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Piperidine and 3,3,4,4,5,5-hexafluoropiperidine as terminal groups: Syntheses and properties as new liquid crystals

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ABSTRACT

A series of novel ester liquid crystals with piperidine or 3,3,4,4,5,5-hexafluoropiperidine as terminal group have been prepared in good yield. Some of the new compounds show broad mesomorphic phase range and good thermal stability. Their structures were modified by varying the terminal N-heterocycles, lateral fluorine substituent on the benzene ring, and the number of the cyclohexane ring in the molecules. The compounds **3/2-0F**, **5/2-0F** and **3/2-1F** exhibited nematic phase (N), and **5/2-1F** displayed smectic B phase. Compared with compound **3/2-1F** (N), **5/2-1F** has a longer n-pentyl substituent on the cyclohexane ring. Variation of the terminal N-heterocycles from piperidine to 3,3,4,4,5,5-hexafluoropiperidine causes the absence of mesomorphism behaviors.

1. Introduction

Liquid crystals have been proved to be truly fascinating materials in terms of their fundamental properties, and tremendous success in commercial applications. An increasing amount of researches have been carried out on liquid crystals containing fluorine atoms in the back-bone structure, which are regarded as very useful in influencing the melting point, viscosity, birefringence and dielectric anisotropy [1–15]. The fluorinated substituent can be designed as the terminal group [16], the linking bridge [17], and the lateral substitute [18–20].

The highly polarized 3,4-difluorobenzene and 3,4,5-trifluorobenzene are commercially available. These expensive polyfluorobenzenes were used as the key intermediate to achieve high dielectric anisotropy and low viscosity liquid crystals. The introduction of a polar ring substituted polyfluorobenzene into the liquid crystalline core is a promising approach for the design of novel liquid crystals. N-heterocycle will be highly valuable for further investigation because of their large dielectric constant, electron transport properties, and strong electron-withdrawing properties.

We have a continuing interest in heterocycle and its fluorinated derivatives for new photoelectric materials, many of which meet the liquid crystal criteria. A large number of molecules that contain N, O-heterocycle derivatives have been reported to be liquid crystal materials [21]. A new class of N-heterocycles based liquid crystals that employed 3,4-difluoropyrrole, 3,3,4,4-tetrafluoropyrrolidine, and pyrrolidine as terminal group, as shown in Scheme 1, were synthesized by our group [21b]. These compounds exhibit broad nematic phase range, good thermal stability and strongly positive dielectric anisotropy. Their properties were modified by varying the terminal heterocycles and/or the length of the alkyl chains on the cyclohexane liquid crystal building block. Modification of the N-heterocycles structure from pyrrolidine to piperdine will show marked influences in the properties of these liquid crystals. The simple 3,3,4,4,5,5-hexafluoropiperidine was used as terminal group to further prepare the high fluorine content ($F > 20\%$) compounds so as to investigate the effect of the highly polarized N-heterocycles on the mesomorphic behavior.

In this study, we describe the design and synthesis of cyclohexane-based liquid crystals with piperidine, 3,3,4,4,5,5-hexafluoropiperidine as terminal group in an effort to establish the impact of the N-heterocycle and its fluorinated derivative on the physical and chemical properties of liquid crystal.

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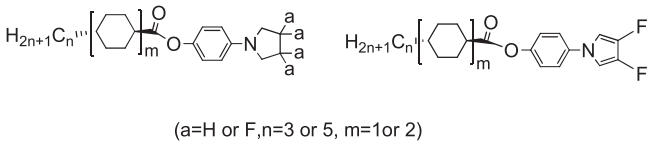


Scheme 1. N-heterocycles based liquid crystals.

2. Results and discussion

2.1. Synthesis

The synthetic route for the piperidine-, 3,3,4,4,5,5-hexafluoropiperidine-based ester liquid crystals (**n/m-0F**, **n/m-1F**, **n/m-6F**, **n/m-7F**) is outlined in Scheme 2.

In our previous study, we reported the synthesis of trifluoromethanesulfonic acid 1,5-pentanediyl ester (**2**) and trifluoromethanesulfonic acid 2,2,3,3,4,4-hexafluoro-1,5-pentanediyl ester (**4**) by the esterification reaction between glycol compounds (**1**, **3**) and trifluoromethanesulfonic anhydride [21b]. Then the 4-(piperidine or 3,3,4,4,5,5-hexafluoropiperidine-1-yl)phenol derivatives (**0F**, **1F**, **6F**, **7F**) were easily obtained by the nucleophilic substitution of trifluoromethanesulfonic acid 1,5-pentanediyl ester (**2**) and trifluoromethanesulfonic acid 2,2,3,3,4,4-hexafluoro-1,5-pentanediyl ester (**4**) with 4-aminophenol or 4-amino-3-fluorophenol in ethanol using Et_3N as a base at 90 °C for 24 h. Combine 4-(piperidine or 3,3,4,4,5,5-hexafluoropiperidine-1-yl)phenol derivatives (**0F**, **1F**, **6F**, **7F**) and the cyclohexane-based liquid crystal building block, trans-4′-alkyl-(1,1′-mono or bicyclohexyl)-4-carboxylic acid (**5**), in dried trichloromethane using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) as catalyst/base at 80 °C for 12 h to yield the novel compounds **n/m0F**, **n/m1F**, **n/m6F**, **n/m7F**. These novel molecules with different fluorine content (*F* 0–29%) give rise to interesting mesomorphic behavior and physicochemical properties.

