^{19}F and ^{13}C GIAO-NMR chemical shifts for the identification of perfluoro-quinoline and -*iso*quinoline derivatives

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Abstract

Reaction of perfluoroquinoline **1** and perfluoro*iso*quinoline **2** with benzylamine gave mono- and di-aminated quinoline and *iso*quinoline systems respectively depending upon the reaction conditions by selective S_NAr processes. Optimised model geometries of the aminated derivatives at MP2/6-31G* were in very good agreement with available X-ray crystallographic data and were used to compute ^{19}F and ^{13}C GIAO-NMR shifts. Comparison with observed ^{19}F and ^{13}C NMR shifts give excellent correlations, indicating that ^{19}F and ^{13}C GIAO-NMR computations are powerful tools in structurally identifying polyfunctional, polycyclic perfluoroheteroaromatic compounds and aiding NMR resonance assignment.

1. Introduction

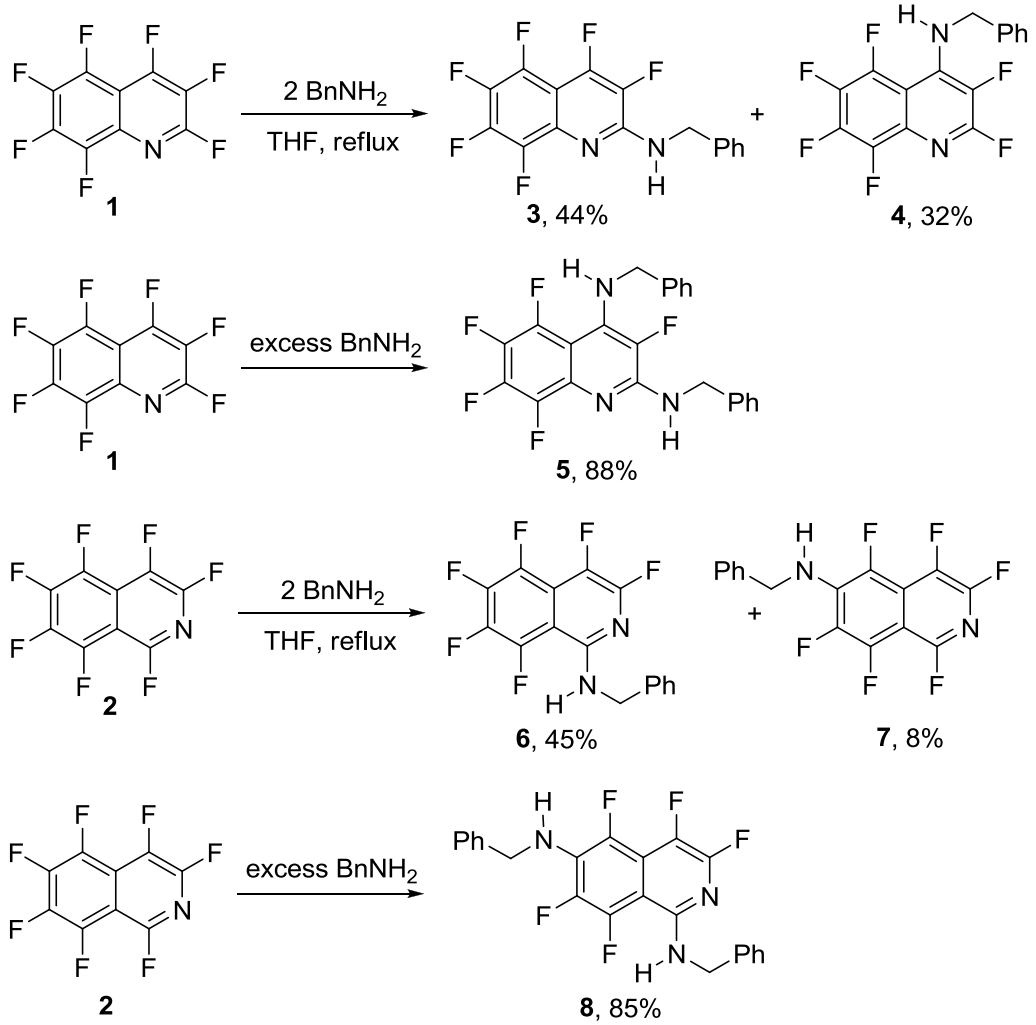
The chemistry of perfluoroheteroaromatic derivatives has developed considerably since the first efficient synthesis of the most simple member of this chemical class, pentafluoropyridine, was reported in the 1960s and many reactions of perfluoroheteroaromatic systems, principally nucleophilic aromatic substitution processes, have been described.[1] Indeed, a wide range of macrocycles,[2] polysubstituted polyfluorinated systems,[3] biologically active heterocyclic systems,[4] glycosyl donors[5] and ring-fused derivatives[6] have been prepared recently using S_NAr chemistry. The product identification arising from many S_NAr processes involving monocyclic perfluoroaromatic substrates, such as pentafluoropyridine, is relatively simple to establish by ^{19}F NMR spectroscopic analysis due to large chemical shift differences associated with fluorine atoms *ortho*, *meta* and *para* to ring nitrogen of the highly fluorinated heterocyclic product.[2-6] However, product identification and spectral assignments by ^{19}F NMR spectroscopy of more complex polycyclic substrates such as perfluoro-quinoline and –*iso*quinoline can be ambiguous due to the complexity of their ^{19}F NMR spectra because of the similar coupling constant ranges for fluorine atoms *ortho* and *para* to one another, limiting development of the chemistry of these potentially very useful polyfluorinated heteroaromatic scaffolds. Consequently, simple and accurate methods of product identification for products derived from S_NAr processes involving perfluorinated polycyclic substrates are required for the chemistry of perfluoroheteroaromatic systems to develop further.

The use of ^{1}H and ^{13}C GIAO-NMR shift computations for the structural characterisation of many organic systems have been shown to be highly effective for accurate compound identification.[7,8] However, ^{19}F NMR shift computations have not been widely used for compound identification.[7,9,10] In this paper, we explore the use of GIAO-NMR calculations for ^{19}F and ^{13}C NMR chemical shift predictions and subsequent structural confirmation and spectral assignment of products derived from representative model perfluoro-quinoline **1** and -*iso*quinoline **2** in comparison with appropriate unambiguous X-ray crystallographic analysis where possible.

Perfluoro-quinoline **1** and -*iso*quinoline **2** were synthesised some years ago [11] and a very limited number of nucleophilic aromatic substitution processes have been reported [12,13] involving **1** and **2** as substrates. Reaction of perfluoroquinoline with ammonia and perfluorocarbanionic nucleophiles give, in general, mixtures of products derived from substitution at the 2- and 4-positions depending upon the nature of the nucleophile.[13] Perfluoro*iso*quinoline **2** is reported to react with oxygen and nitrogen nucleophiles to give products arising from substitution at the 1-position whereas sulfur nucleophiles are less selective and give predominantly products substituted at the 6-position, providing an indication of the synthetic possibilities of these scaffolds for further chemistry upon development of suitable simple structural identification techniques.[13] Previous identification of substituted derivatives of **1** and **2** have relied exclusively on ^{19}F NMR spectra where some shifts were assumed by comparison with related hydrocarbon analogues, by the use of the substituent chemical shift (SCS) method and fluorine-fluorine or carbon-fluorine couplings which can aid NMR resonance assignments.

