Accepted Manuscript

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PII: S0040-4020(17)30039-X

DOI: 10.1016/j.tet.2017.01.026

Reference: TET 28396

To appear in: *Tetrahedron*

Received Date: 1 September 2016

Revised Date: 29 December 2016

Accepted Date: 9 January 2017

Please cite this article as: Skolyapova AD, Selivanova GA, Tretyakov EV, Bogdanova TF, Shchegoleva LN, Bagryanskaya IY, Gurskaya LY, Shteingarts VD, Interaction of polyfluorinated 2-chloroquinolines with ammonia, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.01.026.

Tetrahedron
journal homepage: www.elsevier.com

Interaction of polyfluorinated 2-chloroquinolines with ammonia

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Polyfluorinated 2-chloroquinolines
Nucleophilic substitution
Ammonia
Polyfluorinated aminoquinolines
DFT calculations

ABSTRACT

We have studied the interaction of polyfluorinated (in the benzene moiety) 2-chloroquinolines with liquid and aqueous ammonia as an approach to the synthesis of halogen-containing aminoquinolines. 5,7-Difluoro-, 5,6,8-trifluoro-, and 5,7,8-trifluoro-2-chloroquinolines mostly form products of substitution of the Cl atom, whereas 5,7-difluoro-2,6-dichloroquinoline, 5,6,7,8-tetrafluoro-, and 6,7-difluoro-2-chloroquinolines yield products of substitution of an F atom at various positions. The replacement of liquid ammonia with aqueous causes an increase in the proportion of the products of aminodechlorination relative to the products of aminodefluorination. For 2-chloro-6,8-difluoroquinoline this replacement leads to 2-amino-6,8-difluoroquinoline as the main product instead of the 8-amino-derivative. Activation energy values estimated by DFT calculations for the reactions in question agree with the reaction regioselectivity observed experimentally.

1. Introduction

Compounds containing the quinoline core possess a broad range of biological activities and are widely used in pharmacology.[1] Fluorinated quinolines are of special interest,[1,2] because the presence of several fluorine atoms in a quinolone – in addition to its possible specific effects on bioactivity[3] – makes functionalization of the benzene moiety considerably easier and potentially more diverse.[4] Substituted quinolines are also known to easily form chelate complexes with Zn and Al cations; these complexes show enhanced fluorescence as compared with the quinolines themselves.[5] The use of fluorinated quinolines may shed light on the fundamental relationship between the number and location of fluorine atoms in the benzene ring, and on the complexation reaction with metal ions as well as physical properties of the metal complexes.

Until recently, the polyfluorinated quinolines were a group of compounds that were difficult to obtain. Fortunately, convenient methods of selective hydrodehalogenation of perfluoroarenes (and particularly *ortho*-hydrodefluorination of readily available *N*-acetylpolyfluoroarylamines using zinc in aqueous ammonia) were developed recently.[6] The same method was also applied to selective hydrodechlorination of polyfluorochloroarylamines without their prior transformation into *N*-acetyl derivatives.[7] This approach provided a relatively simple route for the synthesis of a broad family of 2-chloroquinolines polyfluorinated on the benzene moiety.[8]

The amino group is one of the functional groups that is promising in terms of the development of methods for more profound functionalization of polyfluorinated quinolines. This can explain the emergence of relatively novel studies devoted to the development of methods for introduction of an amino group into polyfluoroquinolines. In particular, the interaction of polyfluorinated quinolines with uncharged nitrogen-centered nucleophiles was shown to lead to substitution of a fluorine atom in the benzene ring,[9] whereas charged nitrogen-centered nucleophiles are added to the pyridine moiety.[10] The reaction of the perfluorinated quinoline with benzylamine was found to yield substitution products of the fluorine atom at position 2 or 4.[11] Regarding previous research on fluorinated quinolines containing a Cl atom at position 2, in the reactions with nitrogen-centered nucleophiles (ethylamine, acetamide, and piperazine) only monofluoroderivatives were studied. They undergo aminodechlorination exclusively, forming the corresponding 2-aminoquinolines.[12] With 2-chloroquinolines containing two or more fluorine atoms in the benzene ring, the ratio of the rates of substitution of fluorine and chlorine atoms may start favoring the process of aminodefluorination, which can lead to useful (in

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terms of synthesis) functionalization of the benzene moiety. Here we studied the interaction of 5,6,7,8-tetrafluoro- (**1a**), 5,6,7-trifluoro- (**1b**), 5,7,8-trifluoro- (**1c**), 5,7-difluoro- (**1d**), 6,7-difluoro- (**1e**), and 6,8-difluoro- (**1f**) 2-chloroquinolines and 2,6-dichloro-5,7-difluoroquinoline (**1g**) with aqueous or liquid ammonia in order to determine the dependence of the orientation of aminodehalogenation on reaction conditions and on the number and positions of fluorine atoms in the substrate. Starting materials **1a-1g** were synthesized by literature methods,[8] from polyfluoroanilines obtained as described in supporting information. The new 3,4-difluoroanilide of cinnamic acid (**1ea**), 6,7-difluoroquinolin-2-one (**1eb**), 4-chloro-3,5-difluoroanilide of cinnamic acid (**1ga**), 6-chloro-5,7-difluoroquinolin-2-one (**1gb**), 6,8-difluoroquinolin-2-one (**1fb**), and the known 2,4-difluoroanilide of cinnamic acid (**1fa**) described in the experimental section were obtained as reaction intermediates in the synthesis of **1e-1g**.

2. Result and discussion

2.1. Reactions with liquid ammonia

The reaction of quinoline **1a** with liquid ammonia at 70 °C in a steel autoclave leads to a substitution of both the chlorine atom and fluorine atom resulting in formation of 2-amino-5,6,7,8-tetrafluoroquinoline (**2**), 6-amino-2-chloro-5,7,8-trifluoro- (**3**), and 7-amino-2-chloro-5,6,8-trifluoroquinoline (**4**) in the ratio 1:1:12, respectively (Table 1, entry 1).

Aminoquinolines **3** (5%) and **4** (65%) are new compounds. Quinoline **2** (5%) was obtained earlier via the interaction of 5,6,7,8-tetrafluoroquinoline with potassium amide (11%).[10]

The predominance of aminodefluorination over aminodechlorination, characterized by $\Omega \approx 0.1$, where Ω is a molar ratio of aminodechlorination product to aminodefluorination products, points to a stronger activating effect of the four fluorine atoms relative to the nitrogen of the heterocycle. Aminodefluorination of **1a** is realized at position 7 (6-NH_2/7-NH_2 ≈ 1:11) and is consistent with orientation of the substitution of a fluorine atom in 5,6,7,8-tetrafluoroquinoline under the influence of either liquid or aqueous ammonia (6-NH_2/7-NH_2 = 1:5 and 1:4 respectively).[9] The observed regioselectivity is the result, on the one hand, of the influence of atoms F(5) and F(8), which deactivate each other but at the same time activate atoms F(6) and F(7), and on the other hand, of the –M-effect of the N atom of the heterocycle.

Assuming that the presence of *para*-arranged fluorine atoms may determine the direction of aminodehalogenation, we introduced into the reaction compounds **1b** and **1c** lacking a fluorine atom either at position 6 or 7. In both cases, products of aminodechlorination [2-amino-5,6,8-trifluoroquinoline (**5**) and 2-amino-5,7,8-trifluoroquinoline (**7**), respectively] turn out to be the main products, whereas the products of aminodefluorination [6-amino-2-chloro-5,8-difluoroquinoline (**6**) and 7-amino-2-chloro-5,8-difluoroquinoline (**8**)] are formed in small amounts: for **1b** $\Omega \approx 49.0$, for **1c** $\Omega \approx 11.2$ (Table 1, entries 2 and 3). It should be noted that orientation of aminodefluorination **1b** and **1c** is in agreement with the results of ammonolysis of 5,6,8-trifluoro- and 5,7,8-trifluoroquinolines by aqueous ammonia.[9]

Only quinoline **7** (55%) was previously known and obtained with the yield of 12% by the interaction of 5,7,8-trifluoroquinoline with potassium amide.[10] The other aminoquinolines, **5** (70%), and **8** (11%), were obtained for the first time. Ammonolysis of trifluoroquinolines **1b** and **1c** by liquid ammonia is somewhat more difficult than that of tetrafluoroquinoline **1a** but markedly easier than ammonolysis of difluoroquinoline **1e**, where aminodefluorination again starts to dominate (Table 1, compare entries 1–3 with 4). Nonetheless, the interaction of **1e** with liquid ammonia produced 2-amino-6,7-difluoroquinoline (**9**), 6-amino-2-chloro-7-fluoroquinoline (**10**), and 7-amino-2-chloro-6-fluoroquinoline (**11**) in the ratio 4:1:15 ($\Omega = 0.2$) with yields 14%, 4%, and 65%, respectively (Table 1, entry 4).

That is, two *ortho*-arranged fluorine atoms at positions 6 and 7 turned out to be sufficient for predominance of aminodefluorination, and the presence of *para*-arranged fluorine atoms was not crucial for the direction of the reaction.

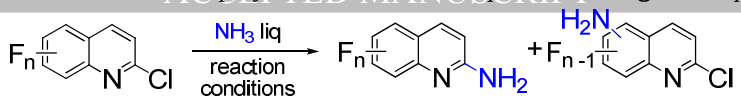
The reaction of difluoroquinoline **1d** with liquid ammonia yields 2-amino-5,7-difluoroquinoline (**12**) mostly, and two isomeric products of aminodefluorination: 5-amino-2-chloro-7-fluoroquinoline (**13**) and 7-amino-2-chloro-5-fluoroquinoline (**14**) in the ratio 15:4:1, $\Omega = 2.9$ (Table 1, entry 5). Therefore, in the case of **1d**, the aminodechlorination is preferred due to the inductive effect of the nitrogen atom of the heterocycle. The formation of quinoline **12** (as well as isomeric 4-amino-5,7-difluoroquinoline) was observed previously in a reaction of 5,7-difluoroquinoline with potassium amide, but compound **12** was not isolated.[10] Quinolines **12**–**14** were obtained with yields of 49%, 11%, and 3%, respectively. Regioselectivity of aminodefluorination of **1d** at position 5 corresponded closely to that for the interaction of 5,7-difluoroquinoline with aqueous ammonia.[9]

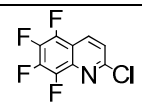
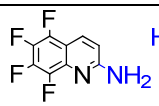
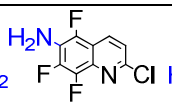
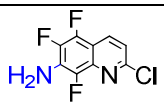
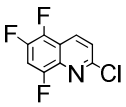
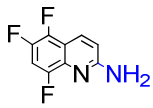
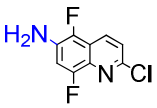
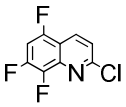
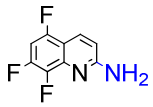
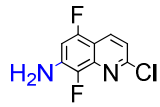
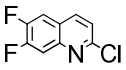
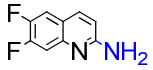
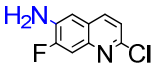
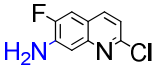
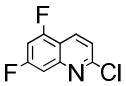
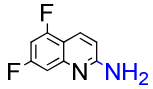
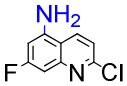
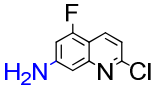
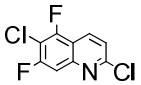
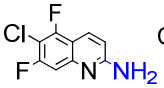
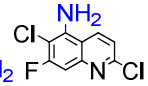
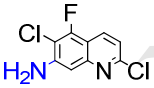
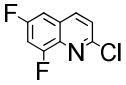
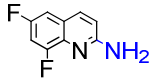
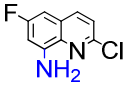
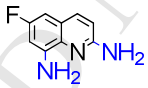
Ammonolysis of **1g** by liquid ammonia also leads to three products: 2-amino-6-chloro-5,7-difluoroquinoline (**15**), isomeric 5-amino-2,6-dichloro-7-fluoroquinoline (**16**), and 7-amino-2,6-dichloro-5-fluoroquinoline (**17**) in the ratio 1:7:1, $\Omega = 0.1$ (Table 1, entry 6). Novel aminoquinolines **15**–**17** were obtained with yields 7%, 53%, and 11%, respectively. Therefore, introduction of a chlorine atom at position 6 leads to noticeable activation of the benzene cycle in the reaction with ammonia in comparison with its structural analog **1d** and allows for introduction of an amino group mostly at position 5.