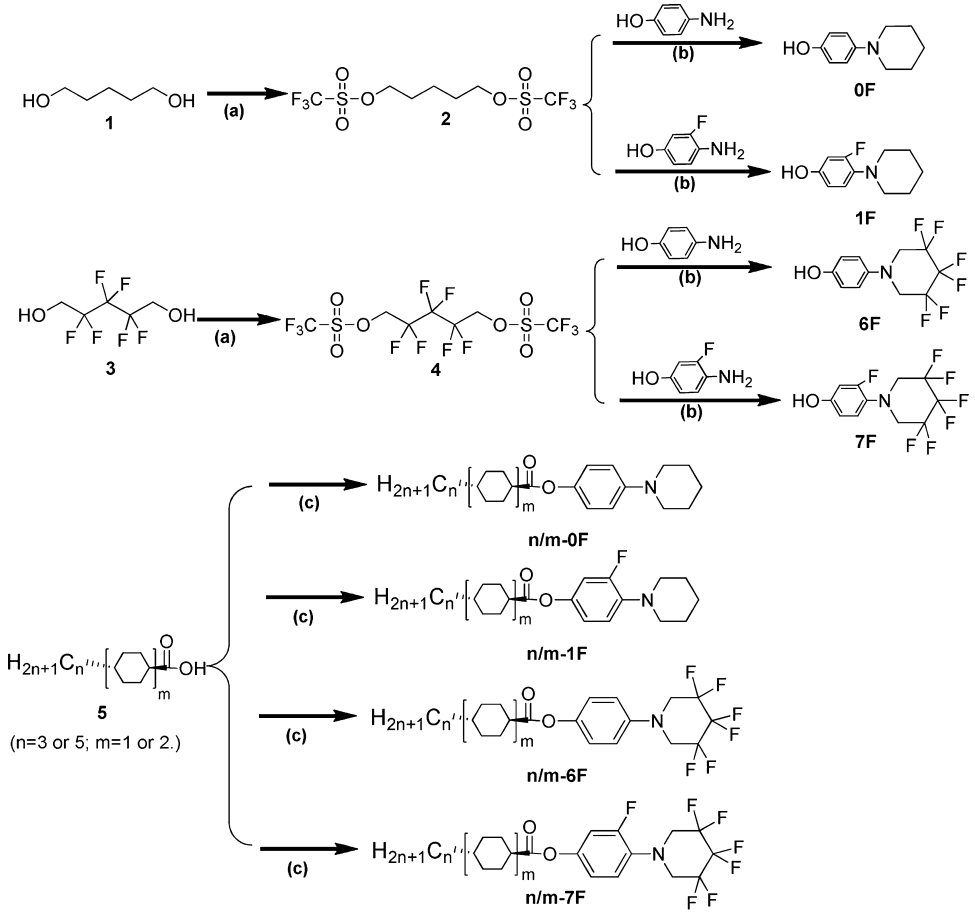
2.2. Liquid crystalline properties

Investigations have centered on the significant modifications of fluorine content of the terminal N-heterocycle to the influence of melting points, transition temperatures, and mesophase morphology.

The new compounds were investigated for their potential liquid crystalline properties by a combination of hot stage polarizing optical microscopy and differential scanning calorimetry (DSC). The transition temperatures are presented in Table 1. The assignment of the mesophases was based on their optical texture, which are presented in Figs. 1 and 2.

There are three factors that will affect the compounds' mesomorphic behavior, including: (1) the structure of the N-heterocycles; (2) the polyfluoroalkyl or fluorine substituent on the N-heterocycles; (3) the nature of the cyclohexane liquid crystal building block.

Compounds **3/2-0F**, **5/2-0F** and **3/2-1F** show nematic phase, and compound **5/2-1F** shows smectic B phase. The nematic phase was deduced, as evidenced by its marbled texture, which can be seen in



Reagents and conditions: (a) $(CF_3SO_2)_2O$,CH_2Cl_2, RT, 12h; (b) Et_3N, EtOH, 90°C, 24h; (c) DCC, DMAP, CHCl3, 80°C, 12h.

Scheme 2. Synthesis of novel ester liquid crystals with N-heterocycle as end group.

Table 1
Thermal behavior of the new compounds.

Compound	Phase transition temperature (°C)	T_d (°C)
3/1-0F	Cr 81.3	233.5
5/1-0F	Cr 87.9	229.8
3/2-0F	Cr 171.2 N 223.2 I	315.1
5/2-0F	Cr 186.5 N 221.2 I	329.6
3/1-1F	Cr 57.8	246.7
5/1-1F	Cr 69.4	272.1
3/2-1F	Cr 157.7 N 209.7 I	263.2
5/2-1F	Cr 172.8 SmB 200.0 I	330.2
3/1-6F	Cr 107.4	217.8
5/1-6F	Cr 98.3	246.9
3/2-6F	Cr 165.9	290.3
5/2-6F	Cr 153.9	307.8
3/1-7F	Cr 93.9	235.7
5/1-7F	Cr 77.6	242.4
3/2-7F	Cr 149.7	274.8
5/2-7F	Cr 142.6	155.1

Cr, crystal; N, nematic; I, isotropic; SmB, smectic B; T_d, decomposition temperature.

Figs. 1 and 2. This transition also could be evaluated from the DSC trace, two endothermic peaks at 171.2 °C and 223.2 °C, 186.5 °C and 221.2 °C, 157.7 °C and 209.7 °C were observed for **3/2-0F**, **5/2-0F** and **3/2-1F**, respectively.

In our previous studies, compounds with five-membered pyrrolidine and 3,3,4,4-tetrafluoropyrrolidine as terminal groups, show thermotropic liquid crystalline Nematic and SmG phase respectively. The introduction of terminal six-membered fluorinated heterocycle, 3,3,4,4,5,5-hexafluoropiperidine causes an absence of mesomorphic behaviors in comparison with compounds containing pyrrolidine, piperidine and 3,3,4,4-tetrafluoropyrrolidine as terminal group. This can be attributed to the expansion of the terminal N-heterocycle size which induces changes in shape types and the width of the molecule. A rise in the number of CF_2 groups from 3,3,4,4-tetrafluoropyrrolidine to 3,3,4,4,5,5-hexafluoropiperidine will result in the increasing repulsion force between CF_2 groups. Thus the coplanar structure of the molecule is destroyed.

The position of the fluorine atom has an important influence on the behavior of the liquid crystal phase. Generally, any unit that protrudes from the side of the mesogenic core will cause a disruption in the intermolecular forces of attraction and molecular packing. Replacing the hydrogen with fluorine on the phenyl group of **n/m-0F** and **n/m-6F**, gave **n/m-1F** and **n/m-7F**. The lateral fluorine substituent reduces the melting point, e.g. **3/2-0F**, Mp. 171.2 °C; **3/2-1F**, Mp. 157.7 °C; **5/2-0F**, Mp. 186.5 °C; **5/2-1F**, Mp. 172.8 °C. It may be attributed to fluorine is sufficiently small to preserve reasonable liquid crystalline, but the lateral fluorine substituent in the benzene increases the width of the liquid crystal molecules. It destroys the coplanarity of the compound, which would lead to a certain degree of distortion. At the same time the introduction of lateral fluorine and the longer n-pentyl substituent on the cyclohexane ring enable the liquid crystals to give the liquid crystals unusual smectic textures, **5/2-0F**, (Cr 186.5 °C N 221.2 °C), **5/2-1F**, (Cr 172.8 °C SmB 200.0 °C). Fluorine has the highest electronegativity of all the elements, and the lateral one on benzene can increase the polarization as well as the lateral intermolecular attraction. When the lateral attraction is greater than the terminal attraction, the smectic phase forms preferentially.