2. Results and discussion

Reactions of perfluoro-quinoline **1** and –*iso*quinoline **2** with benzylamine, selected as the model primary amine nucleophile due to the likely formation of suitable crystals of the substituted products for corroborative X-ray crystallography, are collated in Scheme 1. Heating a solution of perfluoroquinoline with two equivalents of benzylamine in THF led to two products **3** and **4** in an approximately 4:3 ratio. Separation and isolation of these products was possible using column chromatography and X-ray crystallography (Fig. 1) confirmed the structure of major product **3** arising from substitution of fluorine located at the 2-position. Reaction of **1** in neat benzylamine at ambient temperature gave a single disubstituted product and X-ray diffraction confirmed the structure of 2,4-disubstituted quinoline **5** (Fig. 2). Monosubstituted isomer **4**, derived from substitution of fluorine at the 4-position, was deduced by comparison with the structure of disubstituted **5**.



SCHEME 1. Reactions of perfluoro-quinoline **1** and –*iso*quinoline **2** with benzylamine

By a similar process, reaction of perfluoro*iso*quinoline **2** with two equivalents of benzylamine in THF at reflux temperature gave two monosubstituted products **6** and **7** in the ratio of 6:1 by ^{19}F NMR analysis of the crude product mixture. X-ray diffraction analysis of crystals of the major isomer confirmed the structure of **6** (Fig. 3), arising from substitution at C-1, while the minor isomer was the 6-substituted derivative **7**. Reaction of *iso*quinoline **2** in neat benzylamine gave a single disubstituted product **8** in high yield. The identities of **7** and **8** were determined by computations *vide infra*.

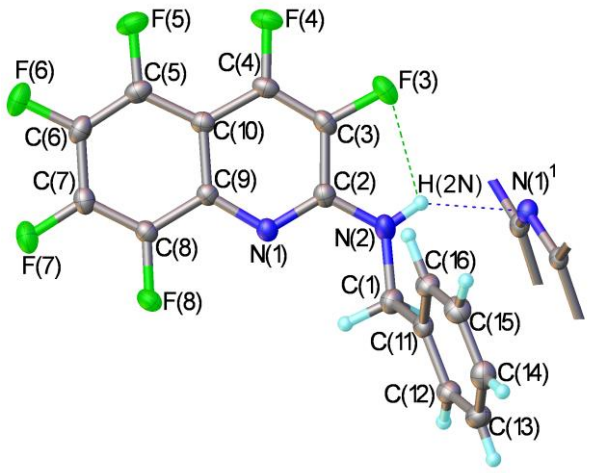


FIGURE 1. Molecular structure of *N-benzyl-3,4,5,6,7,8-hexafluoroquinolin-2-amine* **3**, showing thermal ellipsoids (at the 50% probability level) and intermolecular contacts. Torsion angle C(2)-N(2)-C(1)-C(11) 111.1(2)°. Symmetry operation (1): 1 – *x*, ½ +*y*, ½ – *z*. Drawn using OLEX2 graphics [14].

Molecular structures for **3**, **5** and **6** are shown in Figs. 1-3 and selected bond lengths are listed in Tables 1 and 2. The quinoline or isoquinoline moieties are planar and the adjacent nitrogen atoms always have planar-trigonal (sp^2) geometry where the planes practically coincide with the perfluoroaromatic rings, resulting in substantial π-conjugation indicated by shortened C-N bond distances [15]. Such conformations maximise intramolecular N-H…F interactions. Generally, 'organic' fluorine is regarded to be a poor acceptor of hydrogen bonds [16], participating in such interactions only in the absence of any more effective acceptor but, in **3**, **5** and **6**, such acceptors are seemingly available in the form of heterocyclic N atoms. Structures **5** and **6** show no N-H…N bonding although **3** contains an intermolecular contact H(2N)…N(1) (Fig. 1). This is too long to be considered a hydrogen bond (2.35 Å, assuming the idealised N–H bond length of 1.03 Å [17],compared to the usual range for N-H…N hydrogen bonds (1.8–2.1 Å) [18]) and is directed at 57° to the quinoline plane (i.e. is *not* directed along the N(1) lone electron pair). In **5**, H(2N) forms an intermolecular contact with a phenyl carbon atom along the direction of its p_π orbital, at 2.72 Å (cf. the sum of van der Waals radii of 2.87 Å [12]). In both cases, the intramolecular NH…F contact is shorter than N-H…N contacts, if awkwardly directed, while H(3N) in **5** and H(1N) in **6**

indisputably form intramolecular N-H…F hydrogen bonds. This situation could be due to the heterocyclic nitrogen atoms becoming sterically masked by the adjacent substituents and their being electrophilicity depleted by electronegative fluorine atoms, but could also indicate that the polarisability of organic fluorine is underestimated [19].

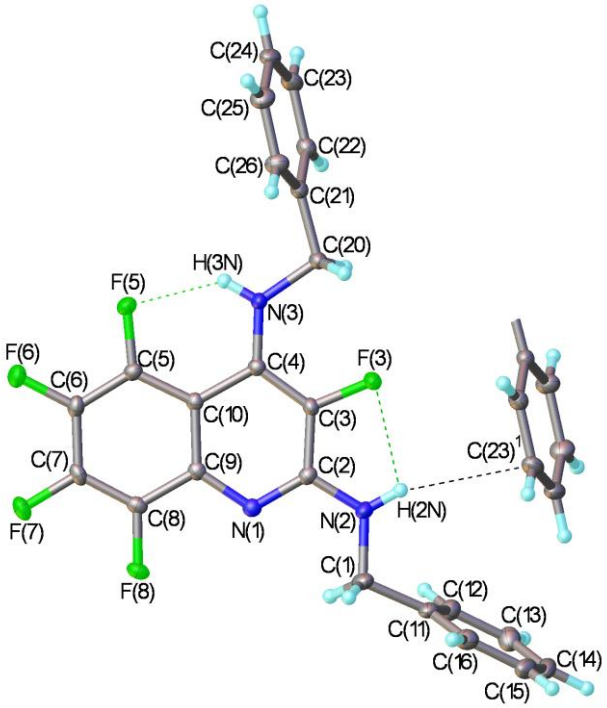


FIGURE 2. Molecular structure of *N*^{2},*N*^{4}*-benzyl-3,5,6,7,8-pentafluoroquinolin-2,4-diamine* **5**. Torsion angles (°): C(2)-N(2)-C(1)-C(Ph) 167.7(1), C(4)-N(4)-C(20)-C(Ph) 179.1(1). Symmetry operation (1): 1 – *x*, –*y*, 1 – *z*.

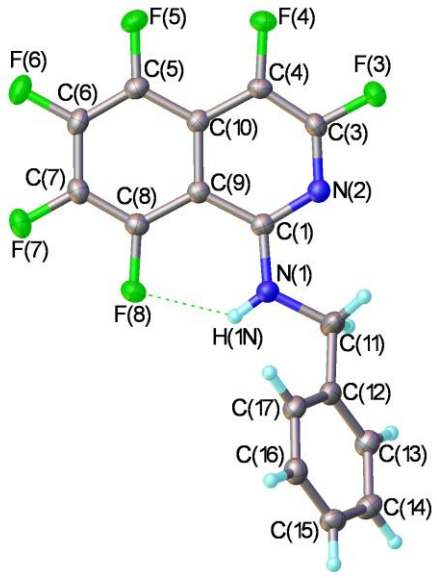


FIGURE 3. Molecular structure of *N-benzyl-3,4,5,6,7,8-hexafluoroisoquinolin-1-amine* **6**. Torsion angle C(1)-N(1)-C(11)-C(Ph) 161.0(1)°.