Like quinoline **1d**, difluoroquinoline **1f** contains *meta*-arranged to each other fluorine atoms, but its ammonolysis by liquid ammonia at 90 °C leads to 2-amino-6,8-difluoroquinoline (**18**) and 8-amino-2-chloro-6-fluoroquinoline (**19**), with predominance of the product of aminodefluorination, $\Omega = 0.3$ (Table 1, entry 7). Quinolines **18** and **19** are isolated with the yield 20% and 59%, respectively. Orientation of aminodefluorination of **1f** is consistent with the orientation of methoxydefluorination of 6,8-difluoroquinoline by means of sodium methylate, where only the substitution of the fluorine atom at position 8 was observed.[13] In both compounds, position 8 is activated by both the -I effect of the nitrogen atom of the heterocycle and the *meta*-atom of fluorine.

Ammonolysis of **1f** at 150 °C, i.e., at the temperature above critical for ammonia ($T_{crit} \approx 132$ °C),[14] leads to formation of compound **19**, also as the main product (Table 1, entry 8), albeit at a greater value of $\Omega = 0.5$. ^{19}F NMR spectroscopy and gas chromatography with mass spectrometry (GC-MS) detected trace amounts of 2,8-diamino-6-fluoroquinoline (**20**) in the reaction mixture. Thus, elevation of the temperature of the reaction above critical does not change the direction of ammonolysis but noticeably affects the ratio of products.

Table 1. Conditions and results of the reaction of polyfluorinated 2-chloroquinolines **1a–g** with liquid ammonia



№	Quinoline	*T*, °C	Time, h	Products, isolated yield [a]	Amount in a mixture, mol %, according to NMR ^{19}F and GC-MS	Ω [b]
1	 **1a**	70	9	 **2**, 5%;  **3**, 5%;  **4**, 65%	**2** (7), **3** (8), **4** (85)	≈**0.1**
2	 **1b**	70	12	 **5**, 70%;  **6**	**5** (98), **6** (2)	**49.0**
3	 **1c**	70	12	 **7**, 55%;  **8**, 11%	**1c** (2), **7** (90), **8** (8)	**11.2**
4	 **1e**	90	24	 **9**, 14%;  **10**, 4%;  **11**, 65%	**1e** (2), **9** (19), **10** (5), **11** (74)	≈**0.2**
5	 **1d**	70	24	 **12**, 49%;  **13**, 11%;  **14**, 3%	**1d** (2), **12** (73), **13** (20), **14** (5)	**2.9**
6	 **1g**	70	12	 **15**, 7%;  **16**, 53%;  **17**, 11%	**15** (11), **16** (75), **17** (14)	≈**0.1**
7	 **1f**	90	28	 **18**, 20%;  **19**, 59%	**1f** (2), **18** (24), **19** (74)	≈**0.3**
8	**1f**	150	24	 **18** **19** **20**	**18** (33), **19** (63), **20** (4)	**0.5**

[a] After thin layer chromatography (TLC).

[b] A molar ratio of the aminodechlorination product to the aminodefluorination products

2.2. Reactions with aqueous ammonia

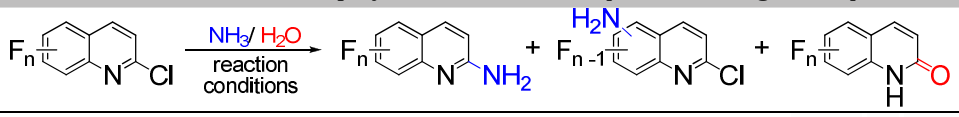
In aqueous ammonia, ammonolysis requires somewhat more rigid reaction conditions than in liquid ammonia (a dipolar aprotic solvent) because the molecules of ammonia in an aqueous solution are solvated and are also partially in the state of the conjugated acid NH_4^+, and their nucleophilicity is lower. For example, to achieve high conversion, we had to keep **1a** at 85 °C for 24 h. Meanwhile, except for the products of monosubstitution **2**–**4**, which were obtained earlier during ammonolysis of **1a** in liquid ammonia, we detected a minor product of double substitution: 2,7-diamino-5,6,8-trifluoroquinoline (**21**) (Table 2, entry 1). During ammonolysis at 100 °C, the proportion of **21** increased appreciably (Table 2, entry 2). It should be noted that aminodehalogenation of **1a** proceeds mostly in the benzene moiety both in liquid ammonia and in aqueous, but the share of aminodechlorination increases from Ω = 0.1 in liquid ammonia to 0.5 in aqueous ammonia.

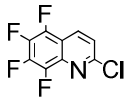
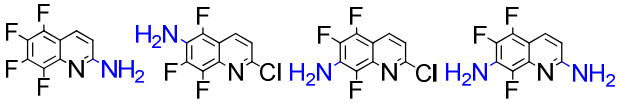
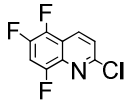
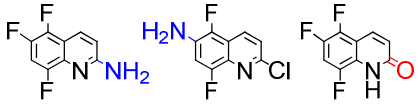
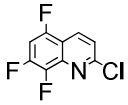
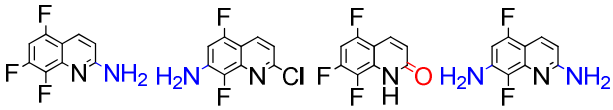
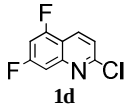
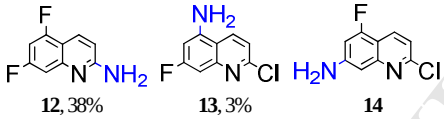
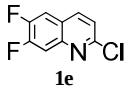
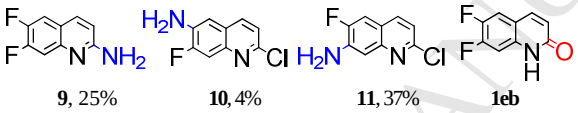
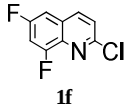
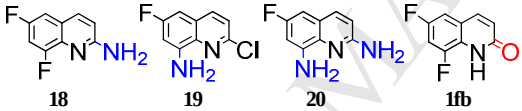
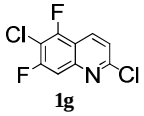
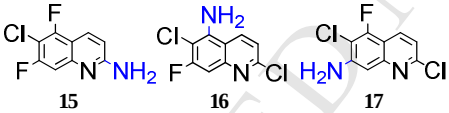
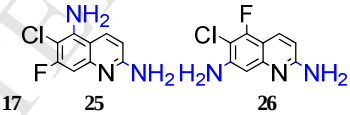
Ammonolysis of **1b** and **1c** in aqueous ammonia at 120 °C, just as in liquid ammonia, leads to formation of aminoquinolines **5**–**8** (Table 2, entries 3 and 4). In addition, we registered products of substitution of a chlorine atom with a hydroxy group: 5,6,8-trifluoroquinoline-2-one (**22**) and 5,7,8-trifluoroquinoline-2-one (**23**) as well as a product of double substitution: 2,7-diamino-5,8-difluoroquinoline (**24**).

Ammonolysis of **1d** in aqueous ammonia at 120 °C leads, just as in liquid ammonia, to formation of 2-aminoquinoline **12** as the main product and minor products of aminodefluorination: **13** and **14** (Table 2, entry 5). At the same time, the contribution of aminodechlorination becomes even more dominant (Ω = 8.0 in aqueous ammonia, and Ω = 2.9 in liquid ammonia).

Stirring of **1e** with aqueous ammonia at 120 °C causes incomplete conversion of the substrate (77%) and formation of aminoquinolines **9**–**11** in the ratio Ω ≈ 0.7 (according to ^{19}F NMR spectroscopic data). Minor amounts of 6,7-difluoroquinoline-2-one (**1eb**) are also detected (Table 2, entry 6). Thus, the use of aqueous ammonia instead of the liquid one raises Ω substantially (from 0.2 to 0.7).

Table 2. Conditions and results of the reaction of polyfluorinated 2-chloroquinolines **1a–g** with aqueous ammonia.



№	Quinoline	*T*, °C	Time, h	Products, isolated yield [a]	Amount in a mixture, mol %, according to NMR ^{19}F and GC-MS	Ω[b]
1	 **1a**	85	24	 **2**, 38% **3**, 5% **4**, 47% **21**	**1a** (10), **2** (30) **3** (3), **4** (55), **21** (2)	**0.5**
2	**1a**	100	3	**2**, 23% **3**, 14% **4**, 33% **21**	**2** (25), **3** (8), **4** (41), **21** (26)	
3	 **1b**	120	7	 **5**, 52% **6** **22**[c]	**1b** (8), **5** (80), **6** (1), **22** (11)	**80.0**
4	 **1c**	120	7	 **7**, 52% **8** **23**[c] **24**	**7** (87), **8** (3), **23** (4), **24** (6)	**29.0**
5	 **1d**	120	10	 **12**, 38% **13**, 3% **14**	**1d** (10), **12** (80), **13** (5), **14** (5)	**8.0**
6	 **1e**	120	22	 **9**, 25% **10**, 4% **11**, 37% **1eb**	**1e** (23), **9** (30), **10** (2), **11** (44), **1eb** (1)	**≈0.7**
7	 **1f**	150	10	 **18** **19** **20** **1fb**	**18** (55), **19** (17), **20** (6), **1fb** (22)	**3.2**
8	 **1g**	100	1	 **15** **16** **17**	**1g** (71), **15** (11), **16** (13), **17** (5)	**0.6**
9	**1g**	100	5	 **15** **16** **17** **25** **26**	**1g** (13), **15** (27), **16** (34), **17** (13), **25** (10), **26** (3)	

[a] After thin layer chromatography (TLC).

[b] A molar ratio of the aminodechlorination product to the aminodefluorination products.

[c] Known compound[8].

Quinoline **18** is the main product during ammonolysis of **1f** in aqueous ammonia at 150 °C, in contrast in liquid ammonia (Table 2, entry 7). According to ^{19}F NMR data, appreciable amounts of 6,8-difluoroquinoline-2-one (**1fb**) and small amounts of quinoline **20** were obtained.

The reaction of **1g** with aqueous ammonia at 100 °C with low conversion leads to aminoquinolines **15**–**17** in the ratio ~2:2.5:1, respectively, at Ω = 0.6 (Table 2, entry 8). That is, again, as in the above cases, the proportion of 2-aminoquinoline increases in comparison with ammonolysis in liquid ammonia (Ω = 0.1). If reaction time is increased (Table 2, entry 9), then the products of diamination (2,5-diamino-6-chloro-7-fluoroquinoline (**25**) and 2,7-diamino-6-chloro-5-fluoroquinoline (**26**)) are formed in addition to aminoquinolines **15**–**17**.

