Synthesis of 8-Fluoro-3,4-dihydroisoquinoline and Its Transformation to 1,8-Disubstituted Tetrahydroisoquinolines

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Abstract: A simple procedure for the synthesis of 8-fluoro-3,4-dihydroisoquinoline is described below, based on a directed ortho-lithiation reaction. This key intermediate was then applied in various transformations. Fluorine–amine exchange afforded the corresponding 8-amino-3,4-dihydroisoquinolines, suitable starting compounds for the synthesis of 1-substituted 8-amino-tetrahydroisoquinolines. On the other hand, reduction and alkylation reactions of 8-fluoro-3,4-dihydroisoquinoline led to novel 1,2,3,4-tetrahydroisoquinoline derivatives that can be used as building blocks in the synthesis of potential central nervous system drug candidates.

Keywords: isoquinoline; lithiation; nucleophilic aromatic substitution; reduction; alkylation; cyclization

1. Introduction

Isoquinolines and their partly saturated congeners (i.e., dihydro- and tetrahydroisoquinolines) constitute an important class of natural and synthetic compounds exhibiting biological activity. N-Acylated 1,8-disubstituted 1,2,3,4-tetrahydroisoquinolines 1 [1] and 2 [2] (Figure 1) proved to be potent calcium channel blockers for the treatment of chronic pain. Nomifensine (3), a norepinephrine–dopamine reuptake inhibitor [3], was launched as an antidepressant, without sedative effects.

Figure 1. 1,8-Disubstituted tetrahydroisoquinoline target compounds (4) and their closest analogies (1–3) from the medicinal chemistry literature.
The observed biological activity and our interest in the elaboration of a simple synthesis of isoquinoline derivatives monosubstituted on the aromatic ring at position 8 prompted us to develop an efficient synthesis of 8-fluoro-3,4-dihydroisoquinoline key intermediate and its further transformation to 1,2,3,4-tetrahydroisoquinolines bearing various cyclic amino substituents at position 8 and diverse lipophilic substituents at position 1 (4, Figure 1).

In general, the syntheses of tetrahydroisoquinolines exhibiting one single substituent on the benzene ring at position 8 require individual solutions. Compounds 1 (see Figure 1) were synthesized starting from N-acetylated arylethylamines 5 (Scheme 1) [1]. The 4-bromo substituent in dihydroisoquinoline intermediate 6 serves as a protecting group, preventing formation of the regioisomeric isoquinoline, which would be the preferred product in the course of Bischler–Napieralski cyclization. Reduction of the C=N double bond of intermediate 6 with sodium borohydride leads to the corresponding tetrahydroisoquinoline 7. The bromine protecting group could then be removed by catalytic hydrogenation to give compound 8, which was transformed in two steps to products 1.

**Scheme 1.** The synthesis of 1,8-disubstituted tetrahydroisoquinolines 1. (a) P₂O₅, POCl₃, toluene, 120 °C, 5 h; (b) NaBH₄, EtOH, rt, 1 h; (c) H₂, 10% Pd/C, Et₃N, EtOH, rt, 22 h; (d) CICH₂COCl; (e) corresponding amine, K₂CO₃.

The disadvantage of the synthetic route shown in Scheme 1 is that in order to introduce a new substituent into position 1 of the isoquinoline, the whole synthetic route has to be repeated with the new substituent in place of the cyclohexyl group.

A simple and widely applicable method has been published for the synthesis of 1-substituted tetrahydroisoquinolines 9 by treatment of 3,4-dihydroisoquinoline (10) with Grignard or organolithium reagents (Scheme 2) [4]. Organolithium reagents react much faster, even under milder conditions, than the corresponding Grignard reagents.

**Scheme 2.** Introduction of substituents into position 1 of tetrahydroisoquinoline 9 [4].

When starting from 8-fluoroisoquinoline (11, Scheme 3), a similar introduction of the substituent into position 1 is more complicated, as demonstrated by the synthesis of compound 2 (see Figure 1) [2]. The C-1 position has to be activated by quaternization with benzyl bromide (12) before treatment with the appropriate Grignard reagent to give 1-aryl derivative 13. Reduction of the hetero ring, followed by removal of the benzyl group to furnish tetrahydro congener 14 and subsequent introduction of the N-substituent, leads to target compound 2.
Scheme 2. Introduction of substituents into position 1 of tetrahydroisoquinoline exhibiting cyclic amino substituents is well documented in the patent literature by treatment of 8-bromoisoquinoline (15) with various amines under Ullmann [5–7] or Buchwald–Hartwig [8–14] conditions (Scheme 4). Several examples are mentioned in patent applications for the reduction of 8-aminoisoquinolines 16 to 1,2,3,4-tetrahydroisoquinolines 17 [8,14–16].