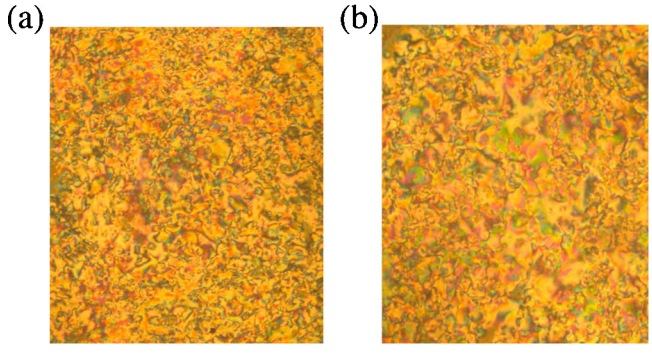


Fig. 1. Optical texture of (a) nemetic phase for **3/2-0F** at 181 °C and optical texture of (b) nemetic phase for **5/2-0F** at 194 °C.

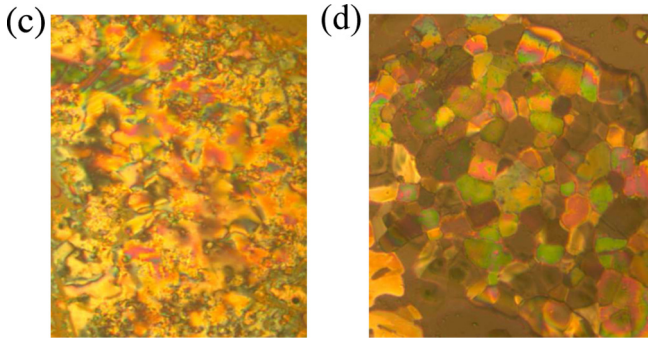


Fig. 2. Optical texture of (c) nemetic phase for **3/2-1F** at 195 °C and optical texture of (d) Smectic B for **5/2-1F** at 180 °C.

The number of the cyclohexane has an important influence on the mesophase morphology of the new liquid crystal molecules. New compounds with one-ring cyclohexane building block are thermally less stable than their two-ring analogs. Compounds, **n/m-0F** and **n/m-1F** with two-ring cyclohexane building block, show thermotropic liquid crystal phases, e.g. **3/2-0F**, **5/2-0F**, **3/2-1F** show nematic phase, and **5/2-1F** show smectic B phase. But compounds containing one-ring cyclohexane building block do not show the behavior of liquid crystal, e.g. **3/1-0F**, **5/1-0F**, **3/1-1F**, **5/1-1F**. The molecules with two-ring cyclohexane building block have trans-geometric configuration. The geometrical arrangement will be more coordinated and lead to a more tightly packed structure. Moreover, the two-ring cyclohexane elongates the molecule to give an appropriate length to width ratio, which is propitious to the forming and stability of mesomorphism.

Different length of alkyl groups markedly influences the properties of these compounds. The liquid crystals exhibit nematic phase and their clearing points vary regularly with the increase of the number of terminal alkyl carbon. Decreasing the number of terminal alkyl carbons can rise the clearing points, e.g. **5/2-0F**, at Cp. 221.2 °C; **3/2-0F**, at Cp. 223.2 °C; **5/2-1F**, at Cp. 200.0 °C; **3/2-1F**, at Cp. 209.7 °C. Lessening the length of alkyl group in the terminal cyclohexane increases the polarization and forms the more tightly packed structure and increases the rigidity of the molecules which is beneficial to the formation of the high clearing points.

2.3. Thermal stability

Thermal stabilities, which range from 250 °C to 330.2 °C, with the exception of **5/2-7F**, depending on the N-heterocycle and the cyclohexane building block, were determined by thermal gravimetric analysis (TGA). The decomposition temperatures of the new compounds are shown in Table 1 and Fig. 3. Data shows that the decomposition temperatures were higher than the clearing point for these compounds. In general, the new compounds with one-ring cyclohexane are thermally less stable than their two-ring cyclohexane analogs. The new compounds with piperidine or 3,3,4,4,5,5-hexafluoropiperidine as terminal group show similar thermal stability, and the piperidine-based compounds are mesophase stable to high temperature.