Earlier, it has been shown that side reactions can occur during amination of polyfluorinated arenes in a steel autoclave in aqueous or alcohol-based solvents.[15] It is possible that these reactions can explain the formation of quinolones **22**, **23**, **1eb**, and **1fb**. Quinolones **22** and **23** are known compounds.[8] New quinolones **1eb** and **1fb** are precursors of **1e** and **1f** and are presented in the experimental section. Formation of diaminoquinolines **20**, **21**, **24**, **25**, and **26** may have occurred due to the higher-temperature ammonolysis with aqueous ammonia versus liquid ammonia (see Supporting data). Reliable determination of the structure of the products required holding X-ray studies of a number of key compounds. XRD data for compounds **1e-g**, **1ea**, **1ga**, **4**, **5**, **11**, **12**, **16**, **18** and **19** are presented in Supporting data.

Thus, orientation of aminodehalogenation of quinolines **1a–e**, **g** in aqueous ammonia resembles that previously observed in liquid ammonia, but the proportion of the products of aminodechlorination at position 2 increases in comparison with the transformations in liquid ammonia for all the substrates. In contrast, in the case of quinoline **1f**, the process of aminodechlorination starts to dominate. Possible reasons for acceleration of aminodechlorination in aqueous ammonia include catalysis of this reaction by the metallic walls of the autoclave[15] or a specific interaction of the substrate with the solvent

(protonation of the heterocyclic nitrogen) or a combination of the two factors.

2.3. Computational results.

To interpret the experimentally observed patterns of nucleophilic substitution in fluorinated 2-chloroquinolines, we performed quantum-chemical calculations of the respective reaction pathways by the DFT method using B3LYP and CAMB3LYP functionals with the standard basis set 6-31+G(d). The reaction transition states were located. The types of stationary structures that we found (a minimum or transition state) were determined by the normal vibration analysis accompanied by intrinsic reaction coordinate (IRC) calculations. All the calculations were conducted by means of the GAMESS package.[16]

The influence of polar media was taken into account within the conductorlike polarizable continuum model (C-PCM). For aqueous ammonia, we used the model solvent H_2O with built-in parameters ε (the dielectric constant) = 78 and R_{solv} (the solvent radius) = 1.39 Å. For liquid ammonia, the parameters were set on the basis of literature data: ε = 21 and 9 for temperatures –20 and 120 °C,[17] respectively, and R_{solv} = 1.9 Å as the average of 1.95 and 1.85 Å as described elsewhere.[18]

The calculations were carried out for all halogen-substituted positions of the quinoline backbone of compounds **1a–g** and also for 5,8-difluoro- (**A**), 7,8-difluoro- (**B**), 6,7,8-trifluoro- (**C**), 5,6,7-trifluoro- (**D**), and 5,6-difluoro-2-chloroquinolines (**E**), whose transformations have not yet been studied. Both functionals yielded similar results. The activation energy values (defined as the difference between total energies of the reaction transition state and prereaction complex) that were obtained in CAMB3LYP calculations are shown in Table 3. Note that the differences in activation energies obtained for various positions are more pronounced in CAMB3LYP calculations in comparison with B3LYP ones, and these differences describe the reaction regioselectivity somewhat better. All the transition states found are structurally similar to σ-complexes. In accordance with the calculation results, the reactions proceed as a one-stage process. Note that analogous results have also been obtained by other researchers.[19]

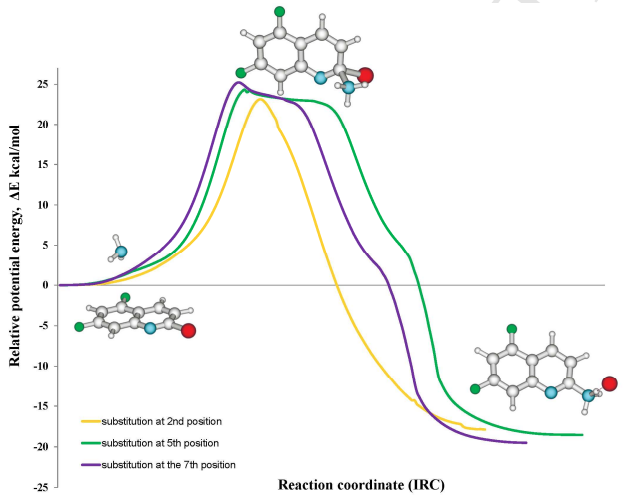


Figure 1. A section of the potential energy surface along the reaction coordinate for quinoline **1d** with aqueous ammonia. Stationary structures for the substitution at position 2 are shown (C-PCM/CAMB3LYP/6-31+G(d)).

A characteristic view of a section of the potential energy surface (PES) along the reaction coordinate is shown in Figure 1 for the interaction of quinoline **1d** with ammonia as an example. The calculated potential energy curves have no clear-cut minima between the reagents and products, corresponding to the Meisenheimer complexes. For compound **1d,** the substitution at position 2 is kinetically preferable (the lowest height of the activation barrier), that is, in accordance with the experimental data.

Table 3. The calculated activation energies (kcal/mol) for reactions of quinolines **1a**–**g** and **A**–**E** with ammonia (C-PCM H_2O/CABM3LYP/6-31+G(d)).

Comp.	Position in quinoline skeleton					Main product	
	2	5	6	7	8	calc	actual
1a	22.3	23.5	24.2	20.5	25.5	7	7
1b	23.1	27.2	26.8		25.9	2	2
1c	21.9	26.8		23.2	27.9	2	2
1d	23.2	24.4		25.3		2	2
1e	25.1		28.5	24.7		7	7
1f	25.8		28.8		24.0	8	2
1g	22.4	22.0	34.0	23.1		5	5
A	23.3	28.9			28.8	2	
B	23.6			25.5	26.2	2	
C	23.5		26.5	22.6	23.8	7	
D	23.4	23.3	26.3	22.7		7	
E	24.7	26.4	29.2			2	

As the chemical experiments showed, replacement of liquid ammonia with aqueous one increases the proportion of the substitution product at position 2 for all the compounds studied. Using quinoline **1f** as an example, we examined the influence of solvent polarity by varying its dielectric permittivity ε (Table 4). The height of activation barriers was calculated for the following values of ε: 78 (water), 21 and 9 (liquid ammonia at –20 °C and 120 °C,[17] respectively), and 1.0 (vacuum). We found that the lower the dielectric permittivity, the lower is the barrier of activation for the substitution at position 8 and smaller the difference between the barriers for substitution at positions 2 and 8. The tendency obtained in the calculations agrees well with that observed in chemical experiments.

Table 4. The calculated activation energies (kcal/mol) for the reaction of **1f** with ammonia taking into account the dielectric permittivity (C-PCM/B3LYP/6-31+G(d)).

Comp.	Position in quinoline core occupied by halogen			Main product (calc.)	ε
	2	6	8		
1f	24.8	29.7	26.6	2	78
	24.9	30.1	25.6	2	21
	25.5	31.1	26.0	2	9
	31.0	39.6	30.6	8	1

The results of the calculations describe well the observed increase in reactivity of fluoroquinolines in terms of a nucleophilic substitution as the number of fluorine atoms increases. Besides, the calculations reproduce the observed patterns of influence of the relative position of fluorine atoms in the benzene moiety on the direction of the reaction. Our results suggest that this calculation may predict regioselectivity for ammonolysis of quinolines **A**–**E**.

3. Conclusion

Orientation of a halogen substitution is determined by the totality of electron effects of the heterocycle and halogen atoms depending on their position. For several polyfluorinated (on the benzene ring) 2-chloroquinolines in the reaction with liquid or aqueous ammonia, we found that 5,7-difluoro-, 5,6,8-trifluoro-, and 5,7,8-trifluoro-2-chloroquinoline mostly form products of substitution of a chlorine atom, whereas 2,6-dichloro-5,7-difluoroquinoline, 5,6,7,8-tetrafluoro-, and 6,7-difluoro-2-chloroquinoline mostly form products of substitution of fluorine atoms at various positions of the benzene ring. The share of products at position 2 increases relative to products of aminodefluorination after replacement of liquid ammonia with aqueous for all the substrates studied. The use of aqueous ammonia instead of liquid for 2-chloro-6,8-difluoroquinoline leads to a change from the predominant substitution of fluorine and formation of 8-amino-2-chloro-6-fluoroquinoline to substitution of chlorine and formation of 2-amino-6,8-difluoroquinoline as the main product. At the level of C-PCM/B3LYP/6-31+G(d) and C-PCM/CAMB3LYP/6-31+G(d), we calculated the pathways of halogen substitution with an amino group during an interaction of polyfluorinated 2-chloroquinolines with ammonia. The transition states found are similar in structure to σ-complexes, and their relative energies correlate with the reaction regioselectivity.

4. Experimental section

4.1. General methods

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on NMR spectrometers Bruker AV-300 (300.13, 282.36 for ^{1}H, ^{19}F correspondingly), Bruker AV-400 (400.13 for ^{1}H), Bruker DRX-500 and Bruker Avance III 500 (500.13, 125.76, 470.51 for ^{1}H, ^{13}C, and ^{19}F, respectively). Chemical shifts (δ) of ^{1}H and ^{13}C are given in ppm relative to TMS using the solvent signals as the internal standard (δH = 2.05 ppm, δC = 29.8 and 206.3 ppm for acetone-d_6, δH = 2.50 ppm, δC = 39.5 ppm for DMSO-d_6, δH = 7.26 ppm, δC = 77.2 ppm for $CDCl_3$), the internal standard for ^{19}F spectra was C_6F_6 (δ = –162.9 ppm). Melting points were determined with a Mettler Toledo FP900 Termosystem. Infrared (IR) spectra were recorded by means of a Vector-22 instrument for samples pelleted with KBr (0.25%). UV spectra were recorded on a Cary 5000 instrument with EtOH. GC-MS analysis was performed on a Hewlett–Packard G1081A instrument consisting of an HP-5890 Series II gas chromatograph and an HP-5971 mass-selective detector (IE, 70 eV) with an HP5 capillary column. The precise molecular weights of ions were determined by high-resolution mass spectrometry on a Thermo Scientific DFS instrument, at ionizing energy of 70 eV. Elemental analysis was carried out using a Euro EA 3000 C, H, N-analyzer. Analysis of Cl was carried out by the mercurimetric titration method, and analysis of F was carried out by a spectrophotometric method.

4.2. Computational section

All the calculations were performed with the GAMESS package.[16] The geometry of systems was optimized by the DFT computational method using the global hybrid functionals B3LYP and CamB3LYP with the 6-31+G(d) basis set. The nature of each stationary point as a true minimum or a first-order transition state was confirmed by calculating harmonic frequencies. The effect of the solvent was taken into account using the conductor polarizable continuum model (CPCM) with parameters of the water, and parameters were taken from the literature on liquid ammonia.[17,18]

4.3. Synthesis

Starting materials: known compounds (**1a**, **1b**, **1c,** and **1d)** and new ones (**1e**, **1f,** and **1g)** were obtained as described previously[8] (see Supporting Information for details). Aminoquinolines **2**–**19** (except **6**) were isolated by TLC on plates with the fixed layer of the sorbent (silica gel LSL_{254} 5/40 μm with addition of 13 wt% plaster) with visual control during irradiation of the dried plate with UV light. Separated fractions were eluted from the sorbent by means of acetone.

4.4. Preparation of N-(polyfluorophenyl)cinnamamides (general procedure).

To a mixture of fluoroaniline and K_2CO_3 in acetone–water cooled in an ice bath, cinnamoyl chloride was added in small portions. The mixture was stirred at 0 °C for 2 h and held at 20 °C for 1 h. The precipitated material was filtered off, washed with water and dried.