Scheme 3. Synthesis of compound 2 [2]. (a) PhCH₂Br, CH₃CN, 90 °C, 3 h; (b) 4-CF₃C₆H₄MgBr, THF, 0 °C to rt, 4 h; (c) NaBH₄, AcOH, THF, rt, 2 h; (d) Pd(OH)₂, H₂, EtOH, 50 psi, 3 h; (e) 4-F-phenyl isocyanate, CH₂Cl₂, rt, 1 h.

The synthesis of 8-aminoisoquinolines 16 exhibiting cyclic amino substituents is well documented in the patent literature by treatment of 8-bromoisoquinoline (15) with various amines under Ullmann [5–7] or Buchwald–Hartwig [8–14] conditions (Scheme 4). Several examples are mentioned in patent applications for the reduction of 8-aminoisoquinolines 16 to 1,2,3,4-tetrahydroisoquinolines 17 [8,14–16].

Scheme 4. Synthesis of 8-aminoisoquinolines 16. (a) NBS, cc. H₂SO₄, –22 to –18 °C, 5 h; (b) KNO₃, cc. H₂SO₄, rt, 1 h; (c) H₂, 10% Pd/C, DMF–Et₃N; (d) NaNO₂, HBr, 0–5 °C, then CuBr, HBr; (e) cyclic amine, Pd(0) cat., base (Buchwald–Hartwig reaction); (f) cyclic amine, Cul, base (K₂CO₃), high temperature, solvent e.g., DMA (Ullmann reaction); (g) H₂, PtO₂; (h) H₂NCH₂CH(OH)₂, toluene, reflux; (i) P₂O₅, H₂SO₄, 0 °C, 4%.

However, the efficient synthesis of starting material 8-bromoisoquinoline (15, Scheme 4) requires a multistep sequence. Bromination of isoquinoline (18) at position 5 [17] followed by nitration at position 8 affords 5-bromo-8-nitroisoquinoline (19). Reduction of the nitro group accompanied with the removal of the bromo substituent results in 8-aminoisoquinoline (20). Diazotization of the amino group followed by treatment with copper(I) bromide and hydrogen bromide gives 8-bromoisoquinoline (15) [18,19]. The seemingly shorter synthesis starting from 2-bromobenzaldehyde (Scheme 4) does not ensure an alternative, since Pomeranz–Fritsch cyclization of Schiff base 21 gives very low, irreproducible yields [20].
2. Results and Discussion

After surveying the literature, we concluded that an efficient synthetic route to target compounds 4 should involve introduction of the lipophilic substituents into position 1 by treating 8-(cyclic amino)-3,4-dihydroisoquinoline 22 with the appropriate lithium reagent (Scheme 5). 8-Fluoro-3,4-dihydroisoquinoline (23) was selected as the precursor of compound 22, expecting that the C=N double bond activates the fluorine atom towards nucleophilic substitution by cyclic amines. Thus, the best of our knowledge, compound 23 is not described in the literature.

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\begin{align*}
\text{Scheme 5. Retrosynthetic analysis of 1,8-disubstituted 1,2,3,4-tetrahydroisoquinolines 4.}
\end{align*}
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Schlosser and coworkers reported a short and efficient synthesis of 8-methoxy-3,4-dihydroisoquinoline. Lithiation of N-pivaloyl-3-methoxyphenylethylamine (24) with butyllithium in diethyl ether at 25 °C for 2 h, followed by treatment with dimethylformamide gave aldehyde 25 (Scheme 6). Acid-catalyzed cyclization of the latter was accompanied by the loss of the pivaloyloxymethyl group resulting in 8-methoxy-3,4-dihydroisoquinoline hydrochloride (26 * HCl) in 79% overall yield [21].