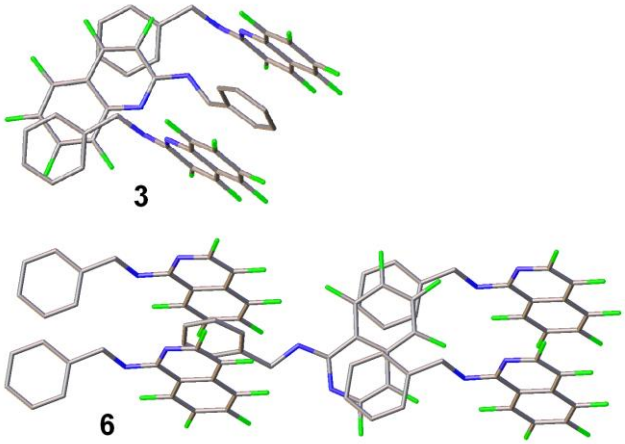


FIGURE 4. Stacking motifs of **3** and **6**. Hydrogen atoms are omitted for clarity

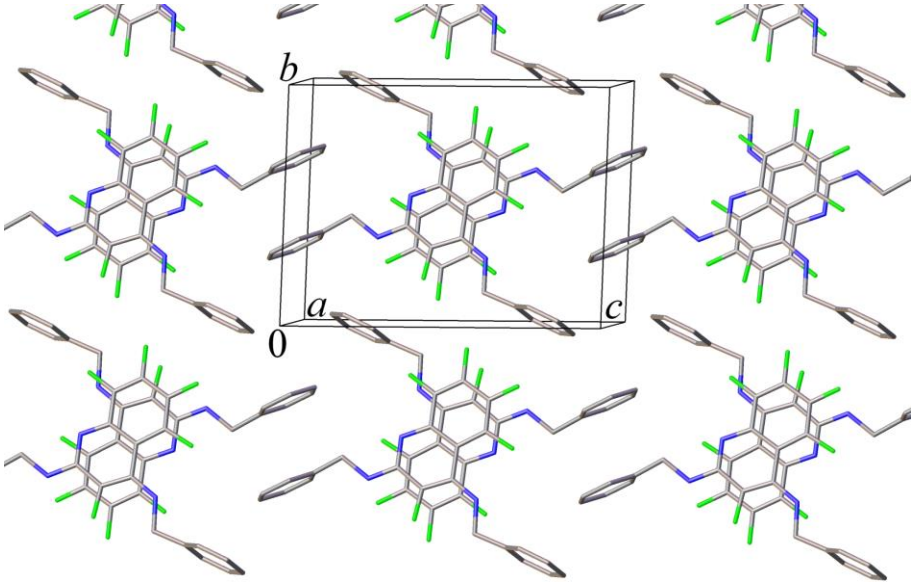


FIGURE 5. Crystal packing of **5**. Hydrogen atoms are omitted for clarity

The crystal packing of **3** and **6** (Figure 4) resemble those of arene-perfluoroarene co-crystals (molecular complexes) [20], comprising slanted stacks of alternating, nearly parallel (within 5.6° in **3** and 1.5° in **6**) hexafluoroquinoline (or -*iso*quinoline) and phenyl moieties, with practically uniform interplanar separations averaging 3.31 Å in **3** and 3.43 Å in **6**. The tighter stacking in **3**,

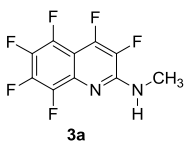
results in it having a higher overall density (by *ca* 1%), and a melting temperature 15°C higher than its isomer **6**.

It is noteworthy that individual, even sterically disparate, arenes and perfluoroarenes nearly always co-crystallise in a 1:1 ratio, such as exists (intramolecularly) in **3** and **6**. Compound **5**, however, which contains two arene groups for each perfluoroarene, adopts an entirely different packing motif (Figure 5) with effectively segregated components. Rigorously parallel quinoline moieties form a stack with near-uniform interplanar separations (3.28-3.29 Å), running parallel to the crystallographic *x* direction. Stacks are arrayed alongside one another in the *y* direction and, between them, segregated phenyl groups form layers parallel to the (0 0 1) plane. Within these layers, phenyl rings form contacts of both the offset face-to-face type (planes parallel, interplanar separation 3.42 Å) and the herringbone type (interplanar angles *ca.* 50°).

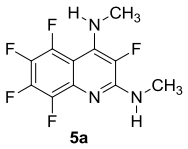
Consequently, with compounds **3**, **5** and **6** in hand and their structures unambiguously confirmed by X-ray crystallography, we were in a position to determine whether computations could be used for product identification by comparison of experimental and calculated NMR resonance data derived from optimised structural geometry calculations. To reduce computational efforts using the computationally-demanding *ab initio* MP2 method, optimised model geometries of structures **3a**, **5a** and **6a** - where each phenyl group was replaced with a hydrogen atom - were used to computationally model products **3**, **5** and **6** respectively. Selected parameters of structures obtained experimentally **3-6** with those obtained computationally **3a-6a** are listed in Tables 1 and 2 for comparison. The agreement between experimental and computed data for **3**, **5** and **6** in Tables 1 and 2 are excellent with differences of less than 0.02 Å in all bond lengths. The agreement in the intramolecular hydrogen-fluorine distances between **3**, **5**, **6** and **3a**, **5a** and **6a** respectively is also excellent. Consequently, these calculations confirm that the MP2-optimised model geometries **3a-8a** can effectively predict the geometries of **3-8** given the agreement between computational and experimental data sets.

TABLE 1. Comparison of observed (X-ray) bond distances in perfluoroquinolines **3** and **5** and calculated values for **3a** and **5a**

	3	**3a**	**5**	**5a**
N(1)-C(2)	1.321(2)	1.327	1.321(1)	1.325
N(1)-C(9)	1.364(2)	1.364	1.359(1)	1.362
C(2)-C(3)	1.431(2)	1.428	1.416(2)	1.418
C(3)-C(4)	1.352(2)	1.365	1.375(2)	1.380
C(4)-C(10)	1.420(2)	1.420	1.455(1)	1.446
C(10)-C(5)	1.407(2)	1.410	1.411(2)	1.413
C(5)-C(6)	1.362(2)	1.379	1.369(2)	1.379
C(6)-C(7)	1.398(2)	1.405	1.394(2)	1.402
C(7)-C(8)	1.368(2)	1.379	1.361(2)	1.378
C(8)-C(9)	1.407(2)	1.415	1.415(2)	1.416
C(9)-C(10)	1.422(2)	1.432	1.426(2)	1.434
C(2)-N(2)	1.350(2) [a]	1.356[a]	1.362(1) [a]	1.369 [b]
C(4)-N(3)			1.360(1) [a]	1.380 [b]
F(3)…H(2N)	2.30(3)[c]	2.33	2.27(2)[c]	2.26
F(5)…H(3N)			1.93(2)[c]	1.91



3a



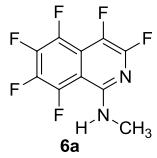
5a

[a] N atom planar [b] N atom pyramidal [c] N-H bond length corrected to 1.03 Å [13]

Table 2. Comparison of observed (X-ray) bond distances in perfluoroisoquinoline **6** and calculated values for **6a**.