*4.4.1. 2,4-Difluoroanilide of cinnamic acid (**1fa**).* A mixture of 2,4-difluoroaniline (5.00 g, 38.76 mmol), cinnamoyl chloride (6.50 g, 39.02 mmol), K_2CO_3 (8.08 g, 58.47 mmol) in acetone–water (50.0 mL) gave **1fa** (9.45 g, 94%). White solid, mp: 140-141 °C, spectrum ^{1}H NMR coincides with [20]; ^{13}C NMR (126 MHz, DMSO-d_6): δ 104.1 (dd, 1C, *J*=24.0, 26.8 Hz, C-3), 111.1 (dd, 1C, *J*=3.5, 21.8 Hz, C-5), 121.7 (s, 1C, C-8), 123.0 (dd, 1C, *J*=3.7, 11.7 Hz, C-1), 125.1 (dd, 1C, *J*=2.3, 9.0 Hz, C-6), 127.8 (s, 2C, C-11, C-15), 129.0 (s, 2C, C-12, C-14), 129.9 (s, 1C, C-13), 134.7 (s, 1C, C-10), 140.8 (s, 1C, C-9), 153.7 (dd, 1C, *J*=12.3, 248.0 Hz, C-4), 158.4 (dd, 1C, *J*=11.0, 243.7 Hz, C-2), 164.0 (s, 1C, C-7). ^{19}F NMR (282 MHz, $CDCl_3$): δ 35.25 (bs, 1F, F-2), 46.74 (bs, 1F, F-4).

*4.4.2. 4-Chloro-3,5-difluoroanilide of cinnamic acid (**1ga**).* A mixture of 4-chloro-3,5-difluoroaniline (1.65 g, 10.09 mmol), cinnamoyl chloride (1.70 g, 10.20 mmol), K_2CO_3 (2.10 g, 15.20 mmol) in acetone–water (40.0 ml) gave **1ga** (2.51 g, 85%). White solid, after crystallization from aqueous EtOH, mp: 184-185 °C; [Found: C, 61.31; H, 3.53; Cl, 12.00; F, 13.13; N, 4.87. $C_{15}H_{10}ClF_2NO$ requires C, 61.34; H, 3.43; Cl, 12.07; F, 12.94; N, 4.77]; IR (KBr) *ν* 3262 (NH), 1663 (C=O), 1624 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg ε): 221 (4.19), 302 (4.53); ^{1}H NMR (300 MHz, acetone-d_6): δ 6.78 (d, 1H, J_{HH}=15.6 Hz, H-8), 7.39-7.47 (m, 3H, H-12, H-13, H-14), 7.59-7.68 (m, 4H, H-2, H-6, H-11, H-15), 7.72 (d, 1H, J_{HH}=15.6 Hz, H-9), 9.86 (bs, 1H, NH); ^{13}C NMR (126 MHz, DMSO-d_6): δ 101.6 (t, 1C, *J*=21.6 Hz, C-4), 103.0 (dd, 2C, *J*=1.9, 26.5 Hz, C-2, C-6), 121.2 (bs, 1C, C-8), 127.9 (s, 2C, C-11, C-15), 129.0 (s, 2C, C-12, C-14), 130.1 (s, 1C, C-13), 134.3 (s, 1C, C-10), 139.5 (t, 1C, *J*=13.1 Hz, C-1), 141.5 (s, 1C, C-9), 157.9 (dd, 2C, *J*=5.5, 244.9 Hz, C-3, C-5), 164.1 (s, 1C, C-7). ^{19}F NMR (282 MHz, acetone): δ 49.73-49.83 (m, 2F, F-3, F-5); HRMS (EI): M^+, found 293.0416. $C_{15}H_{10}ClF_2NO$ requires 293.0414.

*4.4.3. 3,4-Difluoroanilide of cinnamic acid (**1ea**).* A mixture of 3,4-difluoroaniline (5.79 g, 44.85 mmol), cinnamoyl chloride (7.43 g, 44.60 mmol), K_2CO_3 (9.31 g, 67.37 mmol) in acetone–water (50.0 mL) gave **1ea** (10.37 g, 89%). White solid; mp: 147-148 °C; [Found: C, 69.64; H, 4.22; F, 14.62; N, 5.39. $C_{15}H_{11}F_2NO$ requires C, 69.49; H, 4.28; F, 14.66; N, 5.40]; IR (KBr) *ν* 3391 (NH), 3304 (NH), 1668 (C=O), 1624 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg

ε): 221 (4.21), 296 (4.48); ^{1}H NMR (400 MHz, acetone-d_6): δ 6.80 (d, 1H, J_{HH}=15.7 Hz, H-8), 7.27 (td, 1H, J_{HF}=J=9.0 Hz, J_{HF}=10.4 Hz, H-5); 7.37-7.46 (m, 4H, H-11, H-12, H-14, H-15), 7.60-7.64 (m, 2H, H-6, H-13), 7.70 (d, 1H, J_{HH}=15.7 Hz, H-9); 8.00 (ddd, 1H, J=2.5, J_{HF}=7.5, 13.2 Hz, H-2); 9.62 (bs, 1H, NH); ^{13}C NMR (126 MHz, acetone-d_6): δ 109.4 (d, 1C, J=22.3 Hz, C-2), 116.2 (dd, 1C, J=3.4, 5.8 Hz, C-6), 118.1 (dd, 1C, J=1.1, 18.1 Hz, C-5), 122.3 (s, 1C, C-8), 128.7 (s, 2C, C-11, C-15), 129.8 (s, 2C, C-12, C-14), 130.7 (s, 1C, C-13), 135.8 (s, 1C, C-10), 137.4 (dd, 1C, J=3.0, 9.2 Hz, C-1), 142.3 (s, 1C, C-9), 146.9 (dd, 1C, J=12.9, 242.0 Hz, C-4), 150.6 (dd, 1C, J=13.3, 243.5 Hz, C-3), 164.6 (s, 1C, C-7); ^{19}F NMR (282 MHz, acetone): δ 18.50 (dddd, 1F, J=4.0 Hz, J_{HF}=7.5, 10.4 Hz, J_{FF}= 21.8 Hz, F-4), 26.06 (ddd, 1F, J_{HF}=9.0, 13.2 Hz, J_{FF}=21.8 Hz, F-3); HRMS (EI): M^+, found 259.0799. $C_{15}H_{11}F_2NO$ requires 259.0803.

4.5. Preparation of quinolin-2-ones (general procedure).

A mixture of fluoroanilide of cinnamic acid and $AlCl_3$ was stirred at 110–120 °C for 2 h and after cooling ice water was added to the mixture. The precipitated material was filtered off, washed with water and dried.

*4.5.1. 6,7-Difluoroquinolin-2-one (**1eb**).* A mixture of **1ea** (2.49 g, 9.60 mmol) and $AlCl_3$ (3.90 g, 29.24 mmol) gave **1eb** and 5,6-difluoroquinolin-2-one in ratio 10:1, 1.38 g, the yield of mixture 79%. After sublimation and crystallization from EtOH, **1eb**, white solid; mp: 295 °C followed by decomposition; [Found: C, 59.76; H, 2.90; F, 20.70; N, 8.07. $C_9H_5F_2NO$ requires C, 59.76; H, 2.78; F, 20. 98; N, 7.73]; UV (EtOH) λ nm (lg ε): 209 (4.66), 268 (3.53), 291 (3.41), 297 (3.47), 304 (3.67), 310 (3.63), 317 (3.82); ^{1}H NMR (300 MHz, DMSO-d_6): 6.53 (d, 1H, J_{HH}=9.6 Hz, H-3), 7.23 (dd, 1H, J_{HF}=7.1, 11.6 Hz, H-5), 7.80 (dd, 1H, J_{HF}=8.7, 10.9 Hz, H-8), 7.86 (d, 1H, J_{HH}=9.6 Hz, H-4), 11.85 (bs, 1H, NH); ^{13}C NMR (126 MHz, DMSO-d_6): δ 103.4 (d, 1C, J=21.2 Hz, C-8), 115.5 (dd, 1C, J=1.4, 18.3 Hz, C-5), 115.7 (dd, J=2.4, 7.4 Hz, 1C, C-3), 122.4 (d, 1C, J=2.6 Hz, C-9), 136.1 (d, 1C, J=10.1 Hz, C-10), 139.2 (bs, 1C, C-4), 145.0 (dd, 1C, J=14.0, 240.8 Hz, C-6), 150.9 (dd, 1C, J=14.8, 249.6 Hz, C-7), 161.7 (bs, 1C, C-2); ^{19}F NMR (282 MHz, DMSO-d_6): δ 16.91 (ddd, 1F, J_{HF}=7.1, 10.9 Hz, J_{FF}=23.1 Hz, F-7), 29.19 (ddd, 1F, J_{HF}=8.7, 11.6 Hz, J_{FF}=23.1 Hz, F-6).

*4.5.2. 6,8-Difluoroquinolin-2-one (**1fb**).* A mixture of **1fa** (4.04 g, 15.58 mmol) and $AlCl_3$ (6.60 g, 49.50 mmol) gave **1fb** (2.31 g, 82%). After sublimation white solid; mp: 265 °C followed by decomposition; [Found: C, 59.46; H, 2.79; F, 20.96; N, 7.70. $C_9H_5F_2NO$ requires C, 59.68; H, 2.78; F, 20.98; N, 7.73]; IR (KBr) ν 3018 (NH), 1668 (C=O), 1647 (NH) cm^{-1}; UV (EtOH) λ nm (lg ε): 207 (4.34), 224 (4.46), 245 (4.02), 267(3.93), 276 (3.81), 335 (3.63); ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.64 (d, 1H, J_{HH}=9.6 Hz, H-3), 7.43 (ddd, 1H, J=1.3, 8.8 Hz, J_{HH}=2.6 Hz, H-5), 7.45 (ddd, 1H, J_{HH}=2.6 Hz, J=9.0, 11.2 Hz, H-7), 7.91 (dd, 1H, J=1.3 Hz, J_{HH}=9.6 Hz, H-4), 11.88 (bs, 1H, NH); ^{13}C NMR (126 MHz, DMSO-d_6): δ 105.5 (dd, 1C, J=21.8, 28.7 Hz, C-7), 108.9 (dd, 1C, J=3.9, 22.7 Hz, C-5), 121.0 (dd, 1C, J=4.6, 10.6 Hz, C-9), 124.7 (bs, 1C, C-3), 124.8 (dd, 1C, J=1.6, 11.8 Hz, C-10), 139.3 (dd, 1C, J=2.4, 3.6 Hz, C-4), 148.7 (dd, 1C, J=13.0, 249.3 Hz, C-8), 155.9 (dd, 1C, J=11.0, 239.8 Hz, C-6), 161.5 (bs, 1C, C-2); ^{19}F NMR (470 MHz, DMSO-d_6): δ 35.98 (bd, 1F, J=10.6 Hz, F-8), 43.47 (dt, 1F, J=2.6 Hz, 2J=8.9 Hz, F-6); HRMS (EI): M^+, found 181.0333. $C_9H_5F_2NO$ requires 181.0334.

*4.5.3 6-Chloro-5,7-difluoroquinolin-2-one (**1gb**).* A mixture of **1ga** (2.50 g, 8.51 mmol) and $AlCl_3$ (3.42 g, 25.65 mmol) gave **1gb** (1.43 g, 78%). Dark-red solid, 293 °C followed by decomposition; ^{1}H NMR (400 MHz, DMSO-d_6): 6.58 (d, 1H, J_{HH}=9.8 Hz, H-3), 7.08 (dd, 1H, J_{HF}=1.7, 10.1 Hz, H-8), 7.95 (d, 1H, J_{HH}=9.8 Hz, H-4), 12.15 (bs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 98.7 (dd, 1C, J=3.8, 25.3 Hz, C-8), 101.1 (dd, 1C, J=20.2, 22.6 Hz, C-6), 106.2 (dd, 1C, J=2.3, 18.5 Hz, C-9), 122.7 (bs, 1C, C-3), 131.7 (dd, 1C, J=1.7 Hz, J=3.2 Hz, C-4), 138.8 (dd, 1C, J=7.8, 13.7 Hz, C-10), 154.5 (dd, 1C, J=5.7, 252.7 Hz, C-5), 158.1 (dd, 1C, J=4.8, 249.2 Hz, C-7), 161.5 (s, 1C, C-2); ^{19}F NMR (282 MHz, DMSO-d_6): δ 42.82 (dd, 1F, J_{HF}=1.7 Hz, J_{FF}=3.9 Hz, F-5), 51.73 (dd, 1F, J_{FF}=3.9 Hz, J_{HF}=10.1 Hz, F-7); HRMS (EI): M^+, found 214.9946. $C_9H_4ClF_2NO$ requires 214.9944.