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\begin{align*}
\text{Scheme 6. Synthesis of 8-methoxy-3,4-dihydroisoquinoline hydrochloride (26 * HCl). (a) BuLi (hexane), diethyl ether, 25 °C, 2 h; (b) DMF, −78 °C → 25 °C, 1 h; (c) aq. HCl (10%), CH₂Cl₂, 25 °C, 24 h.}
\end{align*}
\]

The ortho-directing ability of fluorine in lithiation reactions of aromatic compounds is well documented in the literature [22–27]. Based on this, we succeeded in extending the aforesaid method for the synthesis of 8-fluoro-3,4-dihydroisoquinoline (23) by a significant modification of the reaction conditions in the metatation step. Acylation of 2-(3-fluorophenyl)ethylamine (27) with pivaloyl chloride led to pivaloylamide 28 (Scheme 7). The lithiation was performed at −78 °C in order to prevent aryne formation by LiF elimination. Due to the poor solubility of compound 28 in diethyl ether at this low temperature, THF was used as the solvent. Subsequent treatment with DMF afforded formyl derivative 29, demonstrating that the lithiation occurred at the common ortho site of the substituents. Cyclization of aldehyde 29 in acidic medium occurred with simultaneous loss of the pivaloyloxymethyl group to give 8-fluoro-3,4-dihydroisoquinoline (23), which was prepared as the hydrochloride hydrate (23 * HCl * H₂O).

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\begin{align*}
\text{Scheme 7. Synthesis of 8-fluoro-3,4-dihydroisoquinoline hydrochloride hydrate (23 * HCl * H₂O). (a) Me₂C-COCl, Et₃N, CH₂Cl₂, 99%; (b) BuLi (hexane), THF, −78 °C, 2 h; (c) DMF, −78 °C → 25 °C, 1 h, 68% for the two steps; (d) aq. HCl (10%), CH₂Cl₂, 25 °C, 24 h, 74%.}
\end{align*}
\]
Next, 8-fluoro-3,4-dihydroisoquinoline hydrochloride hydrate (23 · HCl · H₂O) was heated with morpholine, pyrrolidine and piperidine at 80 °C for several hours in a sealed tube (Scheme 8). In the case of morpholine and pyrrolidine, the required products 22a and 22b were isolated in moderate yields (51% and 49%). Unexpectedly, piperidine derivative 22c was obtained in significantly lower yield (17%). Higher reaction temperatures and longer reaction times did not improve the yields: tarring was observed and HPLC-MS measurements indicated formation of the dehydrogenated byproduct (the corresponding 8-aminoisoquinoline). Analogous reactions starting from base 23 were significantly slower indicating that protonation of the N-2 atom increased the electrophilicity of the C-8 atom, i.e., it promotes the nucleophilic attack at this position.

![Scheme 8](image)

**Scheme 8.** Synthesis of 8-amino-3,4-dihydroisoquinolines 22.

In order to obtain the 1,8-disubstituted target compounds, 8-(pyrrolidin-1-yl)-3,4-dihydroisoquinoline hydrochloride (22b) was treated with various alkyl lithiurns and phenyl lithium (Scheme 9) to afford 1-alkyl(aryl)-8-amino-3,4-dihydroisoquinolines 4 in good yields.

![Scheme 9](image)

**Scheme 9.** Synthesis of 1-alkyl(aryl)-8-amino-1,2,3,4-tetrahydroisoquinolines 4.

Finally we realized that some simple 8-fluoroisoquinoline derivatives easily available from 8-fluoro-3,4-dihydroisoquinoline (23) are not described in the literature. Therefore we treated compound 23 with sodium borohydride to obtain tetrahydroisoquinoline 30 (Scheme 10). Methylation of compound 23 with methyl iodide gave isoquinolinium derivative 31, which was reduced with sodium borohydride to 8-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline 32. To the best of our knowledge, isoquinoline derivatives 30–32 are new. Although compound 30 has been mentioned in the literature [28], its preparation and characterization were not described.

![Scheme 10](image)

**Scheme 10.** Synthesis of new 8-fluoro-1,2,3,4-tetrahydroisoquinoline derivatives 30–32. (a) NaBH₄, MeOH, 1 h, 25 °C; (b) Mel, CH₂Cl₂, 24 h, 25 °C.
3. Experimental Section