	6	**6a**
C(1)-N(2)	1.324(2)	1.332
C(1)-C(9)	1.452(2)	1.446
N(2)-C(3)	1.324(2)	1.332
C(3)-C(4)	1.353(2)	1.372
C(4)-C(10)	1.411(2)	1.414
C(10)-C(5)	1.411(2)	1.415
C(5)-C(6)	1.361(2)	1.378
C(6)-C(7)	1.394(2)	1.404
C(7)-C(8)	1.364(2)	1.378
C(8)-C(9)	1.407(2)	1.410
C(9)-C(10)	1.427(2)	1.435

C(1)-N(1)	1.354(2)[a]	1.363[b]
F(8)…H(1N)	1.99(2)[c]	1.94

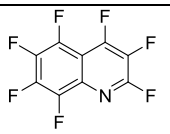
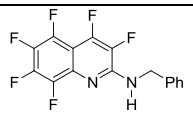
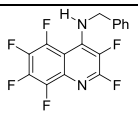
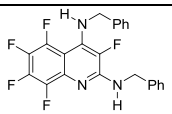


6a

[a] N atom planar [b] N atom pyramidal [c] N-H bond length corrected to 1.03 Å [13]

Observed and computed ^{19}F NMR shift data for the perfluoro-quinoline and *iso*quinoline derivatives **1-8** are collated in Tables 3 and 4. The MP2-optimised model geometries of **3a-8a** were used to calculate ^{19}F and ^{13}C GIAO-NMR chemical shifts for the corresponding phenyl derivatives **3-8**. Calculated ^{19}F NMR shifts with an error range between 4.9 and -4.7 ppm (within a range between *ca*. -70 and -170 ppm in ^{19}F NMR) suggest that these computations are accurate enough to aid ^{19}F NMR peak assignments and unambiguously determine structure identification. Resonance assignments, therefore, were based on calculated values of ^{19}F and ^{13}C NMR shifts and were further confirmed by the measurement of appropriate coupling constants such as *peri* J_{FF} and *ortho* J_{FF} being in the ranges of ca. 50-60 Hz and 15- 20 Hz respectively.

TABLE 3. Calculated and observed ^{19}F NMR chemical shifts for perfluoroquinoline derivatives

								
	1	**1**	**3a**	**3**	**4a**	**4**	**5a**	**5**
Resonance	Calc.	Observed	Calc.	Observed	Calc	Observed	Calc.	Observed
F-2	-72.5	-72.9	-	-	-82.3	-80.2	-	-
F-3	-163.4	-161.3	-166.7	-163.9	-168.2	-164.6	-165.9	-163.2
F-4	-124.0	-124.6	-138.8	-137.5		-		-
F-5	-146.6	-146.5	-149.6	-148.7	-152.4	-149.0	-152.2	-150.1
F-6	-155.5	-154.8	-166.0	-163.7	-164.4	-160.3	-169.6	-167.8
F-7	-152.0	-151.0	-157.6	-155.4	-158.6	-154.6	-160.3	-158.6
F-8	-148.2	-148.8	-156.5	-153.1	-148.4	-148.4	-153.7	-153.4

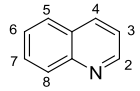
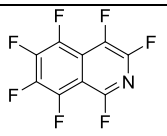
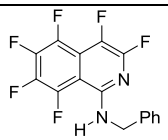
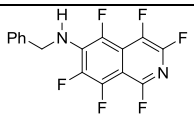
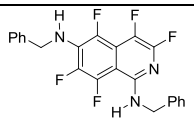
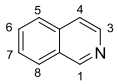


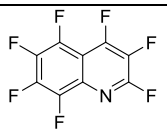
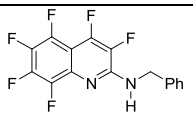
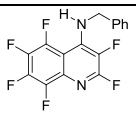
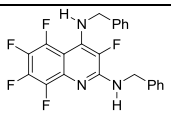
TABLE 4. Calculated and observed ^{19}F NMR chemical shifts for perfluoro*iso*quinoline derivatives

								
	2	**2**	**6a**	**6**	**7a**	**7**	**8a**	**8**
Resonance	Calc.	Observed	Calc.	Observed	Calc.	Observed	Calc.	Observed
F-1	-63.0	-62.1	-	-	-66.8	-65.6	-	-
F-3	-94.4	-96.8	-95.8	-96.4	-97.4	-99.9	-98.5	-101.3
F-4	-156.0	-155.7	-176.4	-172.3	-160.6	-159.3	-179.2	-175.6
F-5	-146.2	-145.9	-146.8	-146.8	-148.6	-147.2	-145.3	-147.7
F-6	-147.1	-145.4	-153.7	-150.6		-		-
F-7	-155.2	-153.1	-164.2	-159.3	-152.8	-150.5	-156.6	-156.8
F-8	-138.7	-139.9	-146.0	-143.0	-144.4	-144.2	-147.7	-148.2



Similarly, observed ^{13}C NMR resonances using ^{19}F-selective-decoupled ^{13}C NMR experiments and computed ^{13}C NMR shift data for perfluoro-quinoline and *iso*quinoline derivatives **1-8** are collated in Tables 5 and 6. The correlation between observed and computed ^{13}C NMR shifts, with an error range between 2.1 and -2.1 ppm (within a range between *ca*. 50 and 150 ppm in ^{13}C NMR), suggest that DFT calculations of ^{13}C NMR chemical shifts can be used with a high degree of confidence for reliable product identification of perfluoroheteroaromatic derivatives. Linear regression fits between observed and calculated NMR shifts gave R values of 0.998 for both ^{19}F and ^{13}C nuclei (Figure 4). Such a high correlation between observed and calculated results indicate that the computational NMR method used here is accurate.[7]

TABLE 5. Calculated and observed ^{13}C NMR chemical shifts for perfluoroquinoline derivatives

								
	1	**1**	**3a**	**3**	**4a**	**4**	**5a**	**5**
Resonance	Calc.	Observed	Calc.	Observed	Calc	Observed	Calc.	Observed
C-2	151.1	152.6	149.0	149.3	152.0	154.1	150.5	150.2
C-3	134.2	133.7	134.8	135.2	130.3	130.4	134.9	133.8
C-4	150.8	152.0	147.4	148.0	141.1	140.3	134.4	134.1
C-5	140.4	140.5	140.8	140.5	143.7	143.4	144.4	143.7
C-6	140.0	139.5	137.1	136.3	137.9	137.7	136.4	134.5
C-7	142.3	142.0	142.1	141.3	140.7	140.5	140.8	139.8
C-8	142.7	141.9	141.6	140.8	143.2	141.9	142.6	140.7
C-9	126.6	127.2	130.3	130.9	128.2	128.7	131.2	132.3
C-10	108.3	107.8	104.2	102.1	106.4	107.5	105.3	104.7

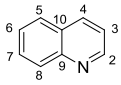
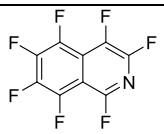
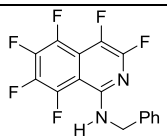
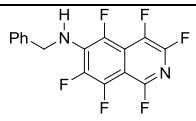
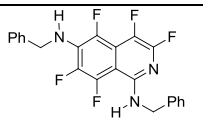
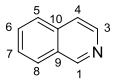


TABLE 6. Calculated and observed ^{13}C NMR chemical shifts for perfluoro*iso*quinoline derivatives

								
	2	**2**	**6a**	**6**	**7a**	**7**	**8a**	**8**
Resonance	Calc.	Observed	Calc.	Observed	Calc.	Observed	Calc.	Observed
C-1	148.5	149.6	148.5	148.1	148.7	149.9	148.6	147.9
C-3	145.6	145.0	148.5	148.2	145.8	144.7	148.6	147.7
C-4	135.6	135.3	128.9	128.5	134.6	133.5	128.1	127.2
C-5	140.8	141.0	141.1	141.2	138.4	137.8	140.4	139.4
C-6	143.0	143.4	141.5	141.7	130.8	131.2	130.4	129.0
C-7	139.3	139.3	137.0	137.4	139.6	140.2	139.8	138.6
C-8	142.7	142.3	144.7	144.2	142.1	141.8	145.7	144.2
C-9	104.5	104.2	101.6	103.2	101.3	103.2	99.6	98.5
C-10	118.0	119.8	118.3	119.3	119.2	119.7	117.6	118.5