4.6. Preparation of 2-chloroquinolines (general procedure).

A mixture of quinolin-2-one and $POCl_3$ was stirred at 95–100 °C for 2 h and then cooled. Ice was added to the mixture. The precipitated material was filtered off, washed with water and dried.

*4.6.1. 2-Chloro-6,7-difluoroquinoline (**1e**).* A mixture of **1eb** and 5,6-difluoroquinolin-2-one in ratio 10:1 (2.42 g, 13.36 mmol) and $POCl_3$ (6.23 g, 40.64 mmol) gave **1e** and 2-chloro-5,6-difluoroquinoline in ratio 10:1 (2.28 g, 85%). After column chromatography **1e** (1.96 g, 73%). White solid; mp: 115 °C; [Found: C, 53.97; H, 1.97; Cl, 17.65; F, 19.06; N, 6.95. $C_9H_4ClF_2N$ requires C, 54.16; H, 2.02; Cl, 17.76; F, 19.04; N, 7.02]; UV (EtOH) λ nm (lg ε): 209 (4.66), 268 (3.53), 291 (3.41), 297 (3.47), 304 (3.67), 310 (3.63), 317 (3.82); ^{1}H NMR (500 MHz, acetone-d_6): 7.54 (d, 1H, J_{HH}=8.7 Hz, H-3), 7.81 (dd, 1H, J_{HF}=7.7, 11.4 Hz, H-5), 7.94 (dd, 1H, J_{HF}=8.7, 10.7 Hz, H-8), 8.38 (d, 1H, J_{HH}=8.7 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 114.7 (d, 1C, J=18.4 Hz, C-5), 115.7 (d, 1C, J=17.2 Hz, C-8), 123.6 (s, 1C, C-3), 125.2 (dd, 1C, J=1.5, 8.6 Hz, C-9), 139.9 (bd, 1C, J=4.4 Hz, C-4), 145.9 (dd, 1C, J=1.3, 11.2 Hz, C-10), 150.9 (dd, 1C, J=15.7, 250.7 Hz, C-6), 151.9 (d, 1C, J=2.8 Hz, C-2), 153.6 (dd, 1C, J=16.1, 253.7 Hz, C-7); ^{19}F NMR (471 MHz, acetone-d_6): δ 27.53 (ddd, 1F, J_{HF}=7.7, 10.7 Hz, J_{FF}=20.6 Hz, F-7), 32.20 (ddd, 1F, J_{HF}=8.7, 11.4 Hz, J_{FF}=20.6 Hz, F-6); HRMS (EI): M^+, found 198.9998. $C_9H_4ClF_2N$ requires 198.9995.

*4.6.2. 2-Chloro-6,8-difluoroquinoline (**1f**).* A mixture of **1fb** (2.35 g, 12.98 mmol) and $POCl_3$ (6.00 g, 39.14 mmol) gave **1f** (2.32 g, 90%). After sublimation, white solid; mp: 111 °C; [Found: C, 54.00; H, 2.39; Cl, 17.89; F, 19.06; N, 7.18. $C_9H_4ClF_2N$ requires C, 54.16; H, 2.02; Cl, 17.76; F, 19.04; N, 7.02]; UV (EtOH) λ nm (lg ε): 201 (4.63), 203 (4.62), 235 (4.61), 275 (3.38), 310 (3.10), 324 (3.11); ^{1}H NMR (300 MHz, acetone-d_6): 7.57 (ddd, 1H, J_{HH}=2.7 Hz, J_{HF}=9.0, 10.4 Hz, H-7), 7.62 (ddd, 1H, J_{HF}=1.5, 9.0 Hz, J_{HH}=2.7 Hz, H-5), 7.66 (bd, 1H, J_{HH}=8.7, H-3), 8.41 (dd, 1H, J_{HF}=1.5, J_{HH}=8.7 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 107.1 (dd, 1C, J=22.5, 30.0 Hz, C-7), 108.2 (dd, 1C, J=5.0, 22.4 Hz, C-5), 125.4 (s, 1C, C-3), 129.5 (dd, 1C, J=2.6, 11.8 Hz, C-9), 135.9 (bd, 1C, J=12.3 Hz, C-10), 139.9 (dd, 1C, J=3.6, 4.9 Hz, C-4), 151.1 (d, 1C, J=2.4 Hz, C-2), 158.4 (dd, 1C, J=13.6, 260.0 Hz, C-8), 160.5 (dd, 1C, J=11.5, 247.9 Hz, C-6); ^{19}F NMR (282 MHz, acetone-d_6): δ 43.44 (ddt, 1F, 2J_{HF}=1.5 Hz, J_{FF}=7.5 Hz, J_{HF}=10.4 Hz, F-8), 53.52 (tdd, 1F, J=0.7 Hz, J_{FF}=7.5 Hz, 2J_{HF}=9.0 Hz, F-6); HRMS (EI): M^+, found 198.9990. $C_9H_4ClF_2N$ requires 198.9995.

*4.6.3. 2,6-Dichloro-5,7-difluoroquinoline (**1g**).* A mixture of **1gb** (1.38 g, 6.40 mmol)) and $POCl_3$ (2.95 g, , 19.24 mmol) gave **1g** (1.30 g, 86%). White solid, mp: 139-141 °C followed by decomposition; [Found: C, 45.82; H, 1.21; F, 16.01; N, 6.21. $C_9H_3Cl_2F_2N$ requires C, 46.19; H, 1.29; F, 16.24; N, 5.99]; ^{1}H NMR (400 MHz, acetone-d_6): 7.68 (dd, 1H, J=0.5 Hz, J_{HH}=8.8 Hz, H-3), 7.72 (ddd, 1H, J_{HH}=0.7 Hz, J_{HF}=2.1, 10.0 Hz, H-8), 8.53 (dd, 1H, J_{HH}=0.6, 8.8 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 109.3 (dd, 1C, J=20.1, 24.2 Hz, C-6), 110.5 (dd, 1C, J=4.7, 21.9 Hz, C-8), 116.1 (dd, 1C, J=1.9, 16.2 Hz, C-9), 124.0 (t, 1C, J=2.7 Hz, C-3), 133.2 (dd, 1C, J=2.2, 3.4 Hz, C-4), 147.0 (dd, 1C, J=4.3, 14.1 Hz, C-10), 154.1 (bd, 1C, J=0.5 Hz, C-2), 155.3 (dd, 1C, J=5.4, 257.8 Hz, C-5), 159.6 (dd, 1C, J=4.3,

251.8 Hz, C-7); ^{19}F NMR (282 MHz, acetone-d_6): δ 44.18 (dd, 1F, J_{HF}=2.1 Hz, J_{FF}=3.6 Hz, F-5), 52.72 (dd, 1F, J_{FF}=3.6 Hz, J_{HF}=10.0 Hz, F-7); HRMS (EI): M^+, found 232.9602. $C_9H_3Cl_2F_2N$ requires 232.9605.

4.7. Reactions of polyfluorinated 2-chloroquinolines with liquid NH_3 (general procedure).

Quinolines were placed into a steel autoclave equipped with two inlet/outlet valves. Then, 10 g of anhydrous liquid NH_3 (without additional purification) was added into the autoclave via self-flow through a measuring funnel with back pressure cooled to −33.8 °C and the autoclave was sealed. The reaction mixture was heated up to the given temperature upon stirring by rotation of the autoclave and kept under these conditions for the necessary period. On completion, the autoclave was cooled, NH_3 was slowly vented through an outlet valve, and the products were dissolved in CH_2Cl_2 (50 mL), unless otherwise stated. The extract was dried with $MgSO_4$, the solvent was filtered and evaporated, and a solid residue was analyzed by GC-MS and ^{19}F NMR spectroscopy. Products were isolated using TLC.

*4.7.1. 2-Amino-5,6,7,8-tetrafluoroquinoline (**2**), 6-amino-5,7,8-trifluoroquinoline (**3**) and 7-amino-5,6,8-trifluoroquinoline (**4**).* The mixture of **1a** (167 mg, 0.71 mmol) with liquid NH_3 was heated for 9 h at 70 °C. The solid residue was extracted with acetone (50 mL). The extract was evaporated, crude product (144 mg) containing **2**, **3** and **4** was purified by TLC (CH_2Cl_2).

2: White solid (7 mg, 5%); R_f 0.14; mp: 234–236 °C; [Found: C, 50.15; H, 1.94; N, 12.90. $C_9H_4F_4N_2$ requires C, 50.01; H, 1.87; N, 12.96]; IR (KBr) *ν* 3507 (NH), 3325 (NH), 1661 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg ε) 239 (4.43), 249 (4.36), 338 (3.54); ^{1}H NMR (500 MHz, acetone-d_6): δ 6.46 (bs, 2H, NH_2), 7.04 (bd, 1H, J_{HH}=9.2 Hz, H-3), 8.08 (dd, 1H, J_{HF}=1.5 Hz, J_{HH}=9.2 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 110.4 (dm, 1C, *J*=14.4 Hz, C-9), 114.8 (bs, 1C, C-3), 130.1-130.3 (m, 1C, C-4), 135.5-135.7 (m, 1C, C-10); 135.4 (dtd, 1C, *J*=1.8, 244.2 Hz, 2*J*=15.1 Hz, C-6), 141.6 (dddd, 1C, *J*=1.9, 4.6, 10.1, 250.0 Hz, C-8), 141.9 (dtd, 1C, *J*=4.8, 248.4 Hz, 2*J*=14.6 Hz, C-7), 142.6 (ddt, 1C, 2*J*=4.6 Hz, *J*=10.6, 249.6 Hz, C-5), 160.1 (bs, 1C, C-2); ^{19}F NMR (282 MHz, acetone): δ -5.58 (dddd, 1F, *J*=0.9 Hz, J_{FF}=2.7, 19.6, 20.2 Hz, F-6), 4.54 (ddd, 1F, *J*=0.7 Hz, J_{FF}=17.9, 19.6 Hz, F-7), 6.68 (dddd, 1F, J_{HF}=1.5 Hz, J_{FF}=2.7, 14.0 Hz, 17.9 Hz, F-8), 10.35 (dd, 1F, J_{FF}=14.0, 20.2 Hz, F-5); HRMS (EI): M^+, found 216.0304. $C_9H_4F_4N_2$ requires 216.0305.

3: White solid (8 mg, 5%); R_f 0.75; mp: 171 °C followed by decomposition; IR (KBr) *ν* 3499 (NH), 3395 (NH), 3200 (NH), 1666 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg ε): 213 (4.40), 258 (4.61), 289 (3.62), 354 (3.68); ^{1}H NMR (500 MHz, acetone-d_6): δ 5.58 (bs, 2H, NH_2), 7.50 (d, 1H, J_{HH}=8.8 Hz, H-3), 8.27 (dd, 1H, J_{HF}=1.4 Hz, J_{HH}=8.8 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 115.7 (ddd, 1C, *J*=1.2, 1.7, 15.5 Hz, C-9), 123.8 (td, 1C, *J*=1.2 Hz, 2*J*=2.7 Hz, C-3), 126.6 (t, 1C, *J*=16.2 Hz, C-6), 129.7-129.9 (m, 1C, C-10), 131.0 (td, 1C, 2*J*=2.2 Hz, *J*=3.5 Hz, C-4), 139.5 (ddd, 1C, *J*=3.6, 7.7, 240.0 Hz, C-5), 142.3 (ddd, 1C, *J*=4.6, 11.1, 251.1 Hz, C-8), 143.8 (ddd, 1C, *J*=9.2, 13.6, 247.2 Hz, C-7), 148.7 (bs, 1C, C-2); ^{19}F NMR (470 MHz, acetone-d_6): δ 6.78 (bt, 1F, J_{FF}=15.9 Hz, F-8), 12.68 (dd, 1F, J_{FF}=10.2, 15.2 Hz, F-7), 13.85 (dd, 1F, J_{FF}=10.2, 16.7 Hz, F-5); HRMS (EI): M^+, found: 232.0006. $C_9H_4ClF_3N_2$ requires 232.0010.