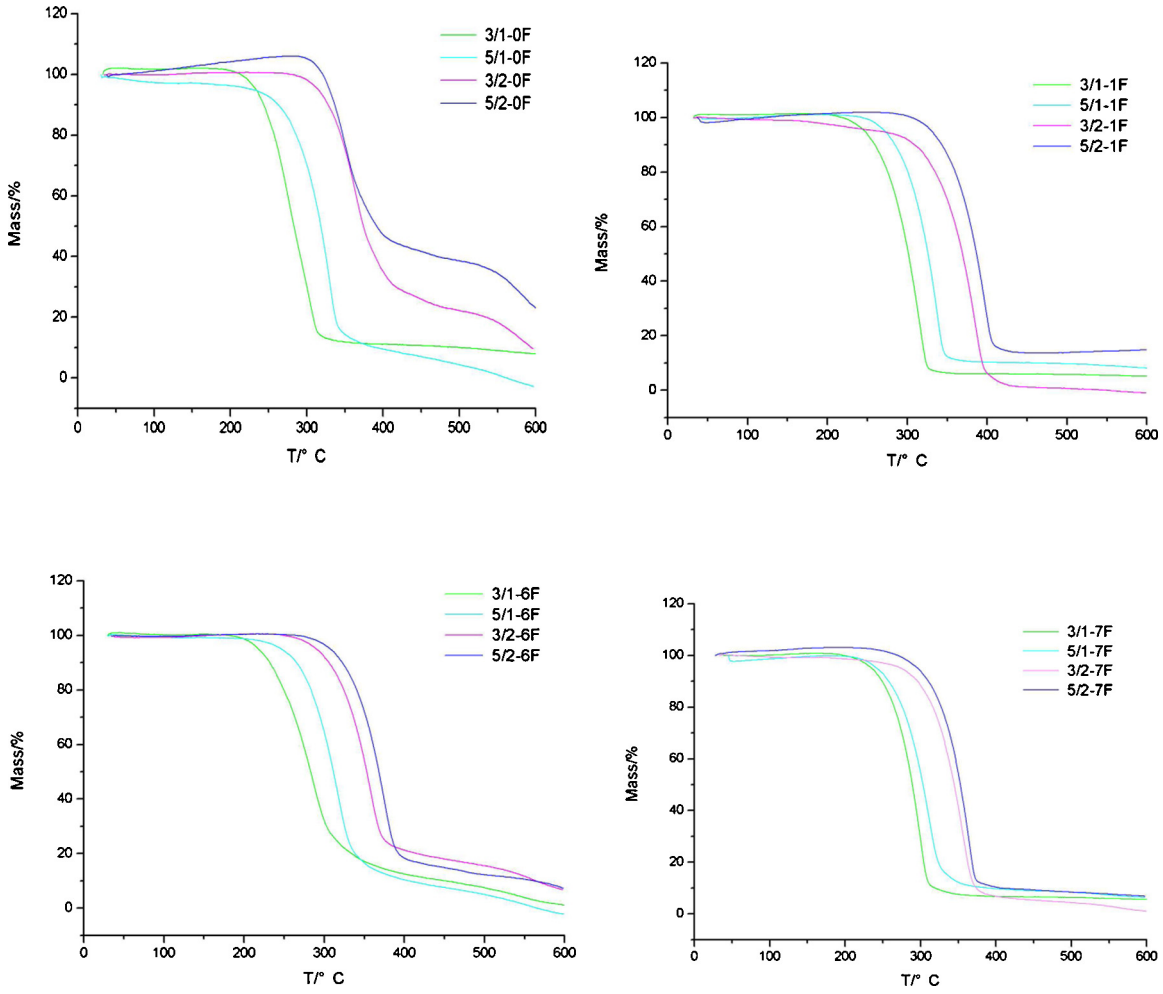


Fig. 3. The thermal stabilities of the new compounds.

2.4. Theoretical study

The geometry optimization of the **3/2-0F**, **3/2-1F**, **3/2-6F** structures were performed by density functional theory (DFT) Becke's three-parameter hybrid function with non-local correlation of Lee–Yang–Parr (B3LYP) method in gas phase [22]. The corresponding frequency analyses were computed at the same level of theory to characterize them as minima (no imaginary frequencies) with help of Gaussian03 (Revision D.01) suite of programs [23]. All of above calculations used a 6−31+G basis set. The computed structures were visualized using the GaussView program [24]. The conformation expression is mainly a thermodynamic problem, so the total energy of each different conformation can reflect the stability of the structure. Piperidine has two different conformations, chair and boat form, their total energy were −1258.4756 A.U. and −1258.4684 A.U. respectively. The molecular total energy of chair form is lower than that of boat form by approximately 18.90 kJ/mol (1 a.u. = 2625.51 kJ/mol), indicating that the chair conformation of the terminal 3,3,4,4,5,5-hexafluoropiperidine compound is more stable than the boat based on the thermodynamic theory. The terminal fluorinated piperidine adopts the twist-boat conformation in comparison with the piperidine, thus molecular ordered arrangement decreases. It can be seen from optimized geometry (Fig. 4) that with the change of terminal N-heterocycle, the co-planar structure of the molecule was destroyed. This is manifested in their dihedral angles and bond angles (Table 2) and comes about as a result of the structures of these molecules, which leads to a change in the number of intermolecular interactions.

The dipole moment could be predicted by DFT calculations in the process of geometric optimization of the structures. Calculation of dipole moments using Gaussian03 shows that **3/2-0F**, **3/2-1F**, and **3/2-6F** have the values at 2.8 D, 0.7 D, and 5.7 D, respectively.

3. Conclusion

Four series of novel ester liquid crystals with piperidine or 3,3,4,4,5,5-hexafluoropiperidine as terminal group have been prepared in good yield.

Their melting points, clearing points, mesomorphism types and decomposition temperatures were determined. The properties of these liquid crystals can be adjusted by using different terminal alkyl groups, the lateral fluorine substituent, the number of the cyclohexane and the terminal N-heterocycle with different fluorine content. The mesophase behavior was affected by altering the terminal N-heterocycle. Changing the terminal group from piperidine to 3,3,4,4,5,5-hexafluoropiperidine gives rise to a markedly decrease in mesomorphic behaviors. Compounds **3/2-6F**, **5/2-6F**, **3/2-7F** and **5/2-7F**, with the terminal 3,3,4,4,5,5-hexafluoropiperidine ring adopting a distorted N1-envelope conformation, melted into isotropic liquids at 165.9 °C, 153.9 °C, 149.7 °C and 142.6 °C directly respectively with no texture of liquid crystal being observed. Comparatively, compounds **3/2-0F**, **5/2-0F**, **3/2-1F** and **5/2-1F** with piperidine as terminal group exhibit nematic phase or smectic B phase and high clearing points. The dipole moment of compound **3/2-0F**, **3/2-6F** is 2.8, 5.7, respectively, which indicate the existence