General

All melting points were determined on a Büchi B-540 (Flawil, Switzerland) capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Bruker ALPHA FT-IR spectrometer (Billerica, MA, USA) in KBr pellets of as a film. $^1$H-NMR, $^{13}$C-NMR and $^{19}$F-NMR spectra were recorded at 295 K on a Bruker Avance III HD 600 (Billerica, MA, USA) (600, 150 and 564.7 MHz for $^1$H, $^{13}$C- and $^{19}$F-NMR spectra, respectively) or at ambient temperature on a Bruker Avance III 400 (Billerica, MA, USA) (400 and 100 MHz for $^1$H and $^{13}$C-NMR spectra, respectively) spectrometer. CDCl$_3$ or CD$_3$OD was used as the solvent, tetramethylsilane (TMS) for $^1$H, $^{13}$C-NMR or trifluoromethane (CFCl$_3$) for $^{19}$F-NMR as the internal standard. Chemical shifts ($\delta$) and coupling constants ($J$) are given in ppm and in Hz, respectively. Mass spectra were recorded on a Bruker O-TOF MAXIS Impact mass spectrometer (Billerica, MA, USA) coupled with a Dionex Ultimate 3000 RS HPLC (Sunnyvale, CA, USA) system with a diode array detector. The reactions were followed by analytical thin-layer chromatography on silica gel 60 F$254$ (Darmstadt, Germany) and HPLC-MS on a Shimadzu LC-20 HPLC equipment (Kyoto, Japan). Purifications by flash chromatography were carried out using Merck 107736 silica gel 60 H (Darmstadt, Germany) using a hexane–ethyl acetate or dichloromethane–methanol solvent system. All reagents were purchased from commercial sources.

N-[2-(3-Fluorophenyl)ethyl]-2,2-dimethylpropanamide (28). Pivaloyl chloride (24.3 mL, 23.8 g, 198 mmol) in dichloromethane (40 mL) was added to a solution of 27 (23.5 mL, 25.0 g, 180 mmol) and triethylamine (30.0 mL, 21.8 g, 216 mmol) in dichloromethane (160 mL) at 0 °C. After stirring for 1 h at room temperature, the mixture was washed with an aqueous sodium hydrogencarbonate solution (5%, 3 x 70 mL). The organic layer was dried over MgSO$_4$ and evaporated. The solid residue was recrystallized from heptane to afford the title compound (3.03 g, 54%) as a pale yellow solid. Mp 86–87 °C.

N-[2-(3-Fluoro-2-formylphenyl)ethyl]-2,2-dimethylpropanamide (29). A solution of BuLi (1.6 M in hexane, 42.1 mL, 67.4 mmol) was added to a solution of 28 (5.01 g, 22.5 mmol) in THF (70 mL) at −78 °C. After stirring for 2 h at −78 °C, DMF (10.4 mL, 9.84 g, 134.8 mmol) was added. The mixture was stirred for 1 h. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (40 mL), and extracted with ethyl acetate (30 and 2 x 10 mL). The combined organic layer was washed with brine (40 mL), and dried over MgSO$_4$. The solvents were evaporated, the residue was purified by flash chromatography (5–30% ethyl acetate in hexane) to afford the title compound (3.03 g, 54%) as a pale yellow solid. Mp 86–87 °C. IR (KBr): ν = 3348, 1633, 1535 cm$^{-1}$. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 7.27 (td, $J_{HH}$ = 7.8 Hz, $J_{HF}$ = 6.1 Hz, 1H), 6.99–6.87 (m, 3H), 5.62 (br s, 1H), 3.49 (td, $J_{CH2-CH2}$ = 6.9 Hz, $J_{CH2-NH}$ = 5.9 Hz, 2H), 2.82 (t, $J$ = 6.9 Hz, 2H), 1.15 (s, 9H). $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ = 178.4, 162.9 (d, $J_{CF}$ = 246 Hz), 141.6 (d, $J_{CF}$ = 7.1 Hz), 130.0 (d, $J_{CF}$ = 8.3 Hz), 124.5 (d, $J_{CF}$ = 2.7 Hz), 115.6 (d, $J_{CF}$ = 21.0 Hz), 113.4 (d, $J_{CF}$ = 20.9 Hz), 40.4, 38.6, 35.4 (d, $I_{CF}$ = 1.7 Hz), 27.5. $^{19}$F-NMR (564.7 MHz, CDCl$_3$): $\delta$ = −113.7 (ddd, $J_{FH}$ = 9.8, 8.9, 6.1 Hz). HRMS calcd. for C$_{13}$H$_{19}$FNO+$^+$ ([M + H]$^+$): 224.1445, found: 224.1446.