4: White solid (107 mg, 65%); R_f 0.48; mp: 168–169 °C; [Found: C, 46.20; H, 1.85; Cl, 15.04; F, 24.81; N, 11.97. $C_9H_4ClF_3N_2$ requires C, 46.48; H, 1.73; Cl, 15.24; F, 24.50; N, 12.04]; IR (KBr) *ν* 3501 (NH), 3395 (NH), 3196 (NH), 1666 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg ε): 213 (4.44), 258 (4.64), 288 (3.69), 353 (3.74);^{1}H NMR (500 MHz, acetone-d_6): δ 5.85 (bs, 2H, NH_2), 7.37 (dd, 1H, *J*=0.6 Hz, J_{HH}=8.7 Hz, H-3), 8.35 (dd, 1H, J_{HF}=1.5 Hz, J_{HH}=8.7 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 109.6 (dt, 1C, 2*J*=1.8 Hz, *J*=14.4 Hz, C-9), 120.4 (bs, 1C, C-3), 130.1-130.4 (m, 1C, C-10), 132.8-133.0 (m, 1C, C-4), 135.0 (ddd, 1C, *J*=1.2, 3.1, 10.9 Hz, C-7), 140.1 (dm, 1C, *J*=241.8 Hz, C-8), 140.3 (ddd, 1C, *J*=7.7, 12.0, 243.6 Hz, C-6), 141.9 (ddd, 1C, *J*=4.7, 15.9, 252.6 Hz, C-5), 152.1 (dt, 2*J*=1.0 Hz, *J*=2.8 Hz, 1C, C-2); ^{19}F NMR (282 MHz, acetone): δ 9.34 (ddd, 1F, AB, *J*=0.6 Hz, J_{FF}=10.3, 18.2 Hz, F-6), 9.59 (dd, 1F, AB, J_{FF}=15.3, 18.2 Hz, F-5), 10.43 (ddd, 1F, J_{HF}=1.5 Hz, J_{FF}=10.3, 15.3 Hz, F-8); HRMS (EI): M^+, found 232.0006. $C_9H_4ClF_3N_2$ requires 232.0010.

*4.7.2. 2-Amino-5,6,8-trifluoroquinoline (**5**) and 6-amino-2-chloro-5,8-difluoroquinoline (**6**).* The mixture of **1b** (100 mg, 0.46 mmol) with liquid NH_3 was heated for 12 h at 70 °C. The crude product (75 mg) containing **5** and **6** was purified by TLC (1:5 ethylacetate-hexane).

5: White solid (64 mg, 70%); R_f 0.32; mp: 233–234 °C; [Found: C, 54.85; H, 2.54; F, 28.75; N, 13.97. $C_9H_5F_3N_2$ requires C, 54.55; H, 2.54; F, 28.76; N, 14.14]; IR (KBr) *ν* 3516 (NH), 3319 (NH), 3150 (NH), 1649 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg ε): 204 (4.35), 236 (4.20), 254 (4.32), 346 (3.37); ^{1}H NMR (500 MHz, acetone-d_6): δ 6.25 (bs, 2H, NH_2), 7.07 (dd, 1H, *J*=0.7 Hz, J_{HH}=9.1 Hz, H-3), 7.38 (td, 1H, J_{HF}=7.3 Hz, 2J_{HF}=10.8 Hz, H-7), 8.11 (dd, 1H, *J*=1.5 Hz, J_{HH}=9.1 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 105.3 (bt, 1C, *J*=24.6 Hz, C-7), 115.2 (ddd, 1C, *J*=2.2, 4.5, 14.1 Hz, C-9), 115.3 (bs, 1C, C-3), 130.1-130.3 (m, 1C, C-4), 135.7 (dt, 1C, 2*J*=1.9 Hz, *J*=12.8 Hz, C-10), 141.7 (ddd, 1C, *J*=4.8, 12.9, 247.3 Hz, C-5), 142.8 (ddd, 1C, *J*=11.4, 13.3, 240.7 Hz, C-6), 152.5 (ddd, 1C, *J*=3.4, 10.0 Hz, 250.8 Hz, C-8), 159.1 (dd, 1C, *J*=0.9, 1.6 Hz, C-2); ^{19}F NMR (470 MHz, acetone-d_6): δ 8.59 (ddd, 1F, J_{HF}=7.3 Hz, J_{FF}=18.0, 20.2 Hz, F-5), 16.79 (dd, 1F, J_{HF}=10.8 Hz, J_{FF}=20.2 Hz, F-6), 34.31 (dd, 1F, J_{HF}=10.8 Hz, J_{FF}=18.0 Hz, F-8); HRMS (EI): M^+, found 198.0400. $C_9H_5F_3N_2$ requires 198.0399.

Compound **6** was not isolated; its NMR spectra were recorded in a mixture of products. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.49 (bs, 2H, NH_2), 7.26 (dd, 1H, J_{HF}=7.6, 11.9 Hz, H-7), 7.50 (d, 1H, J_{HH}=8.9 Hz, H-3), 8.25 (ddd, 1H, *J*=0.3 Hz, J_{HF}=1.7 Hz, J_{HH}=8.9 Hz, H-4); ^{19}F NMR (282 MHz, $CDCl_3$): δ 9.29 (dd, 1F, J_{HF}=7.6 Hz, J_{FF}=18.9 Hz, F-5), 32.91 (dd, 1F, J_{HF}=11.9 Hz, J_{FF}=18.9 Hz, F-8).

*4.7.3. 2-Amino-5,7,8-trifluoroquinoline (**7**) and 7-amino-2-chloro-5,8-difluoroquinoline (**8**).* The mixture of **1c** (100 mg, 0.46 mmol) with liquid NH_3 was heated for 12 h at 70 °C. The crude product (70 mg) containing **7** and **8** was purified by TLC (CH_2Cl_2).

7: White solid (50 mg, 55%); R_f 0.32; mp: 230-232 °C. Spectra ^{1}H, ^{19}F NMR coincide with literature data.[10] IR (KBr) *ν* 3505 (NH), 3323 (NH), 3150 (NH), 1651 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg ε): 201 (4.39), 245 (4.56), 331 (3.54); ^{13}C NMR (126 MHz, acetone-d_6): δ 97.3 (ddd, 1C, *J*=0.8, 24.7, 26.7 Hz, C-6), 111.3 (dt, 1C, 2*J*=2.0 Hz, *J*=17.5 Hz, C-9), 113.6 (bt, 1C, *J*=3.0 Hz, C-3), 130.74 (td, 1C, 2*J*=2.1 Hz, *J*=4.5 Hz, C-4), 140.3 (td, 1C, 2*J*=5.3 Hz, *J*=9.4 Hz, C-10), 141.0 (ddd, 1C, *J*=5.3, 12.2, 245.7 Hz, C-8), 150.0 (ddd, 1C, *J*=12.3, 15.1, 245.1 Hz, C-7), 154.5 (ddd, 1C, *J*=3.9, 13.8, 249.8 Hz, C-5), 160.6 (d, 1C, *J*=1.0 Hz, C-2); HRMS (EI): M^+, found 198.0401, $C_9H_5F_3N_2$ requires 198.0399.

8: White solid (11 mg, 11%); R_f 0.59; [Found: C, 50.14; H, 2.31. $C_9H_5ClF_2N_2$ requires C, 50.37; H, 2.35]; IR (KBr) *ν* 3501 (NH), 3366 (NH), 3209 (NH), 1657 (NH) cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ 5.74 (bs, 2H, NH_2), 7.06 (dd, 1H, J_{HF}=6.4,

11.4 Hz, H-6), 7.26 (d, 1H, J_{HH}=8.7 Hz, H-3), 8.25 (dd, 1H, J_{HF}=1.7 Hz, J_{HH}=8.7 Hz, H-4); ^{19}F NMR (282 MHz, acetone-d_6): δ 5.74 (ddd, 1F, J_{HF}=1.7, 6.4 Hz, J_{FF} =17.9 Hz, F-8), 36.86 (dd, 1F, J_{HF}=11.4 Hz, J_{FF}=17.9 Hz, F-5).

*4.7.4. 2-Amino-6,7-difluoroquinoline (**9**), 6-amino-2-chloro-7-fluoroqinoline (**10**), 7-amino-2-chloro-6-fluoroquinoline (**11**).* The mixture of **1e** (270mg, 1.35 mmol) with liquid NH_3 was heated for 24 h at 90 °C. The crude product – yellow powder (258 mg) containing **9**, **10**, and **11** was purified by TLC (CH_2Cl_2).

9: White solid (34 mg, 14%); R_f 0.11; mp: 153–155 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 6.08 (bs, 2H, NH_2), 6.87 (d, 1H, J_{HH}=9.0 Hz, H-3), 7.32 (dd, 1H, J_{HF}=7.8, 12.6 Hz, H-5), 7.57 (dd, 1H, J_{HF}=9.0, 11.1 Hz, H-8), 7.91 (d, 1H, J_{HH}=9.0 Hz, H-4); ^{19}F NMR (282 MHz, acetone-d_6): δ 17.99 (ddd, 1F, J_{HF}=7.8, 11.1 Hz, J_{FF}=21.4 Hz, F-7), 27.72 (ddd, 1F, J_{HF}=9.0, 12.6 Hz, J_{FF}=21.4 Hz, F-6).

10: White solid (10 mg, 4%); R_f 0.65; mp: 134–136 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 5.39 (bs, 2H, NH_2), 7.18 (d, 1H, J_{HF}=9.6 Hz, H-5), 7.31 (dd, 1H, *J*=0.5, J_{HH}=8.6 Hz, H-3), 7.49 (d, 1H, J_{HF}=12.3 Hz, H-8), 8.06 (bd, 1H, J_{HH}=8.6 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 109.2 (d, 1C, *J*=5.3 Hz, C-5), 112.6 (d, 1C, *J*=19.0 Hz, C-8), 122.3 (d, 1C, *J*=2.4 Hz, C-3), 126.7 (d, 1C, *J*=1.0 Hz, C-9), 137.6 (d, 1C, *J*=0.6 Hz, C-4), 138.7 (d, 1C, *J*=15.0 Hz, C-6), 142.8 (d, 1C, *J*=12.4 Hz, C-10), 147.4 (s, 1C, C-2), 155.9 (d, 1C, *J*=248.6 Hz, C-7); ^{19}F NMR (282 MHz, acetone-d_6): δ 37.43 (dd, 1F, J_{HF}=9.6, 12.3 Hz, F-7); HRMS (EI): M^+, found 196.0200, $C_9H_6ClFN_2$ requires 196.0198.

