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One-pot highly diastereoselective five-component synthesis of polysubstituted 2-hydroxy-2-trifluoromethylpiperidines with four and five stereogenic centers

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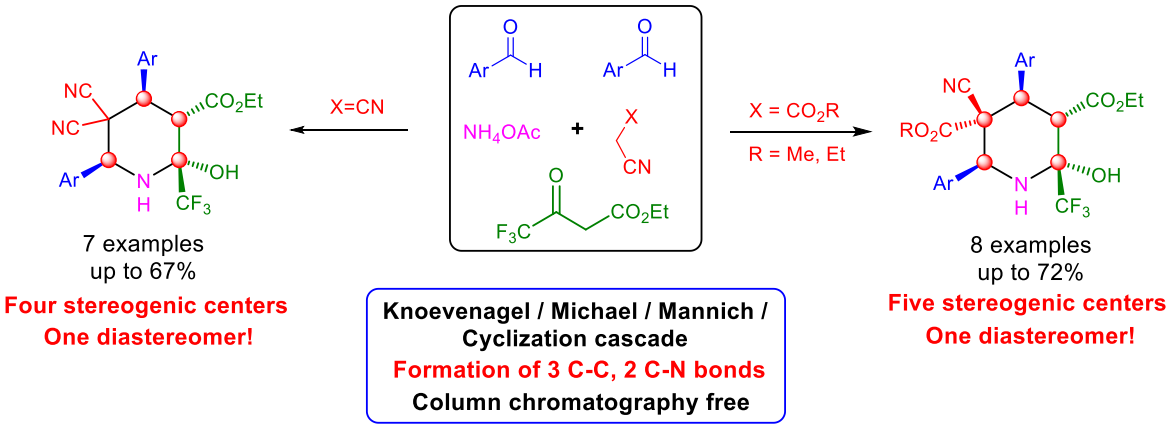
Abstract

The Knoevenagel–Michael–Mannich–cyclization cascade of aldehydes, cyano-containing C-H acids, ethyl 4,4,4-trifluoro-3-oxobutanoate and ammonium acetate provided convenient stereoselective formation of ethyl 5,5-dicyano-4,6-diaryl-2-hydroxy-2-(trifluoromethyl)pi-peridine-3-carboxylates with four stereogenic centers and dialkyl 4,6-diaryl-5-cyano-2-hydroxy-2-(trifluoromethyl)piperidine-3,5-dicarboxylates with five stereogenic centers. The stereoselective formation of individual diastereomers was shown. The configuration of diastereomers was confirmed by NMR spectra and X-ray diffraction analysis. Ammonium acetate played dual role, acting as a base and as a nitrogen source.



Keywords: multicomponent reactions, ethyl 4,4,4-trifluoro-3-oxobutanoate, C-H acids, ammonium acetate, 2-hydroxy-2-trifluoromethylpiperidines, stereoselectivity

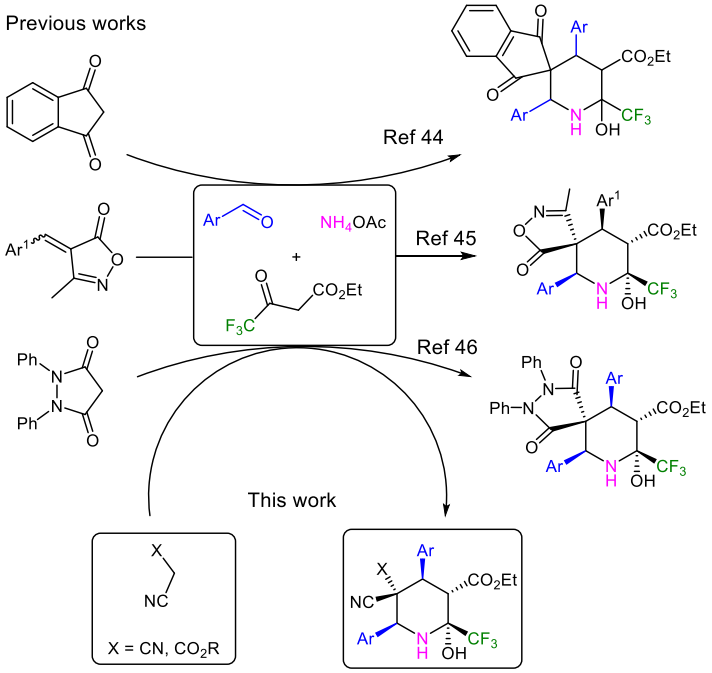
Introduction

Piperidine and its derivatives play an important role in the discovery of drugs exhibiting various biological activities.[1] The piperidine framework is one of the most frequently found in the structure of active substances in pharmaceutical compositions.[2-4] They have a broad spectrum of biological activities: antihypertensive,[5] antimalarial,[6] neuroprotective,[7,8] antibacterial,[9] anticonvulsant.[10] Among medications, 4-phenylpiperidine derivatives are of great importance, because they resemble the morphine pharmacophore.[11,12] 2-Hydroxypiperidines are hepatic metabolites with biological activity and functional properties.[13]

It is known that the introduction of fluorine atom into organic molecules often leads to a sharp change in their physical, chemical, and biological properties.[14-16] In particular, the trifluoromethyl group is the key structural unit in many fluorinated compounds of biological and pharmaceutical importance. As a result, fluorine-containing heterocycles are now widely recognized as important organic molecules showing interesting biological activity with potential for medical and agricultural applications.[17-20]

Currently there are many multistep synthesis methods of substituted piperidines such as allylic cyclization, hydroamination, enyne cyclization, electrocyclization, Aza-Prins reactions, 2-azadiene Diels-Alder reaction etc. [21-25] These techniques often have a number of shortcomings, such as low yields, and special requirements for the purity of solvents. For organic compounds' preparation, domino and multicomponent syntheses are superior to two-component reactions in high atom efficiency,[26,27] time, materials, energy saving, eco-friendliness and access to greater diversity.[28-33] We have used a multicomponent approach in the synthesis of different nitrogen heterocycles from olefins or carbonyls and C-H acids.[34-38]

