

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

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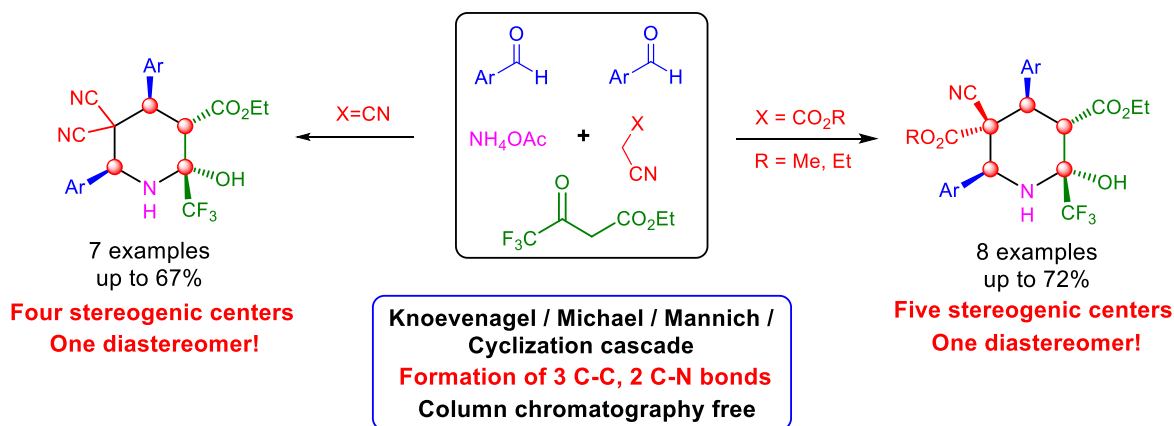
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Abstract

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)piperidine-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

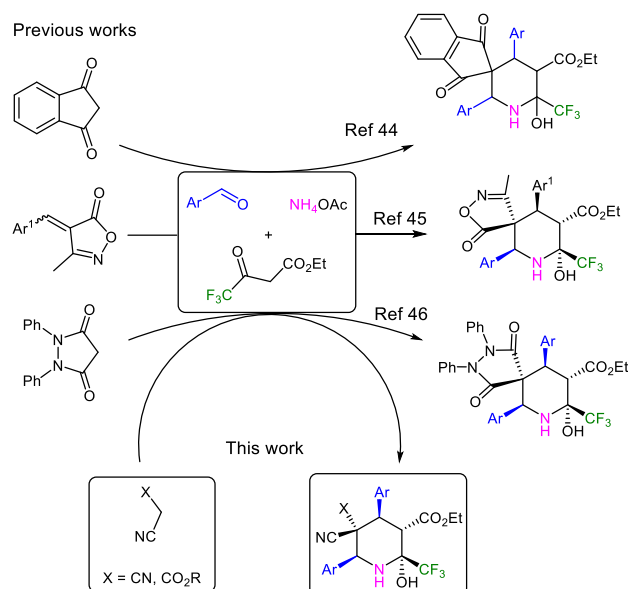
Introduction

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

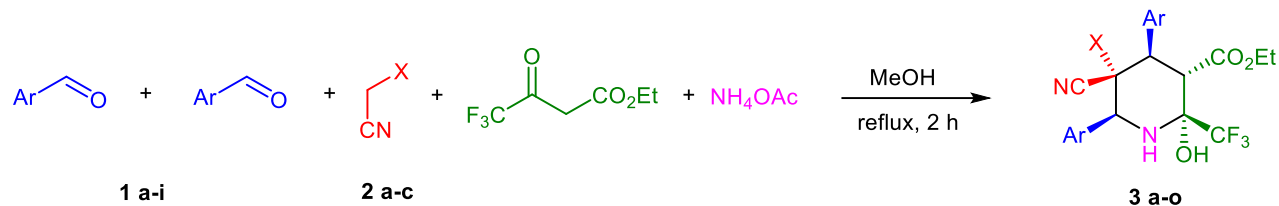
Recently, we have carried out a multicomponent synthesis of substituted piperidines.³⁹⁻⁴³ Ammonium acetate or aqueous ammonia were the nitrogen sources for piperidine cycle. This method was used in the synthesis of polysubstituted 2-hydroxy-2-trifluoromethylpiperidines 5-spyro connected with cycle or 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 polysubstituted 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

