55 mmol, 8 equiv) of $BH_3 \cdot SMe_2$. After 6 h stirring at 0 °C, 5 mL of MeOH was slowly added at 0 °C, followed by evaporation of the solvents in vacuo. Subsequently, the crude product was redissolved in CH_2Cl_2 (10 mL), after which the organic phase was washed with water (2×5 mL), dried ($MgSO_4$) and concentrated to yield 0.16 g (0.55 mmol, 79% yield) of 6-benzyl-8,8-difluoro-7,8-dihydro-7-hydroxy-1,6-naphthyridine-5(6*H*)-one **11b** as yellow crystals (mp=134.1 °C). ^{1}H NMR ($CDCl_3$): δ 2.89 (1H, s(broad), OH); 4.53 (1H, d, J=15.1 Hz, CH_aH$_b$); 5.23 (1H, dd, J=6.5 Hz, 3.6 Hz, CHOH); 5.33 (1H, d, J=15.1 Hz, CH$_a$$H_b$); 7.28–7.41 (5H, m, 5×CH$_{benzyl}$); 7.61–7.65 (1H, m, NCHCHCH); 8.52 (1H, dd, J=7.7 Hz, 1.7 Hz, NCHCHCH); 8.88 (1H, dd, J=5.0 Hz, 1.7 Hz, NCHCHCH). ^{19}F NMR ($CDCl_3$): δ −98.5 (1F, dd, J=273.6 Hz, 6.5 Hz, CF_aF$_b$); −127.5 (1F, d, J=273.6 Hz, CF$_a$$F_b$). ^{13}C NMR ($CDCl_3$): δ 48.6 (CH_2); 80.5 (dd, J=38.1 Hz, J=31.2 Hz, CHOH); 112.4 (dd, J=249.2 Hz, 242.3 Hz, CF_2); 124.6 (C_{ar}C=O); 126.7 (NCHCHCH); 128.1, 128.3, and 129.0 (5×CH$_{benzyl}$); 135.8 (C$_{q,benzyl}$); 137.2 (NCHCHCH); 147.8 (t, J=23.1 Hz, $C_{ar}CF_2$); 153.3 (NCHCHCH); 161.7 (C=O). IR (ATR, cm^{-1}): ν=3300 (OH); 1659 (C=O); 1592; 1428; 1359; 1288; 1232; 1200; 1152; 1068; 944; 910; 832; 797; 767; 728; 698. MS (ES+) m/z (%): 291 (M+H$^+$, 100). MS (ES−) m/z (%): 289 (M−H$^-$, 100). Anal. Calcd for $C_{15}H_{12}F_2N_2O_2$: C, 62.07; H, 4.17; N, 9.65. Found: C, 62.19; H, 4.03; N, 9.88.

3.10. Ethyl (4-chloro-2-cyanophenyl)difluoroacetate 13

The synthetic procedure for compound **13** is analogous to the synthesis of ethyl (3-cyanopyridin-2-yl)difluoroacetate **8**.

Flash chromatography (petroleum ether/EtOAc 8:1, R_f=0.22). Yield=82% (purity: 87%). Colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, t, J=7.2 Hz, CH_3); 4.39 (2H, q, J=7.2 Hz, OCH_2); 7.69 (1H, dd, J=8.5 Hz, 1.7 Hz, CH_{ar}); 7.73 (1H, d, J=8.5 Hz, CH_{ar}); 7.79 (1H, s(broad), CH_{ar}). ^{19}F NMR ($CDCl_3$): δ −101.3 (2F, s, CF_2). ^{13}C NMR ($CDCl_3$): δ 13.8 (CH_3); 64.2 (OCH_2); 112.0 (t, J=255.0 Hz, CF_2); 112.1 (t, J=4.0 Hz, C_{ar}CN); 114.8 (CN); 128.6 (t, J=7.5 Hz, CH_{ar}); 133.3 (CH_{ar}); 134.0 (t, J=25.4 Hz, $C_{ar}CF_2$); 134.4 (CH_{ar}); 137.8 (CCl); 162.2 (t, J=34.0 Hz, C=O). IR (ATR, cm^{-1}): ν=2988; 2236 (CN); 1761 (C=O); 1597; 1567; 1474; 1448; 1391; 1372; 1274; 1250; 1217; 1192; 1111; 1087; 1013; 992; 887; 856; 830; 768; 734; 684; 637. MS (ES+) m/z (%): 277/279 (M+NH$_4^+$, 100).