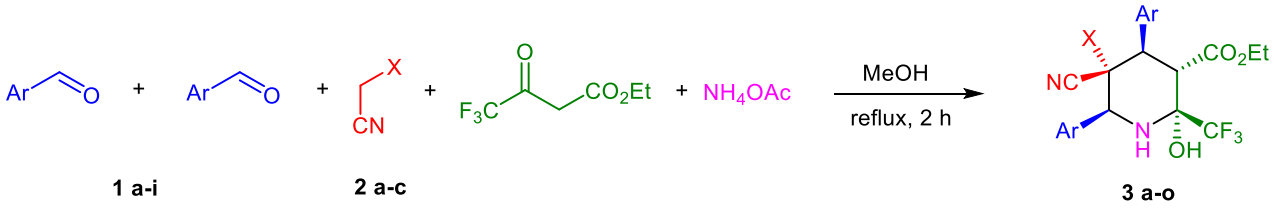
Recently, we have carried out a multicomponent synthesis of substituted piperidines.[39-43] Ammonium acetate or aqueous ammonia were the nitrogen sources for piperidine cycle. This method was used in the synthesis of polysubstituted 2-hydroxy-2-trifluoromethylpiperidines 5-spyro connected with cycle or heterocycle (Scheme 1).[44-46] C-H acid 4,4,4-trifluoro-3-oxobutanoate and ammonium acetate were utilized as fluorine and nitrogen sources respectively.



Scheme 1. Four-and five-component syntheses of substituted 4,6-diaryl-2-hydroxy-2-trifluoromethylpiperidines

Results and Discussion

In present study we report the results of a one-pot five-component reaction between aldehydes **1**, nitriles **2**, ethyl 4,4,4-trifluoro-3-oxobutanoate and ammonium acetate for the direct highly stereoselective formation of substituted 2-hydroxy-2-trifluoromethylpiperidines **3**. (Scheme 2, Table 1).



Scheme 2. Five-component synthesis of polyubstituted 2-hydroxy-2-trifluoromethylpiperidines.

Table 1. Multicomponent transformation of aldehydes **1a-i**, cyano C-H acids **2a-c**, ethyl 4,4,4-trifluoro-3-oxobutanoate and ammonium acetate into 5-substituted ethyl 5-cyano-4,6-diaryl-2-hydroxy-2-(trifluoromethyl)piperidine-3-carboxylates **3a-o**.[a]

Entry	Aldehyde	CH acid	Ar	X	Product	Yield%[b]
1	**1a**	**2a**	C_6H_5	CN	**3a**	54
2	**1b**	**2a**	3-MeC_6H_4	CN	**3b**	67
3	**1c**	**2a**	4-MeC_6H_4	CN	**3c**	47
4	**1d**	**2a**	3-$OMeC_6H_4$	CN	**3d**	61
5	**1e**	**2a**	4-ClC_6H_4	CN	**3e**	57
6	**1f**	**2a**	4-BrC_6H_4	CN	**3f**	52
7	**1g**	**2a**	4-$NO_2C_6H_4$	CN	**3g**	37
8	**1a**	**2b**	C_6H_5	CO_2Me	**3h**	69
9	**1c**	**2b**	4-MeC_6H_4	CO_2Me	**3i**	59
10	**1d**	**2b**	3-$MeOC_6H_4$	CO_2Me	**3j**	72
11	**1h**	**2b**	4-FC_6H_4	CO_2Me	**3k**	70
12	**1f**	**2b**	4-BrC_6H_4	CO_2Me	**3l**	45
13	**1g**	**2b**	4-$O_2NC_6H_4$	CO_2Me	**3m**	33
14	**1h**	**2c**	4-FC_6H_4	CO_2Et	**3n**	52
15	**1i**	**2c**	4-Py	CO_2Et	**3o**	17

[a] Aldehyde 1 (6 mmol), cyano C-H acid (3 mmol) 2, ethyl 4,4,4-trifluoro-3-oxobutanoate (3 mmol), NH_4OAc (6 mmol), methanol (7 mL), refluxing for 2 h.
[b] Isolated yields.

In the present study we report five-component synthesis of ethyl 5,5-dicyano-4,6-diaryl-2-hydroxy-2-(trifluoromethyl)piperidine-3-carboxylates **3a**–**g** with four stereogenic centers and dialkyl 4,6-diaryl-5-cyano-2-hydroxy-2-(trifluoromethyl)piperidine-3,5-dicarboxylates **3h**–**o** with five stereogenic centers (Scheme 2, Table 1). The refluxing of aldehydes **1a-i** (both with electron-withdrawing and electron-donating substituents), cyano-containing C-H acids **2a-c**, ethyl 4,4,4-trifluoro-3-oxobutanoate and ammonium acetate for 2 h lead to formation of **3**. This technique was developed in the study of the five-component synthesis of 1,4,5,6-tetrahydropyridines.[47] The new multicomponent reaction allows us to obtain **3** in low to moderate yields in one step from cheap and available starting materials via the domino process with the formation of three C-C and two C-N bonds. All reactions were monitored via thin-layer chromatography (TLC). Product **3** was isolated in a 17–72% yield by simple filtration after freezing the reaction mixture.

As the NMR spectra of compounds **3** showed only a single set of signals, we assumed the stereoselective formation of individual diastereoisomers. The structure of **3d** is shown in Figure 1. X-ray crystal diffraction data indicated that structure **3d** with four stereogenic centers should be defined as ethyl (2*RS*,3*SR*,4*RS*,6*SR*)-5,5-dicyano-2-hydroxy-4,6-bis(3-methoxyphenyl)-2-(trifluoromethyl)piperidine-3-carboxylate. The structure of **3l** is shown in Figure 2. X-ray indicated that structure **3l** with five stereogenic centers is 3-ethyl 5-methyl (2*RS*,3*SR*,4*RS*,5*RS*,6*SR*)-4,6-bis(4-bromophenyl)-5-cyano-2-hydroxy-2-(trifluoromethyl)piperidine-3,5-dicarboxylate. In both **3d, 3l** diastereomers, we observed bulky aryl substituents in sterically least-hindered positions relative to each other. We suppose that the formation of isomers with the *cis*-configuration of 2-hydroxy- and 3-carbethoxy groups is also associated with the presence of a hydrogen bond between them.