11: White solid (172 mg, 65%); R_f 0.43; mp: 184–185 °C; [Found: C, 54.87; H, 3.22; Cl, 18.03; F, 9.96; N, 14.25. $C_9H_6ClFN_2$ requires C, 54.98; H, 3.08; Cl, 18.03; F, 9.66; N, 14.25]; IR (KBr) *ν* 3453 (NH), 3304 (NH), 3188 (NH), 1647 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg ε): 214 (4.60), 248 (4.53), 278 (3.71), 351 (4.01); ^{1}H NMR (500 MHz, acetone-d_6): δ 5.56 (bs, 2H, NH_2), 7.16 (dd, 1H, *J*=0.6 Hz, J_{HH}=8.5 Hz, H-3), 7.20 (bd, 1H, J_{HF}=8.6 Hz, H-8), 7.53 (d, 1H, J_{HF}=11.6 Hz, H-5), 8.08 (bd, 1H, J_{HH}=8.5 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 110.4-110.5 (m, 1C, C-8), 111.5 (d, 1C, *J*=20.0 Hz, C-5), 119.1 (s, 1C, C-3), 120.5 (d, 1C, *J*=9.5 Hz, C-9), 139.1 (d, 1C, *J*=5.4 Hz, C-4), 142.0 (d, 1C, *J*=15.9 Hz, C-7), 148.0 (s, 1C, C-2), 150.4 (d, 1C, *J*=2.6 Hz, C-10), 153.1 (d, 1C, *J*=246.2 Hz, C-6); ^{19}F NMR (282 MHz, acetone-d_6): δ 32.10 (dd, 1F, J_{HF}=8.6, 11.6 Hz, F-6); HRMS (EI): M^+, found 196.0197. $C_9H_6ClFN_2$ requires 196.0198.

*4.7.5. 2-Amino-5,7-fluorioquinoline (**12**), 5-amino-2-chloro-7-fluoroquinoline (**13**) and 7-amino-2-chloro-5-fluoroquinoline (**14**).* The mixture of **1d** (110 mg, 0.55 mmol) with liquid NH_3 was heated for 24 h at 70 °C. The crude product (90 mg) containing **12**, **13**, and **14** was purified by TLC (1:3 ethylacetate-hexane).

12: White solid (45 mg, 49%); R_f 0.14; mp: 153 –155 °C; [Found: C, 60.07; H, 3.04; F, 21.07; N, 15.03. $C_9H_6F_2N_2$ requires C, 60.00; H, 3.36; F, 21.09; N, 15.55]; IR (KBr) *ν* 3487 (NH), 3325 (NH), 3136 (NH), 1661 (NH) cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ 6.25 (bs, 2H, NH_2), 6.81 (ddd, 1H, J_{HH}=2.4 Hz, J_{HF}=9.4, 10.3 Hz, H-6), 6.89 (d, 1H, J_{HH}=9.1 Hz, H-3), 7.01 (dddd, 1H, *J*=0.7 Hz, J_{HF}=1.4, 11.0 Hz, J_{HH}=2.4 Hz, H-8), 8.03 (d, 1H, J_{HH}=9.1 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 97.5 (dd, 1C, *J*=24.7, 29.3 Hz, C-6), 106.9 (dd, 1C, *J*=4.2, 21.1 Hz, C-8), 110.9 (dd, 1C, *J*=1.9, 16.0 Hz, C-9), 112.6-112.7 (m, 1C, C-3), 130.7 (bd, 1C, *J*=4.5 Hz, C-4), 151.1 (dd, 1C, *J*=5.4, 15.0 Hz, C-10), 160.0 (dd, 1C, *J*=15.7, 252.8 Hz, C-5), 160.8 (s, 1C, C-2), 163.6 (dd, 1C, *J*=15.2, 244.7 Hz, C-7); ^{19}F NMR (282 MHz, acetone): δ 42.57 (ddd, 1F, J_{HF}=1.4, 10.3 Hz, J_{FF}=7.3 Hz, F-5), 53.27 (ddd, 1F, J_{FF}=7.3 Hz, J_{HF}=9.4, 11.0 Hz, F-7); HRMS (EI): M^+, found 180.0492. $C_9H_6F_2N_2$ requires 180.0494.

13: White solid (11 mg, 11%); R_f 0.63; mp: 136–138 °C; [Found: C, 54.99; H, 3.29; N, 14.07. $C_9H_6ClFN_2$ requires C, 54.98; H, 3.08; N, 14.25]; UV (EtOH) *λ* nm (lg ε): 219 (4.21), 261 (4.46), 359 (3.52) nm; ^{1}H NMR (400 MHz, acetone-d_6): δ 6.04 (bs, 2H, NH_2), 6.65 (dd, 1H, J_{HH}=2.5 Hz, J_{HF}=11.4 Hz, H-6), 6.83 (ddd, 1H, J_{HH}=0.7, 2.5 Hz, J_{HF}=10.3 Hz, H-8), 7.32 (dd, 1H, *J*=0.6 Hz, J_{HH}=8.8 Hz, H-3), 8.52 (dd, 1H, J_{HH}=0.7, 8.8 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 98.6 (d, 1C, *J*=28.3 Hz, C-6), 100.9 (d, 1C, *J*=22.3 Hz, C-8), 114.9 (d, 1C, *J*=3.0 Hz, C-9), 119.7 (d, 1C, *J*=2.3 Hz, C-3), 135.0 (s, 1C, C-4), 148.6 (d, 1C, *J*=14.5 Hz, C-5), 151.2 (d, 1C, *J*=15.9 Hz, C-10), 152.2 (s, 1C, C-2), 166.1 (d, 1C, *J*=244.5 Hz, C-7); ^{19}F NMR (282 MHz, acetone): δ 55.58 (dd, 1F, J_{HF}=10.3, 11.4 Hz, F-7); HRMS (EI): M^+, found 196.0197. $C_9H_6ClFN_2$ requires 196.0198.

14: White solid (3 mg, 3%); R_f 0.32; UV (EtOH) *λ* nm (lg ε): 216 (4.28), 258 (4.33), 289 (3.62), 295 (3.63), 368 (3.50); ^{1}H NMR (400 MHz, aceton-d_6): δ 5.76 (bs, 2H, NH_2), 6.84 (d, 1H, J_{HH}=2.0 Hz, H-8), 6.87 (dd, 1H, J_{HH}=2.0 Hz, J_{HF}=12.0 Hz, H-8), 7.14 (d, 1H, J_{HH}=8.6 Hz, H-3), 8.17 (d, 1H, J_{HH}=8.6 Hz, H-4); ^{19}F NMR (282 MHz, acetone): δ 40.55 (d, 1F, J_{HF}=12.0 Hz, F-5); HRMS (EI): M^+, found 196.0194. $C_9H_6ClFN_2$ requires 196.0198.

*4.7.6. 2-Amino-6-chloro-5,7-fluorioquinoline (**15**), 5-amino-2,6-dichloro-7-fluoroquinoline (**16**) and 7-amino-2,6-dichloro-5-fluoroquinoline (**17**).* The mixture of **1g** (100 mg, 0.43 mmol) with liquid NH_3 was heated for 12 h at 70 °C. The crude product (87 mg) containing **15**, **16**, and **17** was purified by TLC (CH_2Cl_2).

15: White solid (7 mg, 8%); R_f 0.06; mp: 215–216 °C; [Found: C, 50.19; H, 2.32; N, 12.75. $C_9H_5ClF_2N_2$ requires C, 50.37; H, 2.35; N, 13.05]; IR (KBr) *ν* 3491 (NH), 3323 (NH), 3146 (NH), 1663 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg ε): 209 (4.37), 244 (4.62), 265 (3.95), 336 (3.71); ^{1}H NMR (400 MHz, acetone-d_6): δ 6.37 (bs, 2H, NH_2), 6.95 (dd, 1H, *J*=0.7 Hz, J_{HH}=9.1 Hz, H-3), 7.17 (ddd, 1H, *J*=0.7 Hz, J_{HF}=2.0, 11.0 Hz, H-8), 8.04 (d, 1H, J_{HH}=9.1 Hz, H-4); ^{19}F NMR (282 MHz, acetone): δ 40.02 (bt, 1F, *J*=2.4 Hz, F-5), 48.08 (dd, 1F, J_{FF}=2.9 Hz, J_{HF}=11.0 Hz, F-7); HRMS (EI): M^+, found 214.0103. $C_9H_5ClF_2N_2$ requires 214.0104.

16: White solid (53 mg, 53%); R_f 0.54; mp: 202–204 °C; [Found: C, 46.52; Cl, 30.58; F, 8.18. $C_9H_5Cl_2FN_2$ requires C, 46.78; Cl, 30.69; F, 8.22]; IR (KBr) *ν* 3472 (NH), 3389 (NH), 1618 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg ε): 219 (4.34), 263 (4.60), 351 (3.55); ^{1}H NMR (400 MHz, acetone-d_6): δ 6.26 (bs, 2H, NH_2), 7.03 (dd, 1H, J_{HH}=0.7 Hz, J_{HF}=10.4 Hz, H-8), 7.41 (dd, 1H, *J*=0.5 Hz, J_{HH}=8.9 Hz, H-3), 8.61 (dd, 1H, J_{HH}=0.7, 8.9 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 101.9 (d, 1C, *J*=22.5 Hz, C-8), 102.4 (d, 1C, *J*=22.7 Hz, C-6), 114.8 (s, 1C, C-9), 120.8 (d, 1C, *J*=2.4 Hz, C-3), 135.1 (d, 1C, *J*=1.7 Hz, C-4), 144.0 (d, 1C, *J*=4.9 Hz, C-5), 148.6 (d, 1C, *J*=15.3 Hz, C-10), 152.4 (s, 1C, C-2), 160.7 (d, 1C, *J*=247.3 Hz, C-7); ^{19}F NMR (282 MHz, acetone-d_6): δ 53.50 (d, 1F, J_{HF}=10.4 Hz, F-7); HRMS (EI): M^+, found 229.9809. $C_9H_5Cl_2FN_2$ requires 229.9808.

17: White solid (11 mg, 11%); R_f 0.20; mp: 215 °C with decomposition; IR (KBr) *ν* 3476 (NH), 3323 (NH), 3202 (NH), 1643 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg ε): 219 (4.27), 258 (4.39), 288 (3.49), 366 (3.56); ^{1}H NMR (400 MHz, acetone-d_6): δ 6.01 (bs, 2H, NH_2), 7.09 (dd, 1H, J_{HH}=0.7 Hz, J_{HF}=1.6 Hz, H-8), 7.23 (d, 1H, J_{HH}=8.6 Hz, H-3), 8.23 (dd, 1H, J_{HH}=0.7, 8.6 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 104.8 (d, 1C, *J*=3.3 Hz, C-7), 108.3 (d, 1C, *J*=18.6 Hz, C-9), 110.8 (d, 1C, *J*=16.3 Hz, C-8), 119.1 (d, 1C, *J*=2.3 Hz, C-3), 132.7 (d, 1C, *J*=3.4 Hz, C-4), 148.3 (d, 1C, *J*=3.4 Hz, C-6), 148.5 (d, 1C, *J*=4.4 Hz, C-10), 152.7 (s,

1C, C-2), 154.8 (d, 1C, *J*=252.6 Hz, C-5); ^{19}F NMR (282 MHz, acetone-d_6): δ 41.43 (bs, 1F, F-5); HRMS (EI): M^+, found 229.9812. $C_9H_5Cl_2FN_2$ requires 229.9808.

*4.7.7. 2-Amino-6,8-difluoroquinoline (**18**), 8-amino-2-chloro-6-fluoroquinoline (**19**).* The mixture of **1f** (135 mg, 0.68 mmol) with liquid NH_3 was heated for 28 h at 90 °C. The solid residue was extracted with acetone (50 mL). The extract was evaporated, crude product (117 mg) containing **18** and **19** was purified by TLC (CH_2Cl_2).