Entr y	Aldehyde	CH acid	Ar	X	Product	Yield% ^b
1	1a	2a	C ₆ H ₅	CN	3a	54
2	1b	2a	3-MeC ₆ H ₄	CN	3b	67
3	1c	2a	4-MeC ₆ H ₄	CN	3c	47
4	1d	2a	3-OMeC ₆ H ₄	CN	3d	61
5	1e	2a	4-ClC ₆ H ₄	CN	3e	57
6	1f	2a	4-BrC ₆ H ₄	CN	3f	52
7	1g	2a	4-NO ₂ C ₆ H ₄	CN	3g	37
8	1a	2b	C ₆ H ₅	CO ₂ Me	3h	69
9	1c	2b	4-MeC ₆ H ₄	CO ₂ Me	3i	59
10	1d	2b	3-MeOC ₆ H ₄	CO ₂ Me	3j	72
11	1h	2b	4-FC ₆ H ₄	CO ₂ Me	3k	70
12	1f	2b	4-BrC ₆ H ₄	CO ₂ Me	3l	45
13	1g	2b	4-O ₂ NC ₆ H ₄	CO ₂ Me	3m	33
14	1h	2c	4-FC ₆ H ₄	CO ₂ Et	3n	52
15	1i	2c	4-Py	CO ₂ Et	3o	17

^a Aldehyde **1** (6 mmol), cyano C-H acid (**2**) (3 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate (3 mmol), NH₄OAc (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-

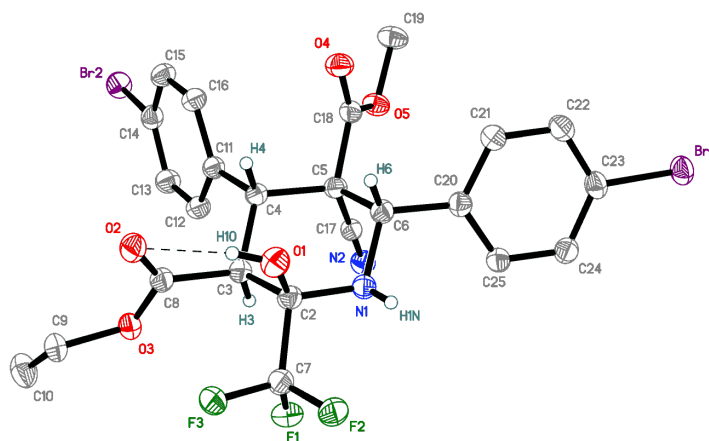
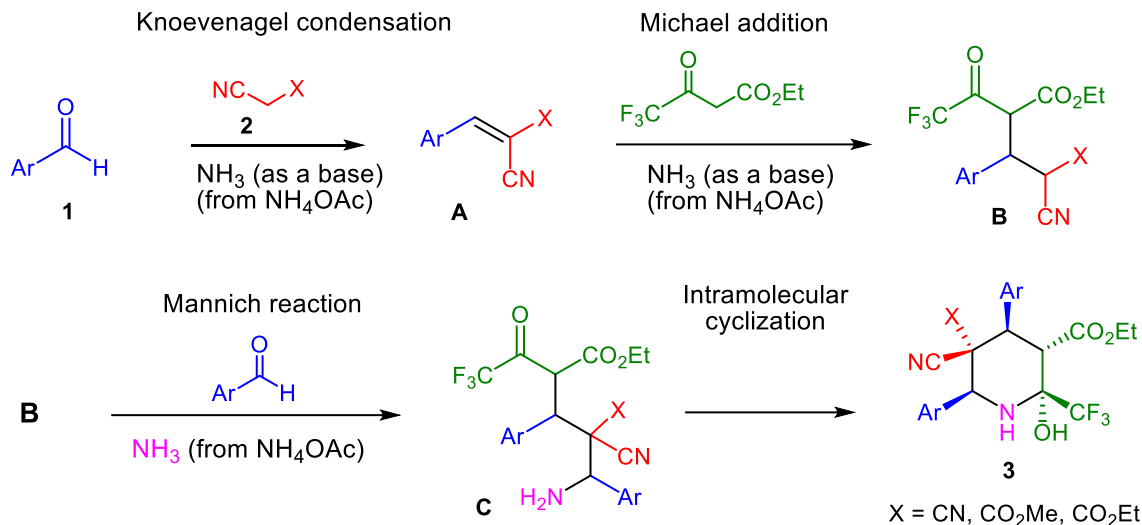