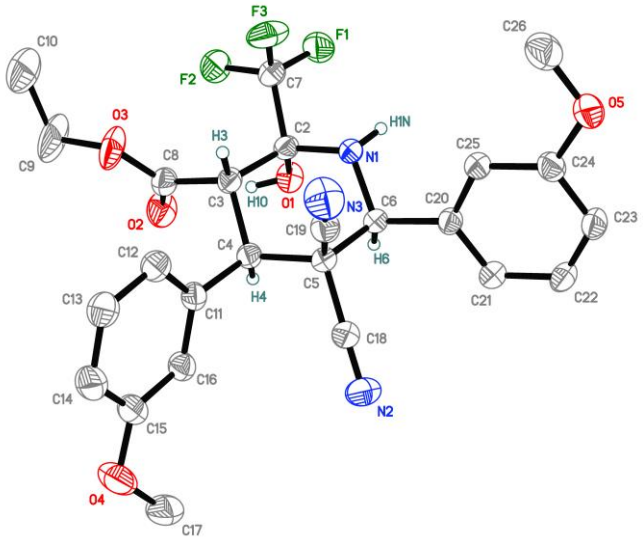


Fig.1. X-ray Structure of **3d**.

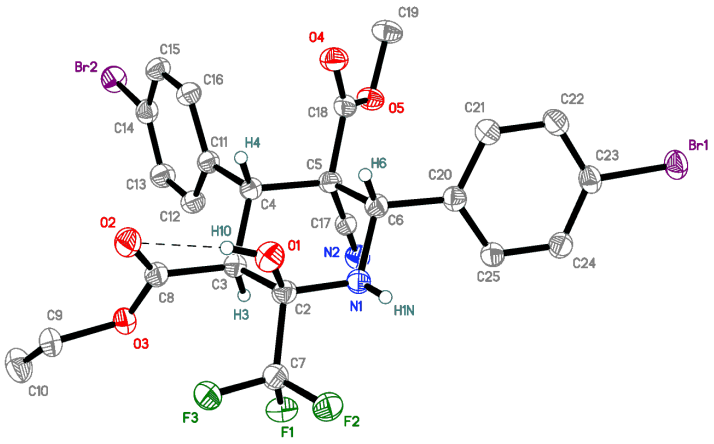


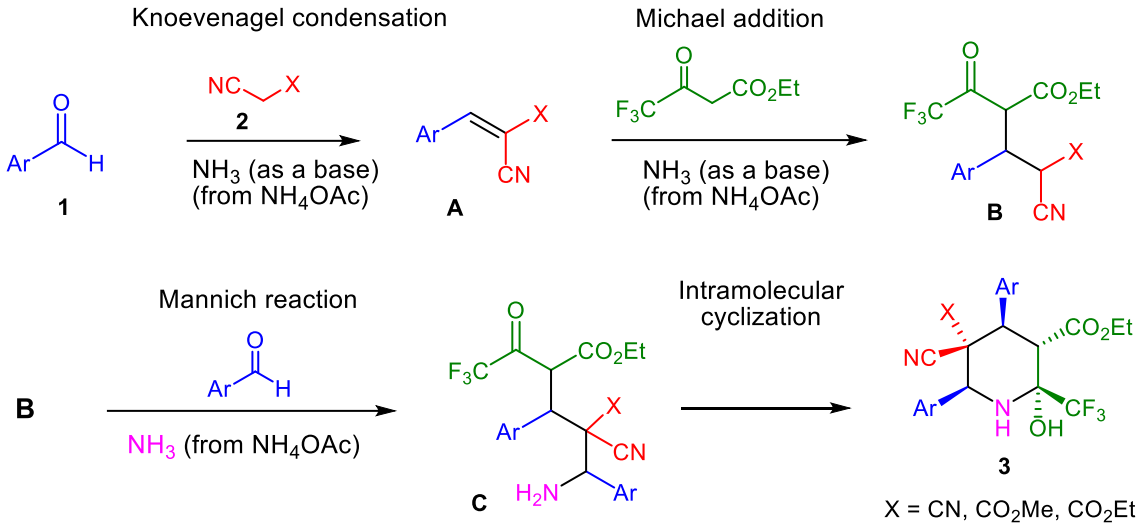
Fig.2. X-ray Structure of **3l**.

A possible reaction pathway is shown in Scheme 3. The multicomponent reaction between aldehydes **1**, cyano C-H acids **2** (malononitrile or alkyl cyanoacetate), esters of 3-oxocarboxylic acids and ammonium acetate is a four-step domino process. At the first stage, the Knoevenagel condensation between aldehydes and cyano C-H acid occurs. Ammonium acetate is a catalyst for this reaction. The formation of cyano olefins **A** under ammonium salts catalysis is already known.[48] The second step of the process is the Michael addition of ethyl 4,4,4-trifluoro-3-oxobutanoate to the electron-poor styrene **A** to form the Michael adduct **B**. The formation of close analogues of intermediate **B** from benzylidenemalononitriles and malononitrile or ethyl cyanoacetate was studied previously by Verboom et al.[49] The subsequent Mannich reaction of **B**, aldehyde **1** (second equivalent) and ammonia, which is formed from ammonium acetate, leads to intermediate **C**. The latter undergoes intra-

molecular cyclization with the formation of a substituted 5-substituted ethyl 5-cyano-4,6-diaryl-2-hydroxy-2-(trifluoromethyl)piperidine-3-carboxylates, which was identified and characterized in this work for the first time.

It should be noted in particular that the domino process stopped at the stage of 2-hydroxy-2-trifluoromethyl derivative **3** formation. Recently, we have found that similar multicomponent reaction (when esters of 3-oxocarboxylic acids were utilized instead of ethyl 4,4,4-trifluoro-3-oxobutanoate), afforded to substituted 1,4,5,6-tetrahydropyridines.[47] A detailed study of the mechanism have showed that this reaction proceeds through the formation of substituted 2-hydroxypiperidines (non-fluorinated analogues of **3**) followed by dehydration to 3,4,5,6-tetrahydropyridines and slow isomerization at rt to 1,4,5,6-tetrahydropyridines.[50] Acidification of the reaction media also promoted isomerization.

Attempts to carry out dehydration of **3** in any of 2-trifluoromethyl tetrahydropyridines were not successful. Continuous refluxing or acidification of **3** did not lead to its conversion.



Scheme 3. Presumed mechanism of substituted 5-cyano-4,6-diaryl-2-hydroxy-2-(trifluoromethyl)piperidines formation.

Conclusions

In conclusion, we have developed a five-component stereoselective single-step synthesis of substituted 2-hydroxy-2-(trifluoromethyl)piperidines, utilizing aromatic aldehydes (both with electron-withdrawing and electron-donating substituents), cyano C-H acids (malononitrile or alkyl cyanoacetates), ethyl 4,4,4-trifluoro-3-oxobutanoate, and ammonium acetate as a nitrogen source for the piperidine cycle. Our method allows to obtain ethyl (2*RS*,3*SR*,4*RS*,6*SR*)-4,6-diaryl-5,5-dicyano-2-hydroxy-2-(trifluoromethyl)piperidine-3-carboxylates with four stereogenic centers and dialkyl (2*RS*,3*SR*,4*RS*,5*RS*,6*SR*)-4,6-diaryl-5-cyano-2-hydroxy-2-(trifluoromethyl)piperidine-3,5-dicarboxylates with five stereogenic centers as a single diastereomers. Products were purified by simple filtration, and column chromatography was avoided entirely.