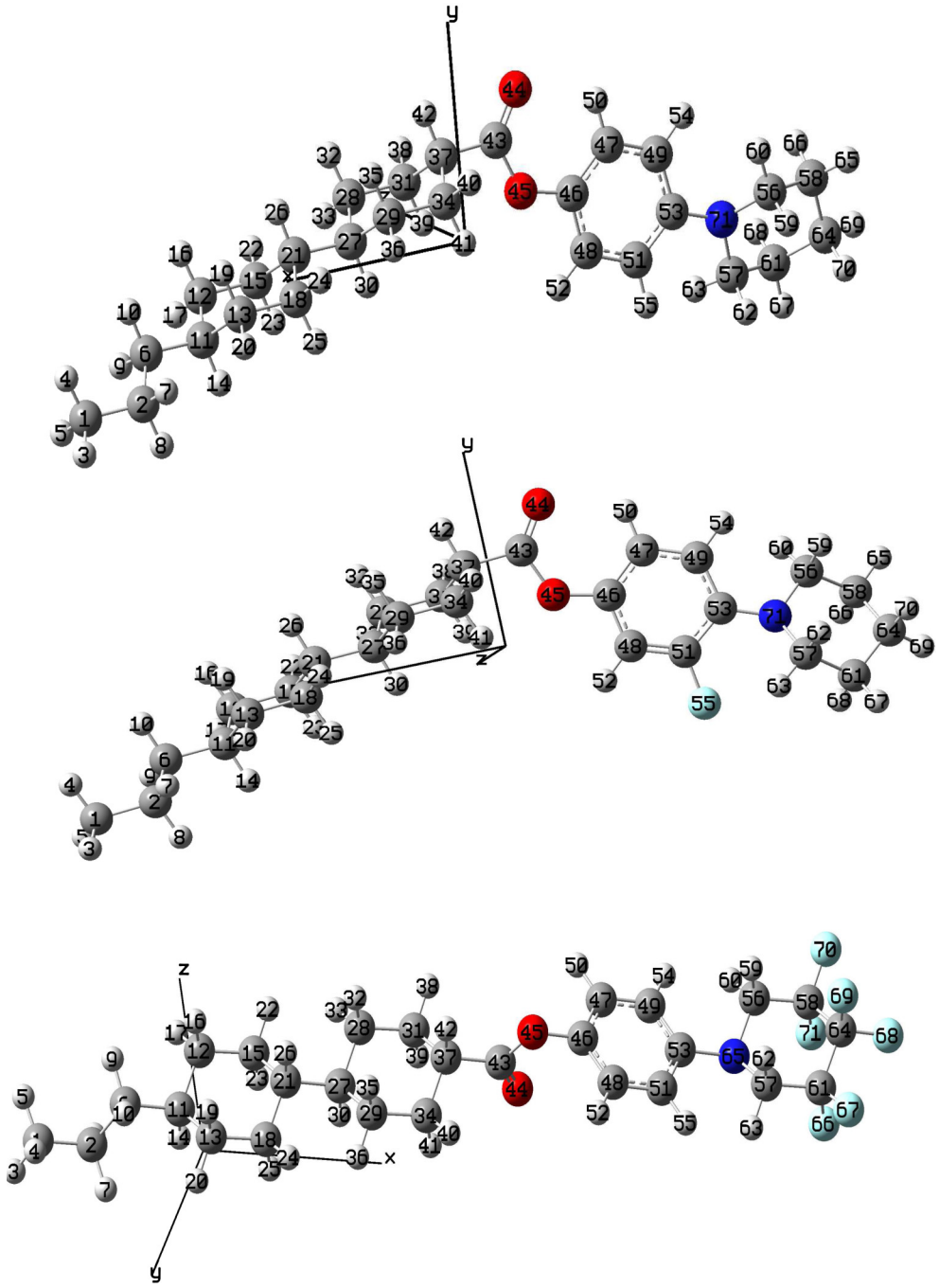


Fig. 4. The optimized geometry of **3/2-0F**, **3/2-1F**, and **3/2-6F**.

of C-F bond influences the polarity of molecule. New compounds with one-ring cyclohexane building block are thermally less stable than their two-ring analogs. These novel liquid crystals can be used for miscellaneous purposes, such as the exact adjustment of the clearing temperature of mixtures for LCDs.

4. Experimental

4.1. General considerations

All the reagents used were analytical reagents purchased from commercial sources and used as received. ^{1}H and ^{19}F were recorded on a 400 MHz nuclear magnetic resonance spectrometer operating at 400 and 376 MHz respectively. Chemical shifts were reported relative to Me_4Si for ^{1}H, and CCl_3F for ^{19}F. LC–MS were recorded on THEROMO LCQ DECA XP MAX (America) liquid chromatography/mass spectrometer. The solvent was CDCl3 unless otherwise specified. The Ms Thermogravimetric analysis (TGA) measurements were performed at a heating rate of 10 °C min^{-1} with a Netzsch STA409PC (Germany) instrument. The DSC was recorded at a scan rate of 2 °C min^{-1} on a Netzsch DSC200PC apparatus. Optical micrographs were observed with a polarizing optical microscope (POM) (*Nikon* LINKAM-THMSE600) equipped with a heating plate (HCS601).

Table 2
Geometrical parameters of 3/2-0F, -1F, -6F calculated by Gaussian03.

No	Dihedral angles (°)		Bond angles (°)		Bond lengths (10^{-1} nm)		Dipole/Debye
3/2-0F	C49-C53-N71-C56	45.58	C53-N71-C56	119.66	N71-C56	1.477	2.8
	C53-N71-C56-C58	−152.31	C53-N71-C57	119.73	C56-C58	1.535	
	C48-C46-O45-C43	−177.83	C53-N71-C58	147.88	C58-C64	1.539	
			C53-N71-C61	148.72	C64-C61	1.539	
			C53-N71-C64	179.50	C61-C57	1.539	
					C57-N71	1.470	
3/2-1F	C49-C53-N71-C56	−17.86	C53-N71-C57	119.38	N71-C57	1.483	0.7
	C53-N71-C56-C58	−154.54	C53-N71-C61	148.52	C57-C61	1.535	
	C48-C46-O45-C43	178.05	C53-N71-C64	178.45	C61-C64	1.539	
			C53-N71-C58	148.60	C64-C58	1.539	
			C53-N71-C56	118.99	C58-C56	1.539	
					C56-N71	1.471	
3/2-6F	C51-C53-N65-C56	−150.86	C53-N65-C57	109.59	N65-C57	1.515	5.7
	C53-N65-C57-C61	−176.58	C53-N65-C61	143.86	C57-C61	1.515	
	C48-C46-O45-C43	−89.98	C53-N65-C64	149.81	C61-C64	1.515	
			C53-N65-C58	143.82	C64-C58	1.515	
			C53-N65-C56	109.59	C58-C56	1.515	
					C56-N65	1.515	

*4.2. General procedure for the preparation of trifluoromethanesulfonic acid 1,5-pentanedily ester **2** and trifluoromethanesulfonic acid 2,2,3,3,4,4-hexafluoro-1,5-pentanediyl ester **4***

1,5-Penanediol **1**, or 2,2,3,3,4,4-hexafluoro-1,5-penanediol **3** (1 mmol), pyridine (3 mmol) and dichloromethylene (20 mL) were stirred at 0 °C. After 30 min, trifluoromethanesulfonic anhydride (2.5 mmol) in 10 mL dichloromethane was slowly added over 1 h. The mixture was stirred for 12 h, then washed with water (3× 20 mL), and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give trifluoromethanesulfonic acid 1,5-pentanedily ester or trifluoromethanesulfonic acid 2,2,3,3,4, 4-hexafluoro-1,5-pentanedily ester.

*4.3. General procedure for the preparation of 4-piperidinyl-phenol (**0F**)*

Trifluoromethanesulfonic acid 1,5-pentanediyl ester **2** (5 mmol), 4-aminophenol (5 mmol), and Et_3N (12.5 mmol) in 15 mL ethanol were placed in a Pyrex glass tube, sealed, heated at 90 °C for 24 h. After cooling, the organic solvent was removed under reduced pressure and the residue was added to 30 mL dichloromethane then washed with water (3× 30 mL), and dried over anhydrous Na_2SO_4. After the solvent was removed, the crude product was purified by chromatography on silica gel with ethyl acetate–dichloromethane (1:5) as an eluent to give white solid, 80% yield. ^{1}H NMR ($CDCl_3$) δ(ppm): 6.86 (s, 2H), 6.72 (s, 2H), 5.30 (s, 1H), 3.01 (s, 4H), 1.73 (s, 4H), 1.53 (s, 2H). MS (ESI) *m/z*: 176.48 $[M]^-$. Anal. Calcd for $C_{11}H_{15}NO$ C 74.54, H 8.53, N 7.90%; found: C 74.45, H 8.516, N 7.81%.