Figure 2. X-ray Structure of **3I**.

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 intramolecular 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 (*2RS,3SR,4RS,6SR*)-4,6-diaryl-5,5-dicyano-2-hydroxy-2-(trifluoromethyl)piperidine-3-carboxylates with four stereogenic centers and dialkyl (*2RS,3SR,4RS,5RS,6SR*)-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. ¹H and ¹³C NMR spectra were recorded with a Bruker AM300 and Bruker DRX 500 at ambient temperature in DMSO-*d*₆ or CDCl₃ solutions. Chemical shift values are given in δ scale relative to Me₄Si. 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 I60 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 $-10\text{ }^{\circ}\text{C}$ 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 $175\text{-}177\text{ }^{\circ}\text{C}$. $^1\text{H-NMR}$ (CDCl_3 , 300.13 MHz): δ 0.86 (t, J 7.1, Hz, 3H, CH_3), 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, OCH_2), 4.89 (s, 1H, CH), 5.44 (s, 1H, OH), 7.41-7.6 (m, 8H, Ar), 7.67-7.74 (m, 8H, Ar); $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$, 75.47 MHz): δ 13.73, 45.79, 46.69, 48.7, 58.74, 61.11, 83.18 (q, J 29.5 Hz, $\text{C}(\text{CF}_3)$), 112.87, 113.39, 123.97 (q, J 287.8 Hz, CF_3), 128.78 (2C), 128.93 (2C), 129.4 (4C), 129.74, 130.27, 134.59, 135.93, 167.38; $^{19}\text{F-NMR}$ ($\text{DMSO-}d_6$, 282.4 MHz): δ -80.75 (s, 3F); IR (KBr): 3390, 3319, 2983, 1705, 1189 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{20}\text{F}_3\text{N}_3\text{O}_3^+$ 444.1530 $[\text{M} + \text{H}]^+$; 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 $147\text{-}150\text{ }^{\circ}\text{C}$. $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ (CDCl_3 , 75.47 MHz): δ 13.18, 21.37, 21.45, 44.40, 47.65, 48.65, 59.93, 62.55, 82.53 (q, J 29.9 Hz, $\text{C}(\text{CF}_3)$), 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; $^{19}\text{F-NMR}$ (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 $\text{C}_{25}\text{H}_{24}\text{F}_3\text{N}_3\text{O}_3^+$ 472.1843 $[\text{M} + \text{H}]^+$ 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 $92\text{-}95\text{ }^{\circ}\text{C}$. $^1\text{H-NMR}$ (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), 3.72 (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); $^{13}\text{C-NMR}$ (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, $\text{C}(\text{CF}_3)$), 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; $^{19}\text{F-NMR}$ (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 $\text{C}_{25}\text{H}_{24}\text{F}_3\text{N}_3\text{O}_3^+$ 472.1843 $[\text{M} + \text{H}]^+$ 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 $164\text{-}167\text{ }^{\circ}\text{C}$; $^1\text{H-NMR}$ (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; $^{13}\text{C-NMR}$ (CDCl_3 , 75.47 MHz): 13.24, 44.41, 47.48, 48.64, 55.38, 59.90, 62.68, 82.51 (q, J^2 30.6 Hz, $\text{C}(\text{CF}_3)$), 