8-Fluoro-3,4-dihydroisoquinoline hydrochloride hydrate (23 · HCl · H$_2$O). A solution of 29 (3.29 g, 13.1 mmol) in dichloromethane (25 mL) and aqueous hydrochloric acid (15%, 60 mL) were vigorously stirred for 24 h at 25 °C. The aqueous layer was extracted with diethyl ether (35 mL), and the organic
layer was extracted with water (15 mL). The combined aqueous layer was evaporated, and the residue was recrystallized from ethanol/diethyl ether to afford the title compound (2.08 g, 78%) as a pale yellow solid. Mp 103–105 °C (ethanol/diethyl ether). IR (KBr): ν = 3471, 1664 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 16.00 (brs, 1H), 9.12 (brs, 1H), 7.78 (ddd, J_HH = 8.4, 7.6 Hz, J_HF = 5.7 Hz, 1H), 7.23–7.18 (m, 2H), 4.11 (t, J = 8.1 Hz, 2H), 3.24 (t, J = 8.1 Hz, 2H). ¹³C-NMR (150 MHz, CDCl₃), δ = 163.0 (d, J_CF = 266 Hz), 159.2 (d, J_CE = 6.4 Hz), 140.3 (d, J_CE = 9.9 Hz), 138.3, 124.5 (d, J_CF = 3.3 Hz), 115.6 (d, J_CF = 19.5 Hz), 112.9 (d, J_CF = 11.8 Hz), 41.3, 24.3 (d, J_CF = 2.2 Hz). ¹⁹F-NMR (564.7 MHz, CDCl₃): δ = −113.1 (dd, J_FH = 8.8, 5.7 Hz). Anal. calcd. for C₉H₁₁ClFNO (203.64): Cl 17.41, N 6.88%. Found: Cl 17.83, N 7.02%.

8-Fluoro-3,4-dihydroisoquinoline (23). To a vigorously stirred mixture of 23·HCl·H₂O (5.89 g, 28.9 mmol) in dichloromethane (100 mL) and water (50 mL) aqueous sodium carbonate (10%, 20 mL) in dichloromethane (100 mL) was added. The solution was stirred for 8 h at 80 °C. The reaction mixture was cooled, dichloromethane (60 mL) was added, and the resulting mixture was extracted with water (2 × 50 mL) and brine (50 mL) and dried over MgSO₄. The solvent was evaporated to afford the title compound (3.99 g, 93%) as a pale brown oil. IR (film): ν = 1671 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 8.65 (t, J = 2.2 Hz, 1H), 7.32 (ddd, J_HH = 8.2, 7.5 Hz, J_HF = 5.7 Hz, 1H), 6.97 (dd, J_HF = 9.4 Hz, J_HH = 8.2 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 3.78 (m, 2H), 2.74 (m, 2H). ¹³C-NMR (150 MHz, CDCl₃), δ = 160.0 (d, J_CE = 254 Hz), 153.3 (d, J_CE = 5.2 Hz), 138.6 (d, J_CF = 2.8 Hz), 132.3 (d, J_CF = 8.8 Hz), 122.9 (d, J_CF = 3.4 Hz), 116.2 (d, J_CF = 12.6 Hz), 114.0 (d, J_CF = 20.6 Hz), 46.9, 24.6 (d, J_CF = 2.7 Hz). ¹⁹F-NMR (564.7 MHz, CDCl₃): δ = −123.9 (dd, J_FH = 9.4, 5.7 Hz). HRMS calcd. for C₉H₉F⁺ ([M + H]+): 201.0714, found: 201.0723.

8-(Morpholin-4-yl)-3,4-dihydroisoquinoline (22a). A mixture of 23·HCl·H₂O (3.45 g, 16.9 mmol) and morpholine (4.42 mL, 4.42 g, 50.8 mmol) was stirred for 16 h at 80 °C in a sealed tube. After the reaction mixture was cooled, dichloromethane (60 mL) was added, and the resulting mixture was extracted with water (3 × 20 mL). The combined organic layer was dried over MgSO₄, and evaporated. The residue was purified by flash chromatography (0–2% methanol in dichloromethane) to afford the title compound (1.68 g, 49%) as an orange oil. IR (film): ν = 2955, 1619, 1238 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 8.63 (brs, 1H), 7.32 (dd, J = 8.1, 7.4 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.87 (d, J = 7.4 Hz, 1H), 3.88 (m, 4H), 3.67 (brt, J = 7.3 Hz, 2H), 3.01 (m, 4H), 2.69 (brt, J = 7.3 Hz, 2H). ¹³C-NMR (150 MHz, CDCl₃), δ = 157.4