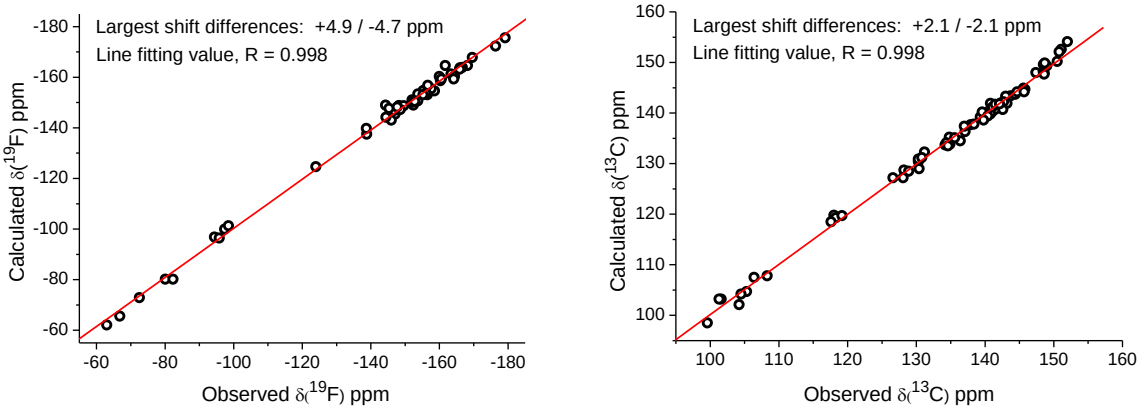


Figure 4. Plots of experimental ^{19}F and ^{13}C NMR shifts for **1-8** vs computed ^{19}F and ^{13}C GIAO-NMR shifts from optimised geometries.

The substitution pattern of minor monosubstituted *iso*quinoline derivative **7** could not be determined by X-ray crystallography. To establish its position of substitution, ^{19}F and ^{13}C GIAO-NMR data on optimised geometries of all possible isomers of the monosubstituted *iso*quinoline were compared with observed ^{19}F and ^{13}C NMR data for **7**. Table 7 lists the linear fit and major

shift error values between observed NMR data for **7** and computed GIAO-NMR data for all isomers. The computed shifts are assumed to be assigned in the same peak order as the observed peaks of **7**. It cn be predicted with some confidence, therefore, that compound **7** is the 6-isomer from the excellent R values and the smallest shift errors in both ^{19}F and ^{13}C NMR data. The ^{19}F and ^{13}C peak assignments determined by ^{19}F-^{19}F couplings, 2D ^{19}F-^{19}F COSY and $^{13}C\{^{19}F$ selective} spectra for **7** are in accord with the peak assignments of the 6-isomer by GIAO-NMR computations. As **6** is confirmed by X-ray crystallography as the 1-isomer and **7** confirmed by GIAO-NMR as the 6-isomer, the disubstituted derivative **8** must be the 1,6-isomer, thus ruling out the need to explore other isomers by computations to establish its identity.

TABLE 7. Best line-fit values, R, and largest shift errors between computed NMR chemical shifts for model monosubstituted perfluoro*iso*quinoline isomers and observed NMR shifts for **7**.

Position of substituent	R value ^{19}F	R value ^{13}C	Largest error (ppm) ^{19}F	Largest error (ppm) ^{13}C
1-	0.913	0.990	46.1	3.8
3-	0.920	0.992	40.1	4.1
4-	0.974	0.977	13.1	4.8
5-	0.999	0.983	6.0	5.0
6-	0.999	0.998	2.5	1.9
7-	0.995	0.978	4.7	5.1
8-	0.997	0.990	5.3	5.1

3. Conclusions

Reaction of perfluoroquinoline **1** with benzylamine gave a mixture of 2- and 4-monosubstituted quinolines and 2,4-disubstituted quinoline was obtained upon reaction with excess benzylamine. Perfluoro*iso*quinoline **2** gave a mixture of 1- and 6-substituted *iso*quinolines upon reaction with benzylamine and a 1,6-disubstituted *iso*quinoline was isolated upon reaction with neat benzylamine. X-ray structural analysis was used to unambiguously identify products **3**, **5** and **6**. Optimised model

geometries of these compounds at MP2/6-31G* were in very good agreement with available X-ray crystallographic data and used to compute ^{19}F and ^{13}C GIAO-NMR shifts of **3 - 8**. Computed ^{19}F and ^{13}C GIAO-NMR shifts were compared with observed ^{19}F and ^{13}C NMR shifts for **1** – **8** and we find that the correlations between experimental and calculated NMR shifts are excellent, indicating that ^{19}F and ^{13}C GIAO-NMR computations are powerful tools in identifying polyfunctional, polycyclic perfluoroheteroaromatic compounds and aiding NMR resonance assignment.

4. Experimental

4.1. General

Perfluoroquinoline **1** and perfluoro*iso*quinoline **2** were synthesised following literature methods.[11] Other materials were obtained commercially (Aldrich, Lancaster or Fluorochem). Proton, carbon and fluorine nuclear magnetic resonance spectra (^1H NMR, ^{13}C NMR and ^{19}F NMR) were recorded on a Varian Inova–500 (^1H NMR, 500 MHz; ^{13}C NMR, 126 MHz; ^{19}F NMR, 470 MHz) or a Varian DD–700 (^1H NMR, 700 MHz; ^{13}C NMR, 176 MHz; ^{19}F NMR, 658 MHz) spectrometer with solvent resonance as the internal standard (^1H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.36 ppm, $(CD_3)_2SO$ at 40.17 ppm; ^{19}F NMR, $CFCl_3$ at 0.00 ppm). ^1H, ^{13}C and ^{19}F spectroscopic data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and assignment. Mass spectra were recorded on a Fisons VG-Trio 1000 Spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph using a 25m HP1 (methyl-silicone) column. Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser. Melting points were recorded at atmospheric pressure and are uncorrected. Column chromatography was carried out on silica gel (Merck no. 109385, particle size 0.040-0.063 mm) and TLC analysis was performed on silica gel TLC plates (Merck).

Perfluoroquinoline **1;** δ_F -72.9 (dd, $^3J_{F2,F3}$ 26.4, $^4J_{F2,F4}$ 26.4, F-2), -124.6 (ddd, $^3J_{F4,F5}$ 47.6, $^4J_{F2,F4}$ 26.3, $^3J_{F3,F4}$ 14.5, F-4), -146.5 (ddd, $^4J_{F4,F5}$ 46.7, $^3J_{F5,F6}$ 15.4, $^5J_{F5,F8}$ 15.4, F-5), -148.8 (dd, $^5J_{F5,F8}$ 16.5, $^3J_{F7,F8}$ 16.5, F-8), -151.0 (ddd, $^3J_{F6,F7}$ 19.2, $^3J_{F7,F8}$ 19.2, $^7J_{F3,F7}$ 7.3, F-7), -154.8 (dd, $^3J_{F5,F6}$ 18.8, $^3J_{F6,F7}$ 18.8, F-6), -161.3 (ddd, $^3J_{F2,F3}$ 26.4, $^3J_{F3,F4}$ 14.5, $^7J_{F3,F7}$ 7.3, F-3)**;** δ_C 107.8 (dd, $^2J_{CF}$ 9.7, $^2J_{CF}$ 9.7, C-10), 127.2 (dd, $^2J_{CF}$ 18.7, $^2J_{CF}$ 13.3, C-9), 133.7 (ddd, $^1J_{CF}$ 268.4, $^2J_{CF}$ 34.9, $^2J_{CF}$ 11.6, C-3), 139.5 (ddd, $^1J_{CF}$ 256.5, $^2J_{CF}$ 14.5, $^2J_{CF}$ 14.5, C-6), 140.5 (dm, $^1J_{CF}$ 258.0, C-5), 141.9 (dd, $^1J_{CF}$ 258.9, $^2J_{CF}$ 14.5, C-8), 142.0 (ddd, $^1J_{CF}$ 259.4, $^2J_{CF}$ 14.8, $^2J_{CF}$ 14.5, C-7), 152.0 (dm, $^1J_{CF}$ 276.6, C-4), 152.6 (dd, $^1J_{CF}$ 249.6, $^2J_{CF}$ 14.8, C-2).