111.59, 112.44, 113.72 (2C), 115.82, 116.17, 120.61 (2C), 123.1 (q, J^1 286.5 Hz, CF_3), 129.99, 130.09, 133.23, 135.70, 159.77, 159.91, 171.98 ppm; $^{19}\text{F-NMR}$ ($\text{DMSO-}d_6$, 282.4 MHz): -80.91 (s, 3F) ppm; IR (KBr): 3392, 3295, 2974, 1698, 1602, 1199 cm^{-1} ; HRMS (ESI) m/z ($\text{M} + \text{H})^+$ calcd for $\text{C}_{25}\text{H}_{24}\text{F}_3\text{N}_3\text{O}_5^+$: 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 $\text{K}\alpha$ -radiation (0.71073 Å). The intensity data were integrated by the SAINT program⁵¹ and were corrected for absorption and decay using SADABS.⁵² The structure was solved by direct methods using SHELXS⁵³ 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 suite⁵¹ was used for molecular graphics. **Crystal Data** for C₂₅H₂₄F₃N₃O₅ **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. ¹H-NMR (CDCl₃, 300.13 MHz): δ 0.94 (t, J 7.1 Hz, 3H, CH₃), 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, OCH₂), 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); ¹³C-NMR (CDCl₃, 75.47 MHz): δ 13.29, 44.16, 47.51, 47.83, 59.22, 62.99, 82.47 (q, J 30.6 Hz, C(CF₃)), 111.04, 112.14, 122.97 (q, J 286.6 Hz, CF₃), 129.32 (2C), 129.43 (2C), 129.62 (2C), 130.2, 130.89 (2C), 132.53, 136.44, 136.76, 171.67; ¹⁹F-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* (for³⁵Cl) calcd for C₂₃H₁₈Cl₂F₃N₃O₃⁺ 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. ¹H-NMR (CDCl₃, 300.13 MHz): δ 0.94 (t, J 7.1 Hz, 3H, CH₃), 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, OCH₂), 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); ¹³C-NMR (CDCl₃, 75.47 MHz): δ 13.28, 44.11, 47.33, 47.93, 59.31, 63, 82.47 (q, J 30.6 Hz, C(CF₃)), 111.02, 112.12, 122.96 (q, J 287 Hz, CF₃), 124.66, 125.03, 129.86 (2C), 130.71, 130.99 (2C), 132.3 (2C), 132.4 (2C), 133.04, 171.65; ¹⁹F-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 ⁷⁹Br) calcd for C₂₃H₁₈Br₂F₃N₃O₃⁺ 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. ¹³C-NMR (DMSO-*d*₆, 75.47 MHz): δ 0.86 (t, J 7 Hz, 3H, CH₃), 3.58 (d, J 12.6 Hz, 1H, CH), 3.84 (q, J 7 Hz, 2H, OCH₂), 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); ¹³C-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(CF₃)), 112.24, 112.68, 123.84 (q, J 287.6 Hz, CF₃), 124.06 (2C), 124.41 (2C), 130.41 (2C), 13.82 (2C), 141.56, 142.45, 148.58, 148.94, 167.03; ¹⁹F-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 C₂₃H₁₈F₃N₅O₇Na⁺ 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. ¹H-NMR (CDCl₃, 300.13 MHz): δ 0.82 (t, J 7.1 Hz, 3H, CH₃), 2.71 (s, NH), 3.32 (s, 3H, OCH₃), 3.8 (d, J 12.7 Hz, 1H, CH), 3.89 (q, J 6.7 Hz, 2H, OCH₂), 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); ¹³C-NMR (CDCl₃, 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(CF₃)), 115.05, 123.41 (q, J 286.5 Hz, CF₃), 127.92 (2C), 128.57 (2C), 128.78 (2C), 129.14, 129.39 (2C), 129.66, 133.15, 135.86, 165.8, 172.86; ¹⁹F-NMR