Experimental Section

General. All melting points were measured with a Stuart SMP30 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM300 and Bruker DRX 500 at ambient temperature in

DMSO-d_6 or $CDCl_3$ solutions. Chemical shift values are given in δ scale relative to Me_4Si. The *J* values are given in hertz. Only discrete or characteristic signals for the 1H NMR are reported. IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. HR-ESI-MS was measured on a Bruker microTOF II instrument; external or internal calibration was done with electrospray calibrant solution (Fluka). All starting materials were obtained from commercial sources and used without purification. All reactions were monitored with thin layer chromatography (TLC) and carried out with Merck precoated plates DC-Alufolien Kieselge l60 F254. X-ray crystallographic analyses were performed with Bruker Quest D8 diffractometer.

General procedure for preparation of polysubstituted 2-hydroxy-2-trifluoromethylpiperidines 3. Synthesis of 3a-n (General method). A mixture of aldehydes **1a–i** (6 mmol), malononitrile and derivatives (3 mmol) **2a-c**, ethyl 4,4,4-trifluoro-3-oxobutanoate (3 mmol), and ammonium acetate (6 mmol) was refluxed in methanol (7 mL) for 2 h. After the reaction completion, the mixture was maintained at –10 °C for 30 min for the complete precipitation of the product, the precipitate was collected by filtration and dried to give piperidine **3**.

Ethyl (2RS,3SR,4RS,6SR)-5,5-dicyano-2-hydroxy-4,6-diphenyl-2-(trifluoromethyl)piperidine-3-carboxylate (3a). White solid; yield: 0.72 g (54%); mp 175-177°C. ^{1}H-NMR (CDCl3, 300.13 MHz): δ 0.86 (t, *J* 7.1, Hz, 3H, CH3), 2.9 (s, NH), 3.76 (d, *J* 12.6 Hz, 1H, CH), 3.85 (d, *J* 12.6 Hz, 1H, CH), 3.88-3.99 (m, 2H, OCH2), 4.89 (s, 1H, CH), 5.44 (s, 1H, OH), 7.41-7.6 (m, 8H, Ar), 7.67-7.74 (m, 8H, Ar); 13C-NMR (DMSO-d6, 75.47 MHz): δ 13.73, 45.79, 46.69, 48.7, 58.74, 61.11, 83.18 (q, *J* 29.5 Hz, C(CF3)), 112.87, 113.39, 123.97 (q, *J* 287.8 Hz, CF3), 128.78 (2C), 128.93 (2C), 129.4 (4C), 129.74, 130.27, 134.59, 135.93, 167.38; 19F-NMR (DMSO-d6, 282.4 MHz): δ -80.75 (s, 3F); IR (KBr): 3390, 3319, 2983, 1705, 1189 cm^{-1}; HRMS (ESI) m/z calcd for $C23H20F3N3O3^+$ 444.1530 $[M + H]^+$; found: 444.1520.

Ethyl (2RS,3SR,4RS,6SR)-5,5-dicyano-2-hydroxy-4,6-bis(3-methylphenyl)-2-(trifluoromethyl)piperidine-3-carboxylate (3b). White solid; yield: 0.95 g (67%); mp 147-150°C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 0.87 (t, *J* 7.1 Hz, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.87 (s, 1H, NH), 3.74 (d, *J* 12.6 Hz, 1H, CH), 3.8 (d, *J* 12.6 Hz, 1H, CH), 3.85-4.03 (m, 2H, OCH_2), 4.83 (s, 1H,CH), 5.46 (s, 1H, OH), 7.21-7.41 (m, 6H, Ar), 7.47-7.52 (m, 2H, Ar); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ13.18, 21.37, 21.45, 44.40, 47.65, 48.65, 59.93, 62.55, 82.53 (q, *J* 29.9 Hz, C(CF_3)), 111.49, 112.50, 123.15 (q, *J* 287.2 Hz, CF_3), 125.45, 128.8, 128.87 (2C), 128.91 (2C), 130.74, 131.25, 131.84, 134.33, 138.68, 138.88, 172.12; ^{19}F-NMR ($CDCl_3$, 282.4 MHz): δ -83.89 (s, 3F); IR (KBr,cm^{-1}): 3403, 3313, 2983, 2252, 1698, 1188; HRMS (ESI) m/z calcd for $C_{25}H_{24}F_3N_3O_3^+$ 472.1843 $[M + H]^+$ found: 472.1834.

Ethyl (2RS,3SR,4RS,6SR)-5,5-dicyano-2-hydroxy-4,6-bis(4-methylphenyl)-2-(trifluoromethyl)piperidine-3-carboxylate (3c). White solid; yield: 0.66 g (47%); mp 92-95°C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 0.89 (t, *J* 7.1 Hz, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 2.85 (s, 1H, NH), 372 (d, *J* 12.6 Hz, 1H, CH), 3.8 (d, *J* 12.6 Hz, 1H, CH), 3.94 (q, *J* 7,1 Hz, 2H, OCH_2), 4.83 (s, 1H, CH), 5.45 (s, 1H, OH), 7.19-7.32 (m, 4H, Ar), 7.42 (d, *J* 8 Hz, 2H, Ar), 7.57 (d, *J* 8 Hz, 2H, Ar); ^{13}C-NMR ($CDCl_3$, 75.47 MHz):δ 13.2, 21.15, 21.25, 44.4, 48.1, 48.3, 59.6, 62.6, 82.6 (q, *J* 30.4 Hz, C(CF_3)), 111.6, 112.6, 123.2 (q, *J* 286.7 Hz, CF_3), 128.2 (2C), 129, 129.3(2C), 129.6 (2C), 129.7 (2C), 131.5, 140, 140.5, 172.1; ^{19}F-NMR ($CDCl_3$, 282.4 MHz): δ -83.91 (s, 3F); IR (KBr, cm^{-1}): 3435, 3326, 2984, 1714, 1198, 1185; HRMS (ESI) m/z: calcd for $C_{25}H_{24}F_3N_3O_3^+$ 472.1843 $[M + H]^+$ found: 472.1847.