Perfluoro*iso*quinoline **2;** δ_F -62.1 (ddd, $^4J_{F1,F8}$ 63.3, $^5J_{F1,F4}$ 33.9, $^4J_{F1,F3}$ 11.3, F-1), -96.8 (s, F-3), -139.9 (dm, $^4J_{F1,F8}$ 60.9, F-8), -145.4 (m, F-6), -145.9 (ddd, $^4J_{F4,F5}$ 47.4, $^3J_{F5,F6}$ 18.0, $^5J_{F5,F8}$ 18.0, F-5), -153.1 (dd, $^3J_{F6,F7}$ 18.0, $^3J_{F7,F8}$ 18.0, F-7), -155.7 (ddd, $^4J_{F4,F5}$ 47.4, $^5J_{F1,F4}$ 33.9, F-4); δ_C 104.2 (dd, $^2J_{CF}$ 30.7, $^2J_{CF}$ 12.4, C-9), 119.8 (dd, $^2J_{CF}$ 11.0, $^2J_{CF}$ 11.0, C-10), 135.3 (dd, $^1J_{CF}$ 259.1, $^2J_{CF}$ 27.1, C-4), 139.3 (ddd, $^1J_{CF}$ 258.4, $^2J_{CF}$ 15.3, $^2J_{CF}$ 15.3, C-7), 141.0 (dm, $^1J_{CF}$ 259.9, C-5), 142.3 (dm, $^1J_{CF}$ 270.0, C-8), 143.4 (ddd, $^1J_{CF}$ 263.4, $^2J_{CF}$ 14.6, $^2J_{CF}$ 14.6, C-6), 145.0 (ddd, $^1J_{CF}$ 243.7, $^2J_{CF}$ 15.0, $^2J_{CF}$ 15.0, C-3), 149.6 (dm, $^1J_{CF}$ 254.7, C-1).

4.2. Reactions of perfluoroquinoline with benzylamine

a) With two equivalents of benzylamine

A mixture consisting of perfluoroquinoline **1** (1.00 g, 3.92 mmol), benzylamine (0.86 mL, 7.88 mmol) and THF (20 mL) was heated at reflux temperature for 4 h. The solution was allowed to cool and water (20 mL) and DCM (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with DCM (2 x 20 mL) and ethyl acetate (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. Column chromatography on silica gel using hexane : DCM (2:1) as elutant gave *N-benzyl-3,4,5,6,7,8-hexafluoroquinolin-2-amine* **3** (0.60 g, 44%) as white crystals; mp 114-115 ^oC (Found: C, 56.4; H, 2.7; N, 8.6. $C_{16}H_8F_6N_2$

requires: C, 56.2; H, 2.4; N, 8.2%); δ_H 4.68 (2H, d, $^3J_{HH}$ 5.8, CH_2), 5.44 (1H, br s, NH), 7.19 – 7.32 (5H, m, ArH); δ_F -137.5 (1F, dd, $^4J_{F4,F5}$ 46.2, $^3J_{F3,F4}$ 15.4, F-4), -148.7 (1F, ddd, $^4J_{F4,F5}$ 46.4, $^3J_{F5,F6}$ 20.8, $^5J_{F5,F8}$ 15.8, F-5), -153.1 (1F, dd, $^3J_{F7,F8}$ 17.8, $^5J_{F5,F8}$ 17.8, F-8), -155.4 (1F, ddd, $^3J_{F6,F7}$ 20.5, $^3J_{F7,F8}$ 20.5, $^7J_{F3,F7}$ 6.2, F-7), -163.7 (1F, dd, $^3J_{F5,F6}$ 20.6, $^3J_{F6,F7}$ 20.6, F-6), -163.9 (1F, s, F-3); δ_C 45.3 (s, CH_2), 102.1 (dd, $^2J_{CF}$ 7.0, $^2J_{CF}$ 7.0, C-10), 127.9 (s, C-2'), 128.3 (s, C-4'), 128.8 (s, C-3'), 130.9 (d, $^2J_{CF}$ 7.2, C-9), 135.2 (dd, $^1J_{CF}$ 259.0, $^2J_{CF}$ 12.6, C-3), 136.3 (ddd, $^1J_{CF}$ 245.6, $^2J_{CF}$ 15.3, $^2J_{CF}$ 15.3, C-6), 137.8 (s, C-1'), 140.5 (dm, $^1J_{CF}$ 253.2, C-5), 140.8 (dd, $^1J_{CF}$ 258.1, $^2J_{CF}$ 55.3, C-8), 141.3 (ddd, $^1J_{CF}$ 251.4, $^2J_{CF}$ 14.2, $^2J_{CF}$ 14.2, C-7), 148.0 (dm, $^1J_{CF}$ 267.5, C-4), 149.3 (dd, $^2J_{CF}$ 11.7, $^3J_{CF}$ 3.5, C-2); *m/z* (EI^+) 342 ($[M]^+$, 8%), 263 (8), 236 (5), 224 (14), 186 (8), 106 (20, $[NHCH_2Ph]^+$), 91 (100, $[CH_2Ph]^+$), 77 (26); and, *N-benzyl-2,3,5,6,7,8-hexafluoroquinolin-4-amine* **4** (0.44 g, 32 %) as a cream solid; mp 113-115 ^oC (Found: C, 56.4; H, 2.5; N, 8.2. $C_{16}H_8F_6N_2$ requires: C, 56.2; H, 2.4; N, 8.2%); δ_H 4.76 (2H, d, $^3J_{HH}$ 4.8, NH*CH*$_2$), 6.16 (1H, d, $^3J_{HF}$ 18.8, *NH*CH_2), 7.24 – 7.34 (5H, m, Ar-H); δ_F -80.2 (1F, d, $^3J_{F2,F3}$ 27.5, F-2), -148.4 (1F, dd, $^3J_{F7,F8}$ 20.5, $^5J_{F5,F8}$ 15.5, F-8), -149.0 (1F, dd, $^5J_{F5,F8}$ 15.8, $^3J_{F5,F6}$ 15.8, F-5), -154.6 (1F, ddd, $^3J_{F6,F7}$ 20.9, $^3J_{F7,F8}$ 20.9, $^7J_{F3,F7}$ 5.6, F-7), -160.3 (1F, ddd, $^3J_{F5,F6}$ 20.9, $^3J_{F6,F7}$ 20.9, $^7J_{F2,F6}$ 4.7, F-6), -164.6 (1F, d, $^3J_{F2,F3}$ 28.2, F-3); δ_C 50.0 (d, $^3J_{CF}$ 11.0, CH_2), 107.5 (s, C-10), 127.4 (s, C-2'), 128.2 (s, C-4'), 128.7 (d, $^2J_{CF}$ 24.8, C-9), 129.1 (s, C-3'), 130.4 (dd, $^1J_{CF}$ 245.7, $^2J_{CF}$ 31.0, C-3), 137.6 (s, C-1'), 137.7 (ddd, $^1J_{CF}$ 254.0, $^2J_{CF}$ 16.3, $^2J_{CF}$ 16.3, C-6), 140.3 (s, C-4), 140.5 (dm, $^1J_{CF}$ 265.4, C-7), 141.9 (dm, $^1J_{CF}$ 252.4, C-8), 143.4 (dd, $^1J_{CF}$ 244.5, $^2J_{CF}$ 16.3, C-5), 154.1 (dd, $^1J_{CF}$ 237.4, $^2J_{CF}$ 15.5, C-2); *m/z* (EI^+) 342 ($[M]^+$, 49%), 224 (32), 186 (24), 91 ($[CH_2Ph]^+$, 100), 77 (20).