(CDCl₃, 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 C₂₄H₂₃F₃N₂O₅⁺: 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. ¹H-NMR (CDCl₃, 300.13 MHz): δ 0.85 (t, *J* 7.1 Hz, 3H, CH₃), 2.32 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 2.66 (s, NH), 3.35 (s, 3H, OCH₃), 3.77 (d, *J* 12.7 Hz, H, CH), 3.9 (q, *J* 7 Hz, 2H, OCH₂), 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); ¹³C-NMR (CDCl₃, 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(CF₃)), 115.2, 123.4 (q, *J* 286.8 Hz, CF₃), 127.7 (2C), 129.2 (4C), 129.4 (2C), 130.2, 133, 138.9, 139.5, 165.9, 172.9; ¹⁹F-NMR (CDCl₃, 282.4 MHz): δ -84. (s, 3F); IR (KBr, cm⁻¹): 3433, 3321, 2982, 2247, 1736, 1718, 1183; HRMS (ESI) m/z : calcd for C₂₆H₂₇F₃N₂O₅⁺ 505.1945 [M + H]⁺ found: 505.1953.

3-Ethyl 5-methyl (2RS,3SR,4RS,5RS,6SR)-5-cyano-2-hydroxy-4,6-bis(3-methoxyphenyl)-2-(trifluoromethyl)piperidine-3,5-dicarboxylate (3j). White solid; yield: 1.16 g (72%); mp 214-217°C. ¹H-NMR (CDCl₃, 300.13 MHz): δ 0.87 (t, *J* 7.1 Hz, 3H, CH₃), 2.71 (s, NH), 3.38 (s, 3H, OCH₃), 3.77 (d, *J* 12.8 Hz, H, CH), 3.82 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 3.88-3.98 (m, 2H, OCH₂), 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); ¹³C-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(CF₃)), 113.88, 114.27, 114.65, 114.84, 115.57, 120.3, 121.04, 124.11 (q, *J* 286.5 Hz, CF₃), 130.05, 130.16, 136.64, 138.21, 159.48, 159.58, 166.11, 167.85; ¹⁹F-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 C₂₆H₂₇F₃N₂O₇⁺ 537.1843 [M + H]⁺ found: 537.1840