3.11. 7-Chloro-4,4-difluoroisoquinoline-1,3(2*H*,4*H*)-dione 14

The synthetic procedure for compound **14** is analogous to the synthesis of 8,8-difluoro-1,6-naphthyridine-5,7(6*H*,8*H*)-dione **9**.

Flash chromatography (petroleum ether/EtOAc 9:1, R_f=0.13). Yield=49%. White crystals (mp=137.0 °C). ^{1}H NMR ($CDCl_3$): δ 7.83 (1H, dd, J=8.4 Hz, 1.7 Hz, CH_{ar}); 7.88 (1H, d, J=8.4 Hz, CH_{ar}); 8.24 (1H, d, J=1.7 Hz, CH_{ar}); 8.40 (1H, s(broad), NH). ^{19}F NMR ($CDCl_3$): δ −92.5 (2F, s, CF_2). ^{13}C NMR ($CDCl_3$): δ 105.6 (t, J=242.9 Hz, CF_2); 126.4 (t, J=5.8 Hz, C_{ar}CO); 127.9 (CH_{ar}); 129.1 (CH_{ar}); 130.1 (t, J=24.8 Hz, $C_{ar}CF_2$); 135.6 (CH_{ar}); 139.6 (CCl); 160.8 (C=O); 161.7 (t, J=31.2 Hz, CF_2CO). IR (ATR, cm^{-1}): ν=3214 (NH); 3123; 2844; 1744 (C=O); 1706 (C=O); 1598; 1584; 1429; 1358; 1307; 1290; 1251; 1158; 1136; 1101; 1076; 1039; 994; 935; 838; 808; 718; 688; 672. GC–MS (EI) m/z (%): 231/233 (M$^+$, 20); 188/190 (M$^+$−CONH, 61); 160/162 (M$^+$−CONHCO, 100); 125 (M$^+$−CONHCO−Cl, 48); 75 (20). Anal. Calcd for $C_9H_4ClF_2NO_2$: C, 46.68; H, 1.47; N, 6.05. Found: C, 46.60; H, 1.18; N, 5.96.

3.12. 3-Bromo-2-cyanopyrazine 16

To a solution of 1.50 g (10.75 mmol, 1 equiv) of 2 chloro-3-cyanopyrazine **15** in propanenitrile (10 mL) was added 3.30 g (21.50 mmol, 2 equiv) of bromotrimethylsilane dropwise, and the resulting mixture was stirred for 16 h at room temperature. Subsequently, the reaction mixture was cooled to 0 °C and quenched with an aqueous solution of 2 M NaOH (10 mL). Afterward, the aqueous phase was extracted with EtOAc (3×10 mL), and the combined organic phases were washed with brine (2×10 mL). After drying ($MgSO_4$) and evaporation of the solvents in vacuo, the product was recrystallized from Et_2O to afford 1.56 g (8.49 mmol, 79% yield) of 3-bromo-2-cyanopyrazine **16** as white crystals (mp=43.5 °C). ^{1}H NMR ($CDCl_3$): δ 8.61 (1H, d, J=2.2 Hz, CH); 8.71 (1H, d, J=2.2 Hz, CH). ^{13}C NMR ($CDCl_3$): δ 114.7 (CN); 133.3 (*C*CN); 143.3 (CBr); 143.4 (CH); 147.0 (CH). IR (ATR, cm^{-1}): ν=3101; 2243 (CN); 1958; 1538; 1515; 1425; 1364; 1336; 1249; 1184; 1161; 1071; 1048; 945; 870; 839; 824; 668; 653. GC–MS (EI) m/z (%): 183/185 (M$^+$, 58); 129/131 (13); 104 (M$^+$−Br, 100); 77 (23); 52 (28). Anal. Calcd for $C_5H_2BrN_3$: C, 32.64; H, 1.10; N, 22.84. Found: C, 32.78; H, 1.15; N, 22.67.