b) With excess benzylamine

Perfluoroquinoline **1** (1.27 g, 5 mmol) and benzylamine (30 mL) were stirred together for 3 h at rt. The reaction mixture was poured into water (400 mL) and filtered through celite. The celite was washed with water and then washed with DCM (3 x 20 mL). The organic extracts were dried ($MgSO_4$) and evaporated to leave a viscous brown oil. Column chromatography on silica gel using

hexane : DCM (2:1) as elutant and recrystallisation from acetonitrile gave *N^2,N^4-dibenzyl-3,5,6,7,8-pentafluoroquinolin-2,4-diamine* **5** (1.89 g, 88%) as a white solid; mp 145 ^{o}C (Found: C, 64.0; H, 3.8; N, 9.6. $C_{23}H_{16}F_5N_3$ requires: C, 64.3; H, 3.8; N, 9.8 %); υ_{max} (KBr)/cm^{-1} 3487, 3426, 3031, 2892, 1663, 1631, 1543, 1506, 1491; δ_H 4.61 (2H, dd, *J* 3.8, *J* 3.8, CH_2), 4.66 (2H, d, *J* 5.6, CH_2), 5.14 (1H, q, *J* 2.8, NH), 5.58 (1H, dt, $^5J_{HF}$ 18.4, NH), 7.32 - 7.19 (10H, m, ArH); δ_F -150.1 (dd, $^3J_{F5,F6}$ 18.1, $^5J_{F5,F8}$ 15.8, F-5), -153.4 (dd, $^3J_{F7,F8}$ 19.0, $^5J_{F5,F8}$ 11.9, F-8), -158.6 (ddd, $^3J_{F6,F7}$ 20.3, $^3J_{F7,F8}$ 20.3, $^7J_{F3,F7}$, 4.5, F-7), -163.2 (s, F-3), -167.8 (dd, $^3J_{F5,F6}$ 21.4, $^3J_{F6,F7}$ 21.4, F-6); δ_C (d_6-dmso) 44.9 (s, CH_2), 50.0 (d, $^4J_{CF}$ 10.6, CH_2), 104.7 (s, C-10), 127.1 (s, C-2'), 127.2 (s, C-4'), 127.4 (s, C-4''), 128.3 (s, C-2''), 128.7 (s, C-3'), 129.0 (s, C-3''), 132.3 (d, $^2J_{CF}$ 8.8, C-9), 133.8 (d, $^1J_{CF}$ 244.5, C-3), 134.1 (s, C-4), 134.5 (ddd, $^1J_{CF}$ 240.7, $^2J_{CF}$ 15.8, $^2J_{CF}$ 15.8, C-6), 139.8 (ddd, $^1J_{CF}$ 249.3, $^2J_{CF}$ 12.8, $^2J_{CF}$ 12.8, C-7), 140.7 (d, $^1J_{CF}$ 239.3, C-8), 140.8 (s, C-1'), 141.0 (s, C-1''), 143.7 (d, $^1J_{CF}$ 256.0, C-5), 150.2 (d, $^2J_{CF}$ 13.4, C-2); *m/z* (ASAP) 429 ([M]$^+$, 100%).

4.3 Reactions of perfluoro*iso*quinoline with benzylamine

a) With two equivalents of benzylamine

A mixture consisting of perfluoroisoquinoline **2** (1.00 g, 3.92 mmol), benzylamine (0.8 mL, 7.32 mmol) and THF (30 mL) was heated at reflux temperature for 4 h. After cooling, water (20 mL) and DCM (10 mL) were added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 10mL) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield a crude cream solid (1.04g) containing **6** and **7** in the ratio of 6:1 by ^{19}F NMR analysis. Column chromatography using hexane and DCM (1:1) as elutant gave *N-benzyl-3,4,5,6,7,8-hexafluoroisoquinolin-1-amine* **6** (0.60 g, 45%) as white crystals; mp 99-100 ^{o}C (Found: C, 56.2; H, 2.3; N, 8.3. $C_{16}H_8N_2F_6$ requires: C, 56.2; H, 2.4; N, 8.2%); δ_H 4.72 (2H, dd, $^3J_{HH}$ 5.2, $^4J_{HF}$ 1.5, CH_2), 6.52 (1H, br d, $^5J_{HF}$ 16.1, NH), 7.14 - 7.31 (5H, m, ArH); δ_F -96.4 (1F, d, $^3J_{F3,F4}$ 21.8, F-3), -143.0 (1F, dd, $^3J_{F7,F8}$ 19.7, $^5J_{F5,F8}$ 15.3, F-8), -146.8 (1F, ddd, $^4J_{F4,F5}$ 50.7, $^3J_{F5,F6}$ 19.1, $^5J_{F5,F8}$ 14.6, F-5), -150.6 (1F, dd, $^3J_{F5,F6}$ 20.1, $^3J_{F6,F7}$ 20.1, F-6), -159.3 (1F, ddd, $^3J_{F6,F7}$ 21.1,

$^{3}J_{F7,F8}$ 21.1, $^{7}J_{F3,F7}$ 5.8, F-7), -172.3 (1F, dd, $^{4}J_{F4,F5}$ 51.3, $^{3}J_{F3,F4}$ 21.9, F-4); δ_C 46.4 (s, CH_2), 103.2 (dd, $^{2}J_{CF}$ 9.9, $^{3}J_{CF}$ 2.5, C-9), 119.3 (m, C-10), 128.0 (s, C-2'), 128.2 (s, C-4'), 128.5 (dd, $^{1}J_{CF}$ 249.7, $^{2}J_{CF}$ 28.4, C-4), 129.1 (s, C-3'), 137.4 (ddd, $^{1}J_{CF}$ 256.1, $^{2}J_{CF}$ 19.9, $^{2}J_{CF}$ 19.9, C-7), 137.9 (s, C-1'), 141.2 (dm, $^{1}J_{CF}$ 258.1, C-5), 141.7 (dm, $^{1}J_{CF}$ 257.1, C-6), 144.2 (dd, $^{1}J_{CF}$ 248.1, $^{2}J_{CF}$ 17.9, C-8), 148.1 (dm, $^{3}J_{CF}$ 18.3, C-1),148.2 (dd, $^{1}J_{CF}$ 237.2, $^{2}J_{CF}$ 13.5, C-3); *m/z* (EI^+) 342 ($[M]^+$, 46%), 236 (32), 224 (26), 186 (33), 91 ($[CH_2Ph]^+$, 100); and, *N-benzyl-1,3,4,5,7,8-hexafluoroisoquinolin-6-amine* **7** (0.11g, 8%) as a cream solid; δ_H 4.68 (3H, m, NH, CH_2), 7.22 – 7.32 (5H, m, ArH); δ_F -65.6 (1F, ddd, $^{4}J_{F1,F8}$ 58.6, $^{5}J_{F1,F4}$ 30.6, $^{5}J_{F1,F5}$ 11.8, F-1), -99.9 (1F, m, F-3), -144.2 (1F, ddd, $^{4}J_{F1,F8}$ 58.7, $^{5}J_{F5,F8}$ 16.0, $^{5}J_{F4,F8}$ 16.0, F-8), -147.2 (1F, ddd, $^{4}J_{F4,F5}$ 51.3, $^{5}J_{F5,F8}$ 11.1, $^{5}J_{F1,F5}$ 11.1, F-5), -150.5 (1F, m, F-7), -159.3 (1F, ddd, $^{4}J_{F4,F5}$ 51.3, $^{5}J_{F1,F4}$ 30.6, $^{3}J_{F3,F4}$ 15.5, F-4); δ_C 49.3 (s, CH_2), 103.2 (m, C-9), 119.7 (m, C-10), 127.7 (s, C-4'), 128.2 (s, C-2'), 129.2 (s, C-3'), 131.2 (m, C-6), 133.5 (dd, $^{1}J_{CF}$ 259, $^{2}J_{CF}$ 27, C-4), 137.8 (dm, $^{1}J_{CF}$ 243, C-7), 137.9 (s, C-1'), 140.2 (dm, $^{1}J_{CF}$ 253, C-8), 141.8 (dm, $^{1}J_{CF}$ 260, C-5), 144.7 (ddd, $^{1}J_{CF}$ 257.1, $^{3}J_{CF}$ 16, $^{2}J_{CF}$ 16, C-3), 149.9 (dm, $^{1}J_{CF}$ 265, C-1); *m/z* (ASAP) 342 ($[M]^+$, 100%).