Ethyl (2RS,3SR,4RS,6SR)-5,5-dicyano-2-hydroxy-4,6-bis(3-methoxyphenyl)-2-(trifluoromethyl)piperidine-3-carboxylate (3d). White solid; yield: 0.92 g (61%); mp 164-167 °C; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): 0.9 (t, *J* 7.1 Hz, 3H, CH_3), 2.9 (s, 1H, NH), 3.72 (d, *J* 12.6 Hz, 1H, CH), 3.81 (d, *J* 12.6 Hz, 1H, CH), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.9-4.03 (m, 2H, OCH_2), 4.84 (s, 1H, CH), 5.46 (s, 1H, OH), 6.94 (m, 4H, Ar), 7.23-7.27 (m, 2H, Ar), 7.3-7.44 (m, 2H, Ar) ppm; ^{13}C-NMR($CDCl_3$, 75.47 MHz): 13.24, 44.41, 47.48, 48.64, 55.38, 59.90, 62.68, 82.51 (q, J^2 30.6Hz,

C(CF_3)), 111.59, 112.44, 113.72 (2C), 115.82, 116.17, 120.61 (2C), 123.1 (q, J^1 286.5Hz, CF_3), 129.99, 130.09, 133.23, 135.70, 159.77, 159.91, 171.98 ppm; ^{19}F-NMR (DMSO-d_6, 282.4 MHz): -80.91 (s, 3F) ppm; IR (KBr): 3392, 3295, 2974, 1698, 1602,1199 cm^{-1}; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{25}H_{24}F_3N_3O_5^+$: 504.1735; found: 504.1741. X-ray diffraction data were collected at 200K on a Bruker Quest D8 diffractometer equipped with a Photon-III area-detector (graphite monochromator, shutterless ω-scan technique), using Mo $K_⍰$-radiation (0.71073 Å). The intensity data were integrated by the SAINT program[51] and were corrected for absorption and decay using SADABS.[52] The structure was solved by direct methods using SHELXS[53] and refined on F^2 using SHELXL-2018.[54] All non-hydrogen atoms were refined with individual anisotropic displacement parameters. Hydrogen atoms H1N, H1O connected to oxygen or nitrogen atoms were refined with individual isotropic displacement parameters, their positions were found from the electron density-difference map. All other hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. The SHELXTL program suite[51] was used for molecular graphics. **Crystal Data** for $C_{25}H_{24}F_3N_3O_5$ **3d**; Formula weight 503.47; Temperature 200(2) K; Wavelength 0.71073 Å; Crystal system Triclinic; Space group P-1; Unit cell dimensions a 11.3023(4) Å a118.3808(8)°, b 11.7265(4) Å b114.1096(8)°, c 12.1006(4) Å c 93.3777(9)°; Volume 1222.29(7) Å3; Z 2; Density (calculated) 1.368 g/cm3; Absorption coefficient 0.111 mm-1; F(000) 524; Crystal size 0.48 x 0.37 x 0.28 mm3; Theta range for data collection 2.435 to 30.498°; Index ranges -16<=h<=16, -16<=k<=16, -17<=l<=17; Reflections collected 40066; Independent reflections 7460 [R(int) 0.0369]; Observed reflections 5547; Completeness to theta 25.242° 99.8 % ; Absorption correction Semi-empirical from equivalents; Max. and min. transmission 0.8498 and 0.8244; Refinement method Full-matrix least-squares on F2; Data / restraints / parameters 7460 / 3 / 347; Goodness-of-fit on F2 1.047; Final R indices [I>2sigma(I)] R1 0.0467, wR2 0.1065; R indices (all data) R1 0.0681, wR2 0.1209; Largest diff. peak and hole 0.329 and -0.368 e. Å-3; Obtained crystal structure was deposited in CCDC No. 2063604.

Ethyl (2RS,3SR,4RS,6SR)-5,5-dicyano-2-hydroxy-4,6-bis(4-chlorophenyl)-2-(trifluoromethyl)piperidine-3-carboxylate (3e). White solid; yield: 0.87 g (57%); mp 167-170 °C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 0.94 (t, *J* 7.1 Hz, 3H, CH_3), 2.86 (s, 1H, NH), 3.69 (d, *J* 12.6 Hz, 1H, CH), 3.83 (d, *J* 12.6 Hz, 1H, CH), 3.98 (q, *J* 7,1 Hz, 2H, OCH_2), 4.85 (s, 1H, CH), 5.42 (s, 1H, OH), 7.41-7.52 (m, 6H, Ar), 7.63 (d, *J* 8.5 Hz, 2H, Ar); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ 13.29, 44.16, 47.51, 47.83, 59.22, 62.99, 82.47 (q, *J* 30.6 Hz, C(CF_3)), 111.04, 112.14, 122.97 (q, *J* 286.6 Hz, CF_3), 129.32 (2C), 129.43 (2C), 129.62 (2C), 130.2, 130.89 (2C), 132.53, 136.44, 136.76, 171.67; ^{19}F-NMR (DMSO-d_6, 282.4 MHz): δ -80.79 (s, 3F);IR (KBr, cm^{-1}): 3402, 3314, 2987, 1711, 1195, 1173; HRMS (ESI) m/z (for ^{35}Cl) calcd for $C_{23}H_{18}Cl_2F_3N_3O_3^+$ 512.0750 $[M + H]^+$ found: 512.0745.

Ethyl (2RS,3SR,4RS,6SR)-5,5-dicyano-2-hydroxy-4,6-bis(4-bromophenyl)-2-(trifluoromethyl)piperidine-3-carboxylate (3f). White solid; yield: 0.94 g (52%); mp 181-183°C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 0.94 (t, *J* 7.1 Hz, 3H, CH_3), 2.86 (s, 1H, NH), 3.69 (d, *J* 12.6 Hz, 1H, CH), 3.82 (d, *J* 12.6 Hz, 1H, CH), 3.98 (q, *J* 7,1 Hz, 2H, OCH_2), 4.84 (s, 1H, CH), 5.41 (s, 1H, OH), 7.42 (d, *J* 7.2 Hz, 2H, Ar), 7.53-7.66 (m, 6H, Ar); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ 13.28, 44.11, 47.33, 47.93, 59.31, 63, 82.47 (q, *J* 30.6 Hz, C(CF_3)), 111.02, 112.12, 122.96 (q, *J* 287 Hz, CF_3), 124.66, 125.03, 129.86 (2C), 130.71, 130.99 (2C), 132.3 (2C), 132.4 (2C), 133.04, 171.65; ^{19}F-NMR (DMSO-d_6, 282.4 MHz): δ -80.77 (s, 3F); IR (KBr, cm^{-1}): 3487, 3305, 2960, 2254, 1726, 1615, 1182; HRMS (ESI) m/z: (for ^{79}Br) calcd for $C_{23}H_{18}Br_2F_3N_3O_3^+$ 599.9740 $[M + H]^+$ found: 599.9754.