*4.4. General procedure for the preparation of 3-fluoro-4-(piperidin-1-yl)-phenol **(1F)***

Trifluoromethanesulfonic acid 1,5-pentanediyl ester **2** (5 mmol), 4-amino-3-fluorophenol (5 mmol), and Et_3N (12.5 mmol) in 15 mL ethanol were placed in a Pyrex glass tube, sealed, heated at 90 °C for 24 h. After cooling, the organic solvent was removed under reduced pressure. 30 mL of dichloromethane was added to the residue and then washed with water (3× 30 mL), dried over anhydrous Na_2SO_4. After the solvent was removed; the crude product was purified by chromatography on silica gel with ethyl acetate–petroleum ether (1:5) as an eluent to give yellow solid, 77.56% yield. ^{1}H NMR ($CDCl_3$) δ(ppm): 6.87 (s, 1H), 6.52 (s, 2H), 5.28 (s, 1H), 2.93 (s, 4H), 1.74 (s, 4H), 1.54 (s, 2H). ^{19}F NMR ($CDCl_3$) δ(ppm): −120.67 to −120.78 (m, 1F). MS (ESI) *m/z*: 196.43 $[M+H]^+$. Anal. Calcd for $C_{11}H_{14}FNO$ C 67.05, H 7.26, N 7.11(%); found: C 66.91, H 7.236, N 6.9(%).

*4.5. General procedure for the preparation of 4-(3,3,4,4,5,5-hexafluoropiperidin-1-yl)-phenol (**6F**)*

Trifluoromethanesulfonic acid 2,2,3,3,4,4-hexafluoro-1,5-pentanediyl ester **4** (5 mmol), 4-aminophenol (5 mmol), and Et_3N (12.5 mmol) in 15 mL ethanol were placed in a Pyrex glass tube, sealed, heated at 90 °C for 24 h. After cooling, the organic solvent was removed under reduced pressure and the residue was added to 30 mL dichloromethane then washed with water (3× 30 mL), and dried over anhydrous Na_2SO_4. After the solvent was removed, the crude product was purified by chromatography on silica gel with dichloromethane as an eluent to give white solid, 78.68% yield. ^{1}H NMR ($CDCl_3$) δ(ppm): 6.88 (d, 2H), 6.79 (d, 2H), 5.02 (s, 1H), 3.57 (s, 4H). ^{19}F NMR ($CDCl_3$) δ(ppm): −123.34 (s, 4F), −139.50 (s, 2F). MS (ESI) *m/z*: 284.48 $[M]^-$. Anal. Calcd for $C_{11}H_9F_6NO$: C 46.33, H 3.18, N 4.91%; found: C 46.32, H 3.213, N 4.87%.

*4.6. General procedure for the preparation of 3-fluoro-4-(3,3,4,4,5,5-hexafluoropiperidin-1-yl)-phenol **(7F)***

Trifluoromethanesulfonic acid 2,2,3,3,4,4-hexafluoro-1,5-pentanediyl ester 4 (5 mmol), 4-amino-3-fluorophenol (5 mmol), and Et_3N (12.5 mmol) in 15 mL ethanol were placed in a Pyrex glass tube, sealed, heated at 90 °C for 24 h. After cooling, the organic solvent was removed under reduced pressure and the residue was added to 30 mL dichloromethane then washed with water (3× 30 mL), and dried over anhydrous Na_2SO4. After the solvent was removed, the crude product was purified by chromatography on silica gel with dichloromethane as an eluent to give light yellow solid, 75.95% yield. ^{1}H NMR ($CDCl_3$) δ(ppm): 6.95 (s, 1H), 6.60 (m, 2H), 5.45 (s, 1H), 3.55 (s, 4H). ^{19}F NMR ($CDCl_3$) δ(ppm): −120.40 (d, J = 12.0 Hz, 2F), −123.64 (s, 5F). MS (ESI) *m/z*: 302.50 $[M]^-$. Anal. Calcd for $C_{11}H_8F_7NO$: C 43.58, H 2.66, N 4.62%; found: C 43.68, H 2.765, N 4.45%.

*4.7. General procedure for the preparation of **n/m-0F**, **n/m-1F**, **n/m-6F** and **n/m-7F***

4-piperidinyl-phenol (**0F**), 3-fluoro-4-(piperidin-1-yl)-phenol (**1F**), 4-(3,3,4,4,5,5-hexafluoropiperidin-1-yl)-phenol (**6F**),

or 3-fluoro-4-(3,3,4,4,5,5-hexafluoropiperidin-1-yl)-phenol (**7F**) (1 mmol), and cyclohexane building block (trans-4-(trans-4-n-alkylcyclohexyl)cyclohexanecarboxylic acid, trans-4-n-alkylcyclohexanecarboxylic acid, (1.2 mmol), N,N′-dicyclohexyl carbodiimide (DCC) (1.2 mmol), 4-dimethylaminopyridine (DMAP) (0.2 mmol) in 10 mL chloroform were placed in a Pyrex glass tube, sealed and heated at 80 °C for 12 h. After cooling, the white solid was filtrated off, the solvent was removed under vacuum, and then the crude product was purified by chromatography on silica gel with dichloromethane, or dichloromethane–petroleum ether (1:3) as eluent to give white solid, 78–88% yield, respectively.

Trans-4-n-propylcyclohexanecarboxylic acid 4′-piperidinyl phenyl ester (**3/1-0F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 6.92 (d, J = 4.6 Hz, 4H), 3.14–3.06 (m, 4H), 2.45 (t, J = 12.2 Hz, 1H), 2.12 (d, J = 11.3 Hz, 2H), 1.86 (d, J = 13.4 Hz, 2H), 1.70 (d, J = 5.3 Hz, 4H), 1.52 (d, J = 19.5 Hz, 4H), 1.39–1.15 (m, 5H), 0.96 (d, J = 28.1 Hz, 5H). MS (ESI) m/z: 330.49 $[M+H]^+$. Anal. Calcd for $C_{21}H_{31}NO_2$: C 76.55, H 9.48, N 4.25%; found: C 76.57, H 9.591, N 4.15%.

Trans-4-n-pentylcyclohexanecarboxylic acid 4′-piperidinyl-phenyl ester (**5/1-0F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 6.92 (s, 4H), 3.10 (s, 4H), 2.43 (t, J = 12.1 Hz, 1H), 2.11 (d, J = 12.7 Hz, 2H), 1.86 (d, J = 12.7 Hz, 2H), 1.70 (s, 4H), 1.61–1.46 (m, 4H), 1.37–1.15 (m, 9H), 0.93 (d, J = 13.3 Hz, 5H). MS (ESI) m/z: 358.49 $[M+H]^+$. Anal. Calcd for $C_{23}H_{35}NO_2$: C 77.27, H 9.87, N 3.92%; found: C 77.44, H 9.961, N 3.90%.