b) With excess benzylamine

Perfluoro*iso*quinoline **1** (1.27 g, 5 mmol) and benzylamine (30 mL) were stirred together for 3 h at rt. The reaction mixture was poured into water (400 mL) and filtered through celite. The celite was washed with water and DCM (3 x 20 mL). The organic extracts were dried ($MgSO_4$) and evaporated to leave a viscous brown oil. Column chromatography on silica gel using hexane : DCM (2:1) as elutant and recrystallisation from ethanol gave *N^1,N^6-dibenzyl-3,4,5,7,8-pentafluoroisoquinolin-1,6-diamine* **8** (1.83 g, 85%) as a white solid; mp 97 – 98 ^{o}C (Found: C, 64.3; H, 3.8; N, 9.8. $C_{23}H_{16}F_5N_3$ requires: C, 64.3; H, 3.8; N, 9.8 %); υ_{max} (KBr)/cm^{-1} 3487, 3393, 3028, 1653, 1545, 1525; δ_H 4.50 (1H, br s, NH), 4.68 (2H, s, CH_2), 4.69 (2H, s, CH_2), 6.29 (1H, br s, NH), 7.40 - 7.29 (10H, m, ArH); δ_F -101.3 (d, $^{3}J_{F3,F4}$ 22.4, F-3), -147.7 (d, $^{4}J_{F4,F5}$ 55.7, F-5), -148.2 (dd, $^{3}J_{F7,F8}$ 15.6, $^{5}J_{F5,F8}$ 11.0, F-8), -156.8 (d, $^{3}J_{F7,F8}$ 15.6, F-7), -175.6 (dd, $^{4}J_{F4,F5}$ 55.7, $^{3}J_{F3,F4}$

22.4, F-4); δ_C 45.9 (s, CH_2), 49.5 (s, CH_2), 98.5 (dd, $^2J_{CF}$ 10.6, $^3J_{CF}$ 4.3, C-9), 118.5 (dd, $^2J_{CF}$ 8.7, $^2J_{CF}$ 8.0, C-10), 127.2 (dd, $^1J_{CF}$ 247.5, $^2J_{CF}$ 27.8, C-4), 127.4 (s, C-2',2''), 127.7 (s, C-4',4''), 129.0 (s, C-3'), 129.1 (s, C-3''), 129.0 (dd, $^2J_{CF}$ 1.6, $^2J_{CF}$ 1.3, C-6), 138.2 (s, C-1'), 138.8 (s, C-1''), 138.6 (dd, $^1J_{CF}$ 244.0, $^2J_{CF}$ 12.9, C-7), 139.4 (dm, $^1J_{CF}$ 210.5, C-5), 144.2 (dd, $^1J_{CF}$ 242.7, $^2J_{CF}$ 13.3, C-8), 147.7 (dd, $^1J_{CF}$ 228.6, $^2J_{CF}$ 15.7, C-3), 147.9 (d, $^3J_{CF}$ 18.7, C-1) ; *m/z* (ASAP) 429 ($[M]^+$, 100%).

4.5 X-ray Crystallography

Crystals of X-ray quality were obtained by slow evaporation of DCM solution of **3** or acetonitrile solution of **5,** and by slow diffusion of hexane into DCM solution of **6**. Single-crystal X-ray diffraction experiments (Table 8) were carried out on Bruker 3-circle diffractometers with CCD area detectors SMART 6000 (for **3** and **6**) or APEX ProteumM (for **5**), using graphite-monochromated Mo-K_α radiation ($\bar{\lambda}$ =0.71073 Å) from a sealed tube (**3**, **6**) or a 60W Mo-target microfocus Bede Microsource® X-ray generator with glass polycapillary X-ray optics (**5**). Crystals were cooled to T=120 K using Cryostream (Oxford Cryosystems) open-flow N_2 gas cryostats. The structures were solved by direct methods and refined by full-matrix least squares against F^2 of all reflections, using SHELXTL 6.12 software [21]. In **3** and **6**, all H atoms were refined in isotropic approximation, in **5** only the amino ones, the rest were treated as 'riding' on the corresponding C atoms.

TABLE 8. Crystal data (T=120 K)

Compound	**3**	**5**	**6**
CCDC dep. no.	925722	925723	925724
Formula	$C_{16}H_8F_6N_2$	$C_{23}H_{16}F_5N_3$	$C_{16}H_8F_6N_2$
Formula weight	342.24	439.17	343.05
Symmetry	orthorhombic	triclinic	monoclinic
Space group (no.)	$P2_12_12_1$ (# 19)	P-1 (# 2)	$P2_1/n$ (# 14)
a, Å	6.2269(5)	7.3099(4)	7.8499(1)
b, Å	8.4363(6)	10.2092(5)	12.3591(2)

c, Å	25.859(2)	15.5910(7)	14.4314(2)
α, °	90	88.943(3)	90
β, °	90	83.130(3)	101.913(1)
γ, °	90	72.420(3)	90
V, Å^3	1358.4(2)	930.48(14)	1369.95(3)
Z	4	2	4
D_x, g cm^{-3}	1.673	1.533	1.659
μ, mm^{-1}	0.16	0.13	0.16
Refls collected	18588	12510	13055
Unique refls	2298, 2178[a,b]	5395, 4126[a]	3135, 2623 [a]
R_{int}, %	2.3	6.2	2.2
$R(F)^a$, w$R(F^2)$, %	3.0, 8.9	4.5, 12.1	3.8, 11.5

[a]Reflections with $I>2\sigma(I)$, [b] Friedel equivalents merged

4.6 Computations

All *ab initio*/DFT computations were carried out using the Gaussian 09 package.[22] The geometries of **1**, **2** and **3a-8a** were optimised at the *ab initio* MP2 method with a 6-31G* basis set. The GIAO-NMR shifts were calculated at the DFT hybrid B3LYP/6-311G* from MP2-optimised geometries. Computed ^{19}F chemical shifts at the GIAO-B3LYP/6-311G*// MP2/6-31G* level were converted to the usual $CFCl_3$ scale: $\delta(^{19}F) = 145.0 - 0.9\sigma(^{19}F)$ and ^{13}C NMR shifts were referenced to TMS: $\delta(^{13}C) = 169.0 - 0.85\sigma(^{13}C)$.

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