Ethyl (2RS,3SR,4RS,6SR)-5,5-dicyano-2-hydroxy-4,6-bis(4-nitrophenyl)-2-(trifluoromethyl)piperidine-3-carboxylate (3g). White solid; yield: 0.59 g (37%); mp 184-187°C. ^{13}C-NMR (DMSO-d_6, 75.47 MHz): δ 0.86 (t, *J* 7 Hz, 3H, CH_3), 3.58 (d, *J* 12.6 Hz, 1H, CH), 3.84 (q, *J* 7 Hz, 2H, OCH_2), 4.37 (s, 1H, NH), 4.71 (d, *J* 12.6 Hz, 1H, CH), 5.26 (s, 1H, CH), 7.30 (s, 1H, OH), 7.8 (d, *J* 8.4 Hz, 2H, Ar), 7.89 (d, *J* 8.4 Hz, 2H, Ar), 8.31-8.4 (m, 4H, Ar); ^{13}C-NMR (DMSO-d_6, 75.47 MHz): δ 13.79, 44.91, 46.69, 47.58, 58.06, 61.5, 83.17 (q, *J* 29.9 Hz, C(CF_3)), 112.24, 112.68,

123.84 (q, *J* 287.6 Hz, CF_3), 124.06 (2C), 124.41 (2C), 130.41 (2C), 13.82 (2C), 141.56, 142.45, 148.58, 148.94, 167.03; ^{19}F-NMR (DMSO-d_6, 282.4 MHz): δ -80.37 (s, 3F); IR (KBr, cm^{-1}): 3393, 3301, 2947, 1715, 1527, 1351, 1197; HRMS (ESI) m/z: calcd for $C_{23}H_{18}F_3N_5O_7Na^+$ 556.1051 $[M + Na]^+$ found: 556.1044

3-ethyl 5-methyl (2RS,3SR,4RS,5RS,6SR)-5-cyano-2-hydroxy-4,6-diphenyl-2-(trifluoromethyl)piperidine-3,5-dicarboxylate (3h). White solid; yield: 0.98 g (69%); mp 162-163°C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 0.82 (t, *J* 7.1 Hz, 3H, CH_3), 2.71 (s, NH), 3.32 (s, 3H, OCH_3), 3.8 (d, *J* 12.7 Hz, 1H, CH), 3.89 (q, *J* 6,7 Hz, 2H, OCH_2), 4.05 (d, *J* 12.7 Hz, 1H, CH), 5.01 (s, 1H, CH), 5.57 (s, 1H, OH), 7.29-7.49 (m, 8H, Ar), 7.5-7.58 (m, 2H, Ar); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ 13.17, 44.72, 47.62, 53.07, 59.21, 59.6, 62.21, 82.85 (q, *J* 29.9 Hz, C(CF_3)), 115.05, 123.41 (q, *J* 286.5 Hz, CF_3), 127.92 (2C), 128.57 (2C), 128.78 (2C), 129.14, 129.39 (2C), 129.66, 133.15, 135.86, 165.8, 172.86; ^{19}F-NMR ($CDCl_3$, 282.4 MHz): δ -84.03 (s, 3F); IR (KBr, cm^{-1}): 3432, 3315, 2986, 1754, 1703, 1196, 1178; HRMS (ESI) m/z: calcd for $C_{24}H_{23}F_3N_2O_5^+$: 477.1632 $[M + H]^+$ found: 477.1635.

3-Ethyl 5-methyl (2RS,3SR,4RS,5RS,6SR)-5-cyano-2-hydroxy-4,6-bis(4-methylphenyl)-2-(trifluoromethyl)-piperidine-3, 5-dicarboxylate (3i). White solid; yield: 0.89 g (59%); mp 138-141°C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 0.85 (t, *J* 7.1 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.66 (s, NH), 3.35 (s, 3H, OCH_3), 3.77 (d, *J* 12.7 Hz, H, CH), 3.9 (q, *J* 7 Hz, 2H, OCH_2), 4 (d, *J* 12.7 Hz, H, CH), 4.96 (s, CH), 5.53 (s, OH), 7.12 (d, *J* 7.8 Hz, 2H, Ar), 7.18 (d, *J* 7.9 Hz, 2H, Ar), 7.27-7.35 (m, 2H, Ar), 7.42 (d, *J* 5.9 Hz, 2H, Ar); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ 13.2, 21.06, 21.2, 44.8, 47.2, 53, 58.9, 59.8, 62.1, 82.8 (q, *J* 30.1 Hz, C(CF_3)), 115.2, 123.4 (q, *J* 286.8 Hz, CF_3), 127.7 (2C), 129.2 (4C), 129.4 (2C), 130.2, 133, 138.9, 139.5, 165.9, 172.9; ^{19}F-NMR ($CDCl_3$, 282.4 MHz): δ -84. (s, 3F); IR (KBr, cm^{-1}): 3433, 3321, 2982, 2247, 1736, 1718, 1183; HRMS (ESI) m/z: calcd for $C_{26}H_{27}F_3N_2O_5^+$ 505.1945 $[M + H]^+$ found: 505.1953.