3.13. Ethyl (3-cyanopyrazin-2-yl)difluoroacetate 17

The synthetic procedure for compound **17** is analogous to the synthesis of ethyl (3-cyanopyridin-2-yl)difluoroacetate **8**.

Flash chromatography (hexane/EtOAc 9:1, R_f=0.05). Yield=41%. Yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.38 (3H, t, J=7.2 Hz, CH_3); 4.45 (2H, q, J=7.2 Hz, OCH_2); 8.83 (1H, d, J=1.9 Hz, CH_{ar}); 8.91 (1H, d, J=1.9 Hz, CH_{ar}). ^{19}F NMR ($CDCl_3$): δ −103.0 (2F, s, CF_2). ^{13}C NMR ($CDCl_3$): δ 13.9 (CH_3); 64.3 (OCH_2); 111.2 (t, J=255.6 Hz, CF_2); 113.2 (CN); 128.8 (*C*CN); 145.4 (CH); 146.7 (CH); 150.1 (t, J=28.9 Hz, $C_{ar}CF_2$); 161.5 (t, J=31.2 Hz, C=O). IR (ATR, cm^{-1}): ν=2987; 2336 (CN); 1774 (C=O); 1561; 1469; 1447; 1409; 1372; 1309; 1286; 1244; 1117; 1061; 1012; 874; 854; 820; 784; 724; 660. GC–MS (EI) m/z (%): 227 (M$^+$, 0.1); 198 (M$^+$−C_2H_5, 0.1); 155 (100); 154 (M$^+$−COOEt, 25); 128 (18); 100 (37).

3.14. 2,2-Difluoro-2-(3-methoxyphenyl)acetamide 21

In a flask of 25 mL, 0.50 g (2.17 mmol) of ethyl 2,2-difluoro-2-(3-methoxyphenyl)acetate **20** was dissolved in a 7 M solution of NH_3 in MeOH (10 mL). The mixture was stirred at room temperature for 90 min, followed by evaporation of the solvent in vacuo to yield 0.44 g (2.17 mmol, 100% yield) of 2,2-difluoro-2-(3-methoxyphenyl) acetamide **21** as white crystals (mp=76.8 °C). ^{1}H NMR ($CDCl_3$): δ 3.84 (3H, s, CH_3O); 6.43 (1H, s(broad), NH_aH$_b$); 6.59 (1H, s(broad), NH$_a$$H_b$); 7.03 (1H, dd, J=8.3 Hz, 2.2 Hz, $CH_3OC_{q,ar}CHCH$); 7.15–7.21 (2H, m, C$HC_{q,ar}(CF_2)CH$); 7.38 (1H, t, J=8.3 Hz, CHCHCH). ^{19}F NMR ($CDCl_3$): δ −102.8 (2F, s, CF_2). ^{13}C NMR ($CDCl_3$): δ 55.3 (CH_3O); 110.8 (t, J=6.3 Hz, $C_{q,ar}CHC_{q,ar}$); 114.3 (t, J=253.3 Hz, CF_2); 116.7 ($CHCHC_{q,ar}OCH_3$); 117.5 (t, J=5.8 Hz, $CHCHC_{q,ar}CF_2$); 129.8 (CHCHCH); 133.9 (t, J=25.4 Hz, $C_{q,ar}CF_2$); 159.6 ($C_{q,ar}OCH_3$); 166.9 (t, J=31.7 Hz, C=O). IR (ATR, cm^{-1}): ν=3394 (NH); 3182 (NH); 1678 (C=O); 1602; 1464; 1421; 1283; 1217; 1179; 1141; 1083; 1075; 1046; 1022; 864; 805; 790; 701; 659. MS (ES+) m/z (%): 219 (M+NH$_4^+$, 100). MS (ES−) m/z (%): 200 (M−H$^+$, 100). Anal. Calcd for $C_9H_9F_2NO_2$: C, 53.73; H, 4.51; N, 6.96. Found: C, 53.92; H, 4.13; N, 7.33.