Trans-4-(trans-4-n-propylcyclohexyl)cyclohexanecarboxylic acid 4′-piperidinylphenyl ester (**3/2-0F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 6.92 (s, 4H), 3.10 (s, 4H), 2.42 (t, J = 12.2 Hz, 1H), 2.13 (d, J = 12.4 Hz, 2H), 1.79 (d, J = 19.0 Hz, 11H), 1.52 (d, J = 23.9 Hz, 2H), 1.30 (d, J = 6.7 Hz, 2H), 1.20–0.76 (m, 15H). MS (ESI) m/z: 412.62 $[M+H]^+$. Anal. Calcd for $C_{27}H_{41}NO_2$: C 78.78, H 10.04, N 3.40%; found: C 78.81, H 10.107, N 3.33%.

Trans-4-(trans-4-n-pentylcyclohexyl)cyclohexanecarboxylic acid 4′-piperidinylphenyl ester (**5/2-0F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 6.92 (s, 4H), 3.10 (s, 4H), 2.42 (t, J = 12.0 Hz, 1H), 2.13 (d, J = 12.7 Hz, 2H), 1.87–1.66 (m, 11H), 1.50 (s, 2H), 1.33–0.80 (m, 21H). MS (ESI) m/z: 440.70 $[M+H]^+$. Anal. Calcd for $C_{29}H_{45}NO_2$: C 79.22, H 10.32, N 3.19; found: C 79.14, H 10.280, N 3.08%.

Trans-4-n-propylcyclohexanecarboxylic acid 3-fluoro-4′-(piperidin-1-yl)-phenol ester (**3/1-1F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 6.92 (s, 1H), 6.77 (s, 2H), 2.97 (s, 4H), 2.43 (s, 1H), 2.08 (s, 2H), 1.85 (d, J = 12.5 Hz, 2H), 1.72 (d, J = 4.9 Hz, 4H), 1.54 (s, 4H), 1.26 (d, J = 50.0 Hz, 5H), 0.89 (s, 5H). ^{19}F NMR ($CDCl_3$) δ(ppm): −120.21 (t, J = 10.8 Hz, 1F). MS (ESI) m/z: 348.42 $[M+H]^+$. Anal. Calcd for $C_{21}H_{30}FNO_2$: C 72.59, H 8.70, N 4.03%; found: C 72.60, H 8.806, N 3.92%.

Trans-4-n-pentylcyclohexanecarboxylic acid 3-fluoro-4′-(piperidin-1-yl)-phenol ester (**5/1-1F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 6.92 (s, 1H), 6.78 (s, 2H), 2.97 (s, 4H), 2.43 (s, 1H), 2.10 (d, J = 14.3 Hz, 2H), 1.86 (d, J = 13.4 Hz, 2H), 1.73 (s, 4H), 1.58 (m, 4H), 1.24 (d, J = 20.8 Hz, 9H), 0.93 (d, J = 35.4 Hz, 5H). ^{19}F NMR ($CDCl_3$) δ(ppm): −120.23 (t, J = 10.6 Hz, 1F). MS (ESI) m/z: 376.48 $[M+H]^+$. Anal. Calcd for $C_{23}H_{34}FNO_2$: C 73.56, H 9.13, N 3.73%; found: C 73.70, H 9.142, N 3.66%.

Trans-4-(trans-4-n-propylcyclohexyl)cyclohexanecarboxylic acid 3-fluoro-4′-(piperidin-1-yl)-phenol ester (**3/2-1F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 6.91 (t, J = 9.0 Hz, 1H), 6.77 (t, J = 10.3 Hz, 2H), 2.97 (s, 4H), 2.41 (t, J = 12.3 Hz, 1H), 2.12 (d, J = 13.1 Hz, 2H), 1.87–1.68 (m, 11H), 1.47 (d, J = 12.7 Hz, 2H), 1.30 (s, 3H), 1.12 (d, J = 20.2 Hz, 9H), 0.87 (s, 5H). ^{19}F NMR ($CDCl_3$) δ(ppm): −120.20 (t, J = 10.5 Hz, 1F). MS (ESI) m/z: 1430.55 $[M+H]^+$. Anal. Calcd for $C_{27}H_{40}FNO_2$: C 75.48, H 9.38, N 3.26%; found: C 75.56, H 9.469, N 3.21%.

Trans-4-(trans-4-n-pentylcyclohexyl)cyclohexanecarboxylic acid 3-fluoro-4′-(piperidin-1-yl)-phenol ester (**5/2-1F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 6.92 (t, J = 9.0 Hz, 1H), 6.78 (t, J = 9.0 Hz, 2H), 2.97 (s, 4H), 2.46–2.37 (m, 1H), 2.12 (d, J = 11.7 Hz, 2H), 1.80 (d, J = 35.5 Hz, 11H), 1.53–1.45 (m, 2H), 1.29 (d, J = 17.0 Hz, 7H). 1.10 (d, J = 20.2 Hz, 9H), 0.87 (s, 5H). ^{19}F NMR ($CDCl_3$) δ(ppm): −120.25 (t, J = 10.3 Hz, 1F). MS (ESI) m/z: 458.63 $[M+H]^+$. Anal. Calcd for $C_{29}H_{44}FNO_2$: C 76.11, H 9.69, N 3.06%; found: C 75.99, H 9.823, N 2.88%.

Trans-4-n-propylcyclohexanecarboxylic acid 3-fluoro-4′-(piperidin-1-yl)-phenol ester (**3/1-6F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 7.03–6.98 (m, 2H), 6.96–6.91 (m, 2H), 3.66 (s, 4H), 2.45 (t, J = 12.2 Hz, 1H), 2.15–2.07 (m, 2H), 1.87 (d, J = 13.7 Hz, 2H), 1.60–1.47 (m, 2H), 1.28 (d, J = 15.8 Hz, 5H), 1.03–0.82 (m, 5H). ^{19}F NMR ($CDCl_3$) δ(ppm): −123.47 (s, 4F), −139.42 (s, 2F). MS (ESI) m/z: 475.04 $[M+K]^+$. Anal. Calcd for $C_{21}H_{25}F_6NO_2$: C 57.66, H 5.76, N 3.20%; found: C 57.73, H 5.838, N 3.14%.