3-Ethyl 5-methyl (2RS,3SR,4RS,5RS,6SR)-5-cyano-2-hydroxy-4,6-bis(3-methoxyhenyl)-2-(trifluoromethyl)piperidine-3,5-dicarboxylate (3j). White solid; yield: 1.16 g (72%); mp 214-217°C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 0.87 (t, *J* 7.1 Hz, 3H, CH_3), 2.71 (s, NH), 3.38 (s, 3H, OCH_3), 3.77 (d, *J* 12.8 Hz, H, CH), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.88-3.98 (m, 2H, OCH_2), 4.02 (d, *J* 12.8 Hz, H, CH), 4.97 (s, CH), 5.53 (s, OH), 6.83-7.09 (m, 5H, Ar), 7.15 (s, H, Ar), 7.19-7.32 (m, 2H, Ar); ^{13}C-NMR (DMSO-d_6, 75.47 MHz): δ 13.79 (2C), 45.79, 46.97, 53.71, 55.51 (2C), 58.64, 60.73, 60.85, 83.31 (q, *J* 29.4 Hz, C(CF_3)), 113.88, 114.27, 114.65, 114.84, 115.57, 120.3, 121.04, 124.11 (q, *J* 286.5 Hz, CF_3), 130.05, 130.16, 136.64, 138.21, 159.48, 159.58, 166.11, 167.85; ^{19}F-NMR (DMSO-d_6, 282.4 MHz): δ -80.99 (s, 3F); IR (KBr, cm^{-1}): 3466, 3294, 2975, 1742, 1721, 1202, 1173; HRMS (ESI) m/z: calcd for $C_{26}H_{27}F_3N_2O_7^+$ 537.1843 $[M + H]^+$ found: 537.1840

3-Ethyl 5-methyl (2RS,3SR,4RS,5RS,6SR)-5-cyano-2-hydroxy-4,6-bis(4-fluorohenyl)-2-(trifluoromethyl)piperidine-3,5-dicarboxylate (3k). White solid; yield: 1.07 g (70%); mp 127-130°C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 0.89 (t, *J* 7 Hz, 3H, CH_3), 2.67 (s, NH), 3.36 (s, 3H, OCH_3), 3.73 (d, *J* 12.8 Hz, H, CH), 3.93 (q, *J* 7,1 Hz, 2H, OCH_2), 4.04 (d, *J* 12.8 Hz, H, CH), 4.98 (s, CH), 5.52 (s, OH), 6.98-7.14 (m, 4H, Ar), 7.33-7.58 (m, 4H, Ar); ^{13}C-NMR($CDCl_3$, 75.47 MHz):δ 13.28, 44.71, 46.75, 53.28, 58.51, 59.66, 62.41, 82.76 (q, *J* 30.6 Hz, C(CF_3)), 114.82, 115.66 (d, $J^2_{C\text{-}F}$ 21.6 Hz, 2C), 115.84 (d, $J^2_{C\text{-}F}$ 21.6 Hz, 2C), 123.28 (q, *J* 287 Hz, CF_3), 128.94 (d, $J^4_{C\text{-}F}$ 3.2 Hz, 1C), 129.75 (d, $J^3_{C\text{-}F}$ 8.4 Hz, 4C), 131.55 (d, $J^4_{C\text{-}F}$ 3.2 Hz, 1C), 163.07 (d, $J^1_{C\text{-}F}$ 249.2 Hz, 1C), 163.42 (d, $J^1_{C\text{-}F}$ 249.2 Hz, 1C), 165.74, 172.63; ^{19}F-NMR ($CDCl_3$, 282.4 MHz): δ -84.02 (s, 3F), -111.2 (s, F), -111.7 (s, F); IR (KBr, cm^{-1}): 3448, 3312, 2983, 1752, 1235, 1184; HRMS (ESI) m/z: calcd for $C_{24}H_{21}F_5N_2O_5^+$: 513.1443 $[M + H]^+$ found: 513.1450.

3-Ethyl 5-methyl (2RS,3SR,4RS,5RS,6SR)-4,6-bis(4-bromophenyl)-5-cyano-2-hydroxy-2-(trifluoromethyl)piperidine-3,5-dicarboxylate (3l). White solid; yield: 0.86 g (45%); mp 187-190°C; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): 0.91 (t, *J* 7.1 Hz, 3H, CH_3), 2.66 (s, NH), 3.38 (s, 3H, OCH_3), 3.73 (d, *J* 12.8 Hz, H, CH), 3.94 (q, *J* 7,1 Hz, 2H, OCH_2), 4.01 (d, *J* 12.8 Hz, H, CH), 4.95 (s, CH), 5.49 (s, OH), 7.31 (d, *J* 8.4 Hz, 2H, Ar), 7.41 (d, *J* 8.4 Hz, 2H, Ar), 7.49 (d, *J* 8.5 Hz, 2H, Ar), 7.53 (d, *J* 8.5 Hz, 2H, Ar) ppm; ^{13}C-NMR (DMSO-d_6, 75.47 MHz): 13.80,

45.23, 46.91, 54.03, 58.24, 60.42, 61.06, 83.26 (q, J^2 29.3 Hz, C(CF_3)), 115.23, 122.59, 122.97, 124.03 (q, J^1 288.2 Hz, CF_3), 130.27 (2C), 130.9 (2C), 131.95 (2C), 132.16 (2C), 134.47, 135.96, 165.93, 167.93 ppm; ^{19}F-NMR ($CDCl_3$, 282.4 MHz): -83.99 (s, 3F) ppm; IR (KBr): 3421, 3314, 2954, 2250, 1742, 1710, 1191 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd (for^{79}Br) $C_{24}H_{21}Br_2F_3N_2O_5^+$: 632.9842; found: 632.9841.

X-ray diffraction data were collected at 100K on a Bruker Quest D8 diffractometer equipped with a Photon-III area-detector (graphite monochromator, shutterless φ- and ω-scan technique), using Mo K⍰-radiation (0.71073 Å). The intensity data were integrated by the SAINT program[51] and were corrected for absorption and decay using SADABS.[52] The structure was solved by direct methods using SHELXS[53] and refined on F^2 using SHELXL-2018.[54] All non-hydrogen atoms were refined with individual anisotropic displacement parameters. The locations of atoms H1N and H1O were found from the electron density-difference map; these atoms were refined with individual isotropic displacement parameters. All other hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. The SHELXTL program suite[51] was used for molecular graphics. **Crystal Data** for $C_{24}H_{21}Br_2F_3N_2O_5$ **3l**; Formula weight 634.25; Temperature 100(2) K; Wavelength 0.71073 Å; Crystal system Monoclinic; Space group $P2_1/n$; Unit cell dimensions a 7.0777(2) Å a90°, b 18.4109(4) Å b92.1060(10)°, c 18.8057(4) Å c 90°; Volume2448.86(10) $Å^3$; Z4; Density (calculated) 1.720 g/cm^3; Absorption coefficient3.372 mm^{-1}; F(000)1264; Crystal size 0.598 x 0.286 x 0.176 mm^3; Theta range for data collection2.433 to 33.282°; Index ranges -10<=h<=10, -28<=k<=28, -28<=l<=28; Reflections collected 73189; Independent reflections9400 [R(int) 0.0500]; Observed reflections7407; Completeness to theta 25.242°99.9%; Absorption correctionSemi-empirical from equivalents; Max. and min. transmission0.0462 and 0.0157; Refinement method Full-matrix least-squares on F^2; Data / restraints / parameters9400 / 0 / 335;Goodness-of-fit on $F^2$1.023;Final R indices [I>2sigma(I)]R1 0.0327, wR2 0.0712; R indices (all data) R1 0.0500, wR2 0.0801; Largest diff. peak and hole0.635 and -0.321 e.$Å^{-3}$. Obtained crystal structure was deposited in CCDC No. 2063207