18: White solid (24 mg, 20%); R_f 0.45; mp: 197-199 °C; [Found: C, 59.64; H, 3.53; F, 21.08; N, 15.51. $C_9H_6F_2N_2$ requires C, 60.00; H, 3.36; F, 21.09; N, 15.55]; IR (KBr) *ν* 3447 (NH), 3306 (NH), 3163 (NH), 1657 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg ε): 234 (4.47), 250 (4.33), 343 (3.59); ^{1}H NMR (300 MHz, acetone-d_6): δ 6.04 (bs, 2H, NH_2), 6.96 (dd, 1H, *J*=0.8 Hz, J_{HH}=8.9 Hz, H-3), 7.13 (ddd, 1H, J_{HH}=2.7 Hz, J_{HF}=9.0, 10.9 Hz, H-7), 7.19 (ddd, 1H, J_{HF}=1.4, 9.0 Hz, J_{HH}=2.7 Hz, H-5), 7.92 (dd, 1H, J_{HF}=1.4, J_{HH}=8.9 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 104.8 (dd, 1C, *J*=23.2, 28.9 Hz, C-7), 107.4 (dd, 1C, *J*=4.7, 21.5 Hz, C-5), 115.1 (s, 1C, C-3), 125.1 (dd, 1C, *J*=4.6, 10.7 Hz, C-9), 135.7 (dd, 1C, *J*=1.5, 10.9 Hz, C-10), 137.2 (dd, 1C, *J*=3.6, 4.6 Hz, C-4), 156.8 (dd, 1C, *J*=11.6, 240.0 Hz, C-6), 156.9 (dd, 1C, *J*=12.8, 254.0 Hz, C-8), 158.6 (bs, 1C, C-2); ^{19}F NMR (282 MHz, acetone-d_6): δ 39.59 (ddt, 1F, 2J_{HF}=1.4 Hz, J_{FF}=4.1 Hz, J_{HF}=10.9 Hz, F-8), 43.72 (td, 1F, J_{FF}=4.1 Hz, 2J_{HF}=9.0 Hz, F-6); HRMS (EI): M^+, found 180.0490. $C_9H_6F_2N_2$ requires 180.0494.

19: White solid (78 mg, 59%); R_f 0.77; mp: 121 °C with decomposition; [Found: C, 54.75; H, 3.02; Cl, 17.85; F, 9.87; N, 14.21. $C_9H_6ClFN_2$ requires C, 54.98; H, 3.08; Cl, 18.03; F, 9.66; N, 14.25]; IR (KBr) *ν* 3476 (NH), 3354 (NH), 1630 (NH) cm^{-1}; UV (EtOH) *λ* nm (lg ε): 260 (4.46), 349 (3.37); ^{1}H NMR (500 MHz, acetone-d_6): δ 6.77 (dd, 1H, J_{HH}=2.6 Hz, J_{HF}=11.1 Hz, H-7), 6.80 (dd, 1H, J_{HH}=2.6 Hz, J_{HF}=9.5 Hz, H-5), 7.45 (d, 1H, J_{HH}=8.6 Hz, H-3), 8.18 (d, 1H, J_{HH}=8.6 Hz, H-4); ^{13}C NMR (126 MHz, acetone-d_6): δ 98.0 (d, 1C, *J*=23.6 Hz, C-5), 99.8 (d, 1C, *J*=29.5 Hz, C-7), 124.1 (s, 1C, C-3), 129.3 (d, 1C, *J*=12.7 Hz, C-9), 135.6 (s, 1C, C-10), 140.0 (d, 1C, *J*=5.9 Hz, C-4), 147.2 (d, 1C, *J*=2.7 Hz, C-2), 147.8 (d, 1C, *J*=14.0 Hz, C-8), 163.1 (d, 1C, *J*=242.6 Hz, C-6); ^{19}F NMR (282 MHz, acetone): δ 51.89 (dd, 1F, J_{HF}=9.5, 11.1 Hz, F-6); HRMS (EI): M^+, found 196.0196. $C_9H_6ClFN_2$ requires 196.0198.

*4.7.8. 2,8-Diamino-6-fluoroquinoline (**20**).* The mixture of **1f** (125 mg, 0.63 mmol) with liquid NH_3 was heated for 24 h at 150 °C. The crude product (104 mg) contained **18**, **19**, and **20**. Compound **20** was not isolated, its NMR spectra were recorded in a mixture of products. ^{19}F NMR (282 MHz, DMSO): δ 42.71 (bt, 1F, 2J_{HF}=10.5 Hz, F-6).

4.8. Reactions of polyfluorinated 2-chloroquinolines with aqueous NH_3 (general procedure).

A mixture of quinoline and aqueous NH_3 (10 mL) was kept in a 50 mL steel rotary autoclave. The products were extracted from the cooled reaction mixture with CH_2Cl_2 (3×25 mL). The extract was dried with $MgSO_4$, the solvent was evaporated, a solid residue was analyzed by GC-MS and ^{19}F NMR spectroscopy. The reaction conditions and yields of products are shown in Table 2.

*4.8.1. 2-Amino-5,6,7,8-tetrafluoroquinoline (**2**), 6-amino-5,7,8-trifluoroquinoline (**3**) and 7-amino-5,6,8-trifluoroquinoline (**4**), 2,7-diamino-5,6,8-trifluoroquinoline (**21**).* Mixture of **1a** (175 mg, 0.74 mmol) with aqueous NH_3 (30mL) was heated for 24 h at 85 °C. The crude product (163 mg) containing **1a**, **2**, **3**, **4** and **21** was purified by TLC (CH_2Cl_2). The fraction with R_f 0.21 contained **2** (61 mg, 38%), the fraction with R_f 0.64 contained **4** (80 mg, 47%) and, the fraction with R_f 0.84 contained **3** (8 mg, 5%).

The compound **21** was not isolated, its NMR spectra was recorded in mixture of products. ^{19}F NMR (282 MHz, acetone): δ -0.68 (dd, 1F, J_{FF}=6.0, 19.4 Hz, F-6), 6.61 (dd, 1F, J_{FF}=14.9, 19.4 Hz, F-5), 7.63 (ddd, 1F, J_{HF}=1.6 Hz, J_{FF}=6.0, 14.9 Hz, F-8).

Mixture of **1a** (150 mg, 0.64 mmol) with aqueous NH_3 (30mL) was heated for 3 h at 100 °C. The crude product (134 mg) containing **2**, **3**, **4**, and **21** was purified by TLC (CH_2Cl_2). The fraction with R_f 0.14 contained **2** (32 mg, 23%), the fraction with R_f 0.48 contained **4** (48 mg, 33%) and, the fraction with R_f 0.75 contained **3** (20 mg, 14%).

*4.8.2. 2-Amino-5,6,8-trifluoroquinoline (**5**) and 6-amino-2-chloro-5,8-difluoroquinoline (**6**).* The mixture of **1b** (100 mg, 0.46 mmol) with aqueous NH_3 was heated for 7 h at 120 °C. The crude product (71 mg) containing **1b**, **5**, **6**, and **22** was purified by TLC (CH_2Cl_2). The fraction with R_f 0.32 contained **5** (48 mg, 52%). Spectrum ^{19}F NMR of **22** in mixture coincides with. [8]

*4.8.3. 2-Amino-5,7,8-trifluoroquinoline (**7**) and 7-amino-2-chloro-5,8-difluoroquinoline (**8**), 2,7-diamino-5,8-difluoroquinoline (**24**).* The mixture of **1c** (97 mg, 0.45 mmol) with aqueous NH_3 was heated for 7 h at 120 °C. The crude product (71 mg) containing **7**, **8**, **23**, and **24** was purified by TLC (CH_2Cl_2). The fraction with R_f 0.45 contained **7** (46 mg, 52%). Spectrum ^{19}F NMR of **23** in mixture coincides with. [8]

The compound **24** was not isolated, its NMR spectra recorded in mixture of products. ^{19}F NMR (282 MHz, acetone): δ 3.61 (ddd, 1F, J_{HF}=1.4, 6.2 Hz, J_{FF}=17.3 Hz, F-8); 33.85 (dd, 1F, J_{HF}=11.4 Hz, J_{FF}=17.3 Hz, F-8).

*4.8.4. 2-Amino-6,7-difluoroquinoline (**9**), 6-amino-2-chloro-7-fluoroqinoline (**10**) and 7-amino-2-chloro-6-fluoroquinoline (**11**).* Mixture of **1e** (175 mg, 0.88 mmol) with aqueous NH_3 (30mL) was heated for 22 h at 120 °C. The crude product (139 mg) containing **1e**, **9**-**11**, and **1eb** was purified by TLC (1:2 CH_2Cl_2-hexane). The fraction with R_f 0.10 contained **9** (40 mg, 25%), the fraction with R_f 0.46 contained **11** (59 mg, 37%) and, the fraction with R_f 0.60 contained **10** (7 mg, 4%).

*4.8.5. 2-Amino-5,7-fluorioquinoline (**12**), 5-amino-2-chloro-7-fluoroquinoline (**13**) and 7-amino-2-chloro-5-fluoroquinoline (**14**).* The mixture of **1d** (94 mg, 0.47 mmol) with aqueous NH_3 was heated for 10 h at 120 °C. The crude product (68 mg) containing **1d**, **12**-**14** was purified by TLC (1:3 CH_2Cl_2-hexane). The fraction with R_f 0.40 contained **12** (32 mg, 38%), the fraction with R_f 0.93 contained **13** (3 mg, 3%).

*4.8.6. 2-Amino-6,8-difluoroquinoline (**18**), 8-amino-2-chloro-6-fluoroquinoline (**19**) and 2,8-diamino-6-fluoroquinoline (**20**).* The mixture of **1f** (100 mg, 0.50 mmol) with aqueous NH_3 was heated for 10 h at 150 °C. The crude product (68 mg) contained **18**-**20** and **1fb**.

*4.8.7. 2-Amino-6-chloro-5,7-fluorioquinoline (**15**), 5-amino-2,6-dichloro-7-fluoroquinoline (**16**), 7-amino-2,6-dichloro-5-fluoroquinoline (**17**), 2,5-diamino-6-chloro-7-fluoroquinoline (**25**) and 2,7-diamino-6-chloro-5-fluoroquinoline (**26**.)* The mixture of **1g** (100 mg, 0.43 mmol) with aqueous NH_3 was heated for 1 h at 100°C. The crude product (90 mg) contained **1g**, **15**-**17**.

The mixture of **1g** (154 mg, 0.66 mmol) with aqueous NH_3 (30 mL) was heated for 5 h at 100 °C. The crude product (91 mg) contained **1g**, **15**-**17**, **25**, and **26**. The compound **25** was not isolated, its NMR spectra recorded in mixture of products. ^{19}F

NMR (282 MHz, acetone): δ 49.00 (d, 1F, J_{HF}=11.4 Hz, F-7). The compound **26** was not isolated, its NMR spectra recorded in mixture of products. ^{19}F NMR (282 MHz, acetone): δ 37.64 (bd, 1F, J_{HF}=1.1 Hz, F-5).

X-ray structural analysis of **1e**, **1f**, **1g**, **4**, **5**, **11**, **12**, **16**, **18**, **19** and starting materials **1ea** and **1ga**. CCDC 1481803 and 1481804 (for **1e**), 1481805 (for **1f**), 1481806 (for **1g**), 1481807 (for **4**), 1481809 (for **5**), 1481808 (for **11**), 1481810 (for **12**), 1481811 (for **16**), 1481812 (for **18**), 1481813 (for **19**), 1481814 (for **1ga**) and 1481815 (for **1ea**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

Authors would like to acknowledge the Multi-Access Chemical Service Center SB RAS for spectral and analytical measurements. We are grateful to Dr. Ilia V. Eltsov, Roman Yu. Peshkov (Novosibirsk State University) and Nadezhda V. Pleshkova (NIOCH SB RAS) for recording NMR spectra. This work was financially supported by the Russian Foundation for Basic Research (grant 14-03-00108).

Supplementary data

Supplementary data (Preparation of starting materials, NMR spectra of new compounds, and XRD data) related to this article can be found on the Internet at http://

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