Trans-4-n-pentylcyclohexanecarboxylic acid 3-fluoro-4′-(piperidin-1-yl)-phenol ester (**5/1-6F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 7.01 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.67 (s, 4H), 2.45 (t, J = 12.2 Hz, 1H), 2.11 (d, J = 11.9 Hz, 2H), 1.87 (d, J = 13.3 Hz, 2H), 1.53 (d, J = 15.9 Hz, 2H), 1.26 (d, J = 18.9 Hz, 9H), 1.03–0.85 (m, 5H). ^{19}F NMR ($CDCl_3$) δ(ppm): −123.47 (s, 4F), −139.42 (s, 2F). MS (ESI) m/z: 464.82 $[M]^-$. Anal. Calcd for $C_{23}H_{29}F_6NO_2$: C 59.35, H 6.28, N 3.01%; found: C 59.56, H 6.418, N 2.94%.

Trans-4-(trans-4-n-propylcyclohexyl)cyclohexanecarboxylic acid 4′-piperidinylphenyl ester (**3/2-6F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 7.01 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.67 (s, 4H), 2.43 (t, J = 12.5 Hz, 1H), 2.14 (d, J = 13.3 Hz, 2H), 1.90–1.65 (m, 6H), 1.51 (d, J = 22.1 Hz, 2H), 1.35–1.22 (m, 2H), 1.19–0.78 (m, 14H). ^{19}F NMR ($CDCl_3$) δ(ppm): −123.46 (s, 4F), −139.42 (s, 2F). MS (ESI) m/z: 518.90 $[M]^-$. Anal. Calcd for $C_{27}H_{35}F_6NO_2$: C 62.42, H 6.79, N 2.70%; found: C 62.53, H 6.885, N 2.63%.

Trans-4-(trans-4-n-pentylcyclohexyl)cyclohexanecarboxylic acid 4′-piperidinylphenyl ester (**5/2-6F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 7.00 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 3.67 (s, 4H), 2.43 (t, J = 12.2 Hz, 1H), 2.13 (d, J = 13.1 Hz, 2H), 1.85 (d, J = 10.5 Hz, 2H), 1.80–1.68 (m, 4H), 1.51 (d, J = 23.2 Hz, 2H), 1.35–0.78 (m, 20H). ^{19}F NMR ($CDCl_3$) δ(ppm): −123.47 (s, 4F), −139.41 (s, 2F). MS (ESI) m/z: 586.71 $[M+K]^+$. Anal. Calcd for $C_{29}H_{39}F_6NO_2$: C 63.60, H 7.18, N 2.56%; found: C 63.76, H 7.293, N 2.47%.

Trans-4-n-propylcyclohexanecarboxylic acid 3-fluoro-4′-(piperidin-1-yl)-phenol ester (**3/1-7F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 7.03 (t, J = 9.0 Hz, 1H), 6.86 (d, J = 20.4 Hz, 2H), 3.63 (t, J = 8.4 Hz, 4H), 2.45 (t, J = 12.2 Hz, 1H), 2.10 (d, J = 13.0 Hz, 2H), 1.87 (d, J = 13.1 Hz, 2H), 1.59–1.46 (m, 2H), 1.27 (d, J = 21.8 Hz, 5H), 0.94 (d, J = 14.5 Hz, 5H). ^{19}F NMR ($CDCl_3$) δ(ppm): −119.87 (t, J = 10.6 Hz, 2F), −123.64 (s, 5F). MS (ESI) m/z: 494.15 $[M+K]^+$. Anal. Calcd for $C_{21}H_{24}F_7NO_2$: C 55.38, H 5.31, N 3.08%; found: C 55.47, H 5.350, N 3.04%.

Trans-4-n-pentylcyclohexanecarboxylic acid 3-fluoro-4′-(piperidin-1-yl)-phenol ester (**5/1-7F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 7.03 (t, J = 9.0 Hz, 1H), 6.91–6.81 (m, 2H), 3.63 (t, J = 9.0 Hz, 4H), 2.50–2.40 (m, 1H), 2.10 (d, J = 12.3 Hz, 2H), 1.91–1.84 (m, 2H), 1.58–1.47 (m, 2H), 1.35–1.17 (m, 9H), 0.94 (d, J = 14.1 Hz, 5H). ^{19}F NMR ($CDCl_3$) δ(ppm): −119.85 (t, J = 10.5 Hz, 2F), −123.65 (s, 5F). MS (ESI) m/z: 500.05 $[M+NH_4]^+$. Anal. Calcd for $C_{23}H_{28}F_7NO_2$: C 57.14, H 5.84, N 2.90%; found: C 57.28, H 5.963, N 2.83%.

Trans-4-(trans-4-n-propylcyclohexyl)cyclohexanecarboxylic acid 4′-piperidinylphenyl ester (**3/2-7F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 7.02 (t, J = 9.0 Hz, 1H), 6.85 (d, J = 20.3 Hz, 2H), 3.63 (t, J = 8.7 Hz, 4H), 2.43 (t, J = 12.1 Hz, 1H), 2.13 (d, J = 12.6 Hz, 2H), 1.85 (d, J = 11.0 Hz, 2H), 1.80–1.68 (m, 4H), 1.53–1.44 (m, 2H), 1.30 (d, J = 15.8 Hz, 2H), 1.19–0.92 (m, 9H), 0.87 (t, J = 7.2 Hz, 5H). ^{19}F NMR ($CDCl_3$) δ(ppm): −119.87 (t, J = 10.6 Hz, 2F), −123.67 (s, 5F). MS (ESI) m/z: 554.51 $[M+NH_4]^+$. Anal. Calcd for $C_{27}H_{34}F_7NO_2$: C 60.33, H 6.38, N 2.61%; found: C 60.36, H 6.455, N 2.55%.

Trans-4-(trans-4-n-pentylcyclohexyl)cyclohexanecarboxylic acid 4′-piperidinylphenyl ester (**5/2-7F**); ^{1}H NMR ($CDCl_3$) δ(ppm): 7.03 (t, J = 9.0 Hz, 1H), 6.91–6.80 (m, 2H), 3.63 (t, J = 9.0 Hz, 4H),

2.43 (s, 1H), 2.13 (d, J = 11.4 Hz, 2H), 1.89 (d, J = 26.9 Hz, 2H), 1.80–1.68 (m, 4H), 1.53–1.45 (m, 2H), 1.36–1.19 (m, 15H), 0.91–0.81 (m, 5H). ^{19}F NMR ($CDCl_3$) δ(ppm): −119.83 (t, J = 10.6 Hz, 2F), -123.63 (s, 5F). MS (ESI) m/z: 566.28 $[M+H]^+$. Anal. Calcd for $C_{29}H_{38}F_7NO_2$: C 61.58, H 6.77, N 2.48%; found: C 61.63, H 6.913, N 2.47%.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2014.08.025.

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