3.15. 2,2-Difluoro-2-(3-methoxyphenyl)ethylamine 23

To an ice cooled solution of 4.10 g (20.38 mmol, 1 equiv) of 2,2-difluoro-2-(3-methoxyphenyl)acetamide **21** in CH_2Cl_2 (90 mL) was added dropwise 4.64 g (5.79 ml, 61.14 mmol, 3 equiv) of $BH_3.SMe_2$. After stirring for 40 h at reflux temperature, the reaction mixture was quenched by carefully adding water/MeOH 1:1 (20 mL) at 0 °C. After extraction with CH_2Cl_2 (3×50 mL), the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford 3.24 g (17.32 mmol, 85% yield) of 2,2-difluoro-2-(3-methoxyphenyl)ethylamine **23** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.31 (2H, s(broad), NH_2); 3.12 (2H, t, J=14.9 Hz, CH_2); 3.84 (3H, s, CH_3O); 6.95–7.08 (3H, m, 3×CH); 7.36 (1H, t, J=8.0 Hz, CHCHCH). ^{19}F NMR ($CDCl_3$): δ −105.6 (2F, t, J=14.9 Hz, CF_2). ^{13}C NMR ($CDCl_3$): δ 49.0 (t, J=30.6 Hz, CH_2); 54.9 (CH_3O); 110.7 (t, J=6.3 Hz,

$C_{q,ar}CHC_{q,ar}$); 115.1 ($CHCHC_{q,ar}OCH_3$); 117.1 (t, J=5.8 Hz, $CHCHC_{q,ar}CF_2$); 121.3 (t, J=242.9 Hz, CF_2); 129.4 ($CHCHCH$); 136.6 (t, J=26.0 Hz, $C_{q,ar}CF_2$); 159.4 ($C_{q,ar}OCH_3$). IR (ATR, cm^{-1}): ν=3395 (NH); 1606; 1589; 1491; 1455; 1435; 1320; 1292; 1281; 1219; 1164; 1034; 1004; 858; 836; 782; 697. GC–MS (EI) m/z (%): 187 (M^+, 100); 158 (41); 157 ($M^+-CH_2NH_2$, 36); 127 (37); 125 (11); 114 (53); 109 (12); 77 (15); 75 (13); 63 (14).

3.16. 1,3,5-Tris[2,2-trifluoro-2-(3-methoxyphenyl)ethyl]-1,3,5-triazinane 25 and 5-[2,2-difluoro-2-(3-methoxyphenyl)ethyl]-1,3,5-dioxazinane 26

In a flask of 10 mL, 0.40 g (2.14 mmol, 1 equiv) of 2,2-difluoro-2-(3-methoxyphenyl)ethylamine **23** was dissolved in 1 mL of an aqueous 37% formaldehyde-solution and stirred for 16 h at reflux temperatures. Afterward, the reaction mixture was cooled to room temperature and extracted with toluene (3×5 mL). Washing of the organic phase with water (2×5 mL), drying (K_2CO_3) and evaporation of the solvent afforded the crude product, which was purified by flash chromatography (hexane/EtOAc/Et_3N 80:10:10) to yield 0.11 g (0.506 mmol, 24% yield) of 1,3,5-tris[2,2-trifluoro-2-(3-methoxyphenyl)ethyl]-1,3,5-triazinane **25** (R_f=0.02) and 20 mg (0.077 mmol, 4% yield) of 5-[2,2-difluoro-2-(3-methoxyphenyl) ethyl]-1,3,5-dioxazinane **26** (R_f=0.16), both as yellow oils.