3-Ethyl 5-methyl (2RS,3SR,4RS,5RS,6SR)-5-cyano-2-hydroxy-4,6-bis(4-nitrohenyl)-2-(trifluoromethyl)piperidine-3,5-dicarboxylate (3m). White solid; yield: 0.56 g (33%); mp 203-206°C. 1H-NMR (CDCl3, 300.13 MHz): δ 0.92 (t, J 7.1 Hz, 3H, CH3), 2.77 (s, NH), 3.37 (s, 3H, OCH3), 3.82 (d, J 12.8 Hz, H, CH), 3.87-4.04 (m, 2H, OCH2), 4.22 (d, J 12.8 Hz, H, CH), 5.14 (s, CH), 5.45 (s, OH), 7.60-7.72 58 (m, 2H, Ar), 7.75 (d, J 8.6 Hz, 2H, Ar), 8.23 (d, J 8.9 Hz, 2H, Ar), 8.27 (d, J 8.9 Hz, 2H, Ar); 13C-NMR (CDCl3, 75.47 MHz): δ 13.32, 44.46, 47.06, 53.67, 58.63, 58.69, 62.83, 82.73 (q, J 30.6 Hz, C(CF3)), 113.95, 123.07 (q, J 287 Hz, CF3), 123.72 (2C), 124 (2C), 129.11 (2C), 130.3, 130.54, 139.76, 142.02, 148.43, 149.08, 165.17, 171.91; 19F-NMR (CDCl3, 282.4 MHz): δ -83.94 (s, 3F); IR (KBr, cm−1): 3426, 3301, 2983, 1722, 1350, 1194; HRMS (ESI) m/z: calcd for C24H21F3N4O9+: 567.1333 [M + H]+ found: 567.1314.

3,5-Diethyl (2RS,3SR,4RS,5RS,6SR)-4,6-bis(4-fluorophenyl)-5-cyano-2-hydroxy-2-(trifluoromethyl)piperidine-3,5-dicarboxylate (3n). White solid; yield: 0.82 g (52%); mp 180-182°C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 0.8 (t, J 7.1 Hz, 3H, CH_3), 0.89 (t, J 7.1 Hz, 3H, CH_3), 2.65 (s, NH), 3.73 (d, J 12.8 Hz, H, CH), 3.76-3.88 (m, 2H, OCH_2), 3.92 (q, J 7,1 Hz, 2H, OCH_2), 4.02 (d, J 12.8 Hz, H, CH), 4.97 (s, CH), 5.53 (s, OH), 6.98-7.14 (m, 4H, Ar), 7.35-7.63 (m, 4H, Ar);^{13}C-NMR($CDCl_3$, 75.47 MHz): δ 13.26, 13.48, 44.84, 46.84, 58.49, 59.45, 62.35, 62.81, 82.78 (q, J 30.1 Hz, C(CF_3)), 114.98, 115.53 (d, $J^2_{C\text{-}F}$ 21.6 Hz, 2C), 115.73 (d, $J^2_{C\text{-}F}$ 21.6 Hz, 2C), 123.3 (q, J 286.6 Hz, CF_3), 129 (d, $J^4_{C\text{-}F}$ 3 Hz, 1C), 129.93 (d, $J^3_{C\text{-}F}$ 8.3 Hz, 4C), 131.58 (d, $J^4_{C\text{-}F}$ 3 Hz, 1C), 163.07 (d, $J^1_{C\text{-}F}$ 249.1 Hz, 1C), 163.4 (d, $J^1_{C\text{-}F}$ 249.1 Hz, 1C), 165.15, 172.65; ^{19}F-NMR (DMSO-d_6, 282.4 MHz): δ -81.02 (s, 3F), -112.46 (s, F), -112.98 (s, F); IR (KBr, cm^{-1}): 3398, 3312, 2988, 1744, 1707, 1514, 1234,1148; HRMS (ESI) m/z: calcd for $C_{25}H_{23}F_5N_2O_5^+$: 527.1600 [M + H]$^+$ found: 527.1594

3,5-Diethyl (2RS,3SR,4RS,5RS,6SR)-4,6-bis(pyridin-4-yl)-5-cyano-2-hydroxy-2-(trifluoromethyl)piperidine-3,5-dicarboxylate (3o). White solid; yield: 0.25 g (17%); mp 193-197°C. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 0.79 (t, *J* 7.1 Hz, 3H, CH_3), 0.89 (t, *J* 7.1 Hz, 3H, CH_3), 2.76 (s, 1H, NH), 3.77 (d, *J* 12.7 Hz, 1H, CH), 3.80-3.89 (m, 2H, OCH_2), 3.94 (q, *J* 7,2 Hz, 2H, OCH_2), 4.03 (d, *J* 12.7 Hz, 1H, CH), 5.31-5.68 (H, 1H, OH), 7.4 (d, *J* 3.3 Hz, 2H, Ar), 7.5 (d, *J* 5.9 Hz, 2H, Ar), 8.63 (d, *J* 5.4 Hz, 2H, Ar), 8.67 (d, *J* 6 Hz, 2H, Ar); ^{13}C-NMR (DMSO-d_6, 75.47 MHz): δ 13.75, 13.93, 45.25, 46.73, 58.11, 59.13, 61.21, 63.68, 83.24 (q, J^2 29.8 Hz, $C(CF_3)$), 114.99, 123.33 (2C), 123.99 (2C), 143.53, 144.84, 150.38 (2C), 150.6 (2C), 165, 167.6; ^{19}F-NMR ($CDCl_3$, 282.4 MHz): δ -84.5 (s, 3F); IR (KBr, cm^{-1}): 3432, 3184, 2996, 2251, 1738, 1603, 1205; HRMS (ESI) m/z: calcd for $C_{23}H_{23}F_3N_4O_5^+$: 493.1693 $[M + H]^+$ found: 493.1697.

Supplementary Material

^{1}H NMR and ^{13}C NMR spectra associated with compounds reported in this article are available as supplementary information.

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