3-Ethyl 5-methyl (2RS,3SR,4RS,5RS,6SR)-5-cyano-2-hydroxy-4,6-bis(4-fluorophenyl)-2-(trifluoromethyl)piperidine-3,5-dicarboxylate (3k). White solid; yield: 1.07 g (70%); mp 127-130°C. ¹H-NMR (CDCl₃, 300.13 MHz): δ 0.89 (t, *J* 7 Hz, 3H, CH₃), 2.67 (s, NH), 3.36 (s, 3H, OCH₃), 3.73 (d, *J* 12.8 Hz, H, CH), 3.93 (q, *J* 7.1 Hz, 2H, OCH₂), 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); ¹³C-NMR(CDCl₃, 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(CF₃)), 114.82, 115.66 (d, *J*²_{C-F} 21.6 Hz, 2C), 115.84 (d, *J*²_{C-F} 21.6 Hz, 2C), 123.28 (q, *J* 287 Hz, CF₃), 128.94 (d, *J*⁴_{C-F} 3.2 Hz, 1C), 129.75 (d, *J*³_{C-F} 8.4 Hz, 4C), 131.55 (d, *J*⁴_{C-F} 3.2 Hz, 1C), 163.07 (d, *J*¹_{C-F} 249.2 Hz, 1C), 163.42 (d, *J*¹_{C-F} 249.2 Hz, 1C), 165.74, 172.63; ¹⁹F-NMR (CDCl₃, 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 C₂₄H₂₁F₅N₂O₅⁺: 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; ¹H-NMR (CDCl₃, 300.13 MHz): 0.91 (t, *J* 7.1 Hz, 3H, CH₃), 2.66 (s, NH), 3.38 (s, 3H, OCH₃), 3.73 (d, *J* 12.8 Hz, H, CH), 3.94 (q, *J* 7.1 Hz, 2H, OCH₂), 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; ¹³C-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(CF₃)), 115.23, 122.59, 122.97, 124.03 (q, *J*¹ 288.2 Hz, CF₃), 130.27 (2C), 130.9 (2C), 131.95 (2C), 132.16 (2C), 134.47, 135.96, 165.93, 167.93 ppm; ¹⁹F-NMR (CDCl₃, 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 ⁷⁹Br) C₂₄H₂₁Br₂F₃N₂O₅⁺: 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 α -radiation (0.71073 Å). The intensity data were integrated by the SAINT program⁵¹ and were corrected for absorption and decay using SADABS.⁵² The structure was solved by direct methods using SHELXS⁵³ 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 suite⁵¹ was used for molecular graphics. **Crystal Data** for C₂₄H₂₁Br₂F₃N₂O₅ **3l**; Formula weight 634.25; Temperature 100(2) K; Wavelength 0.71073 Å; Crystal system Monoclinic; Space group P2₁/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°; Volume 2448.86(10) Å³; Z₄; Density (calculated) 1.720 g/cm³; Absorption coefficient 3.372 mm⁻¹; F(000) 1264; Crystal size 0.598 x 0.286 x 0.176 mm³; Theta range for data collection 2.433 to 33.282°; Index ranges -10 ≤ h ≤ 10, -28 ≤ k ≤ 28, -28 ≤ l ≤ 28; Reflections collected 73189; Independent reflections 9400 [R(int) 0.0500]; Observed reflections 7407; Completeness to theta 25.242° 99.9%; Absorption correction Semi-empirical from equivalents; Max. and min. transmission 0.0462 and 0.0157; Refinement method Full-matrix least-squares on F²; Data / restraints / parameters 9400 / 0 / 335; Goodness-of-fit on F² 1.023; Final R indices [I > 2σ(I)] R₁ 0.0327, wR₂ 0.0712; R indices (all data) R₁ 0.0500, wR₂ 0.0801; Largest diff. peak and hole 0.635 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-nitrophenyl)-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 (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. ¹H-NMR (CDCl₃, 300.13 MHz): δ 0.8 (t, J 7.1 Hz, 3H, CH₃), 0.89 (t, J 7.1 Hz, 3H, CH₃), 2.65 (s, NH), 3.73 (d, J 12.8 Hz, H, CH), 3.76-3.88 (m, 2H, OCH₂), 3.92 (q, J 7.1 Hz, 2H, OCH₂), 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); ¹³C-NMR (CDCl₃, 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(CF₃)), 114.98, 115.53 (d, J²_{C-F} 21.6 Hz, 2C), 115.73 (d, J²_{C-F} 21.6 Hz, 2C), 123.3 (q, J 286.6 Hz, CF₃), 129 (d, J⁴_{C-F} 3 Hz, 1C), 129.93 (d, J³_{C-F} 8.3 Hz, 4C), 131.58 (d, J⁴_{C-F} 3 Hz, 1C), 163.07 (d, J¹_{C-F} 249.1 Hz, 1C), 163.4 (d, J¹_{C-F} 249.1 Hz, 1C), 165.15, 172.65; ¹⁹F-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 C₂₅H₂₃F₅N₂O₅⁺: 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. ¹H-NMR (CDCl₃, 300.13 MHz): δ 0.79 (t, J 7.1 Hz, 3H, CH₃), 0.89 (t, J 7.1 Hz, 3H, CH₃), 2.76 (s, 1H, NH), 3.77 (d, J 12.7 Hz, 1H, CH), 3.80-3.89 (m, 2H, OCH₂), 3.94 (q, J 7.2 Hz, 2H, OCH₂), 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); ¹³C-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, J² 29.8 Hz, C(CF₃)), 114.99, 123.33 (2C), 123.99 (2C), 143.53, 144.84, 150.38 (2C), 150.6 (2C), 165, 167.6; ¹⁹F-NMR (CDCl₃, 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 C₂₃H₂₃F₃N₄O₅⁺: 493.1693 [M + H]⁺ found: 493.1697.

Supplementary Material

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

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