3.17. 1,3,5-Tris[2,2-trifluoro-2-(3-methoxyphenyl)ethyl]-1,3,5-triazinane 25

^1H NMR ($CDCl_3$): δ 2.89 (6H, t, J=13.8 Hz, 3×CH_2CF_2); 3.42 (6H, s, 3×NCH_2N); 3.79 (9H, s, 3×CH_3O); 6.91–6.99 (9H, m, 9×CH_{ar}); 7.30 (3H, t, J=8.0 Hz, 3×$CHCHCH$). ^{19}F NMR ($CDCl_3$): δ −100.4 (6F, t, J=13.8 Hz, 3×CF_2). ^{13}C NMR ($CDCl_3$): δ 55.2 (3×CH_3O); 57.9 (t, J=30.0 Hz, 3×CH_2CF_2); 74.9 (3×NCH_2N); 110.1 (t, J=6.3 Hz, 3×$C_{q,ar}CHC_{q,ar}CF_2$); 115.3 (3×$CHCHC_{q,ar}OCH_3$); 117.6 (t, J=6.3 Hz, 3×$CHCHC_{q,ar}CF_2$); 121.4 (t, J=244.6 Hz, 3×CF_2); 129.4 (3×$CHCHCH$); 137.3 (t, J=25.4 Hz, 3×$C_{q,ar}CF_2$); 159.4 (3×$C_{q,ar}OCH_3$). IR (ATR, cm^{-1}): ν=1606, 1589, 1491, 1455, 1436, 1327, 1292, 1279, 1225, 1180, 1138, 1110, 1067, 1039, 1009, 986, 931, 911, 880, 846, 857, 846, 783, 730, 709, 697. MS (ES+) m/z (%): 620 ($M+Na^+$, 10), 200 (100).

3.18. 5-[2,2-Difluoro-2-(3-methoxyphenyl)ethyl]-1,3,5-dioxazinane 26

^1H NMR ($CDCl_3$): δ 3.64 (2H, t, J=13.8 Hz, CH_2CF_2); 3.83 (3H, s, CH_3O); 4.56 (4H, s(br), CH_2NCH_2); 5.15 (2H, s, OCH_2O); 6.94–7.06 (3H, m, 3×CH_{ar}); 7.33 (1H, t, J=7.7 Hz, $CHCHCH$). ^{19}F NMR ($CDCl_3$): δ −100.5 (2F, t, J=13.8 Hz, CF_2). ^{13}C NMR ($CDCl_3$): δ 55.3 (CH_3O); 57.3 (t, J=30.0 Hz, CH_2CF_2); 84.9 (CH_2NCH_2); 94.9 (OCH_2O); 111.0 (t, J=6.3 Hz, $C_{q,ar}CHC_{q,ar}CF_2$); 115.5 ($CHCHC_{q,ar}OCH_3$); 117.6 (t, J=6.3 Hz, $CHCHC_{q,ar}CF_2$); 121.2 (t, J=243.5 Hz, CF_2); 129.5 ($CHCHCH$); 137.1 (t, J=26.0 Hz, $C_{q,ar}CF_2$); 159.5 ($C_{q,ar}OCH_3$). IR (ATR, cm^{-1}): ν=2933; 2877; 2840; 1745; 1683; 1606; 1589; 1492; 1456; 1436; 1331; 1292; 1280; 1234; 1219; 1175; 1151; 1074; 1030; 960; 931; 880; 859; 846; 788; 732; 709; 698; 662. GC–MS (EI) m/z (%): 259 (M^+, 12); 229 (15); 212 (43); 199 (36); 198 (33); 157 (53); 127 (21); 114 (23); 102 (99); 72 (25); 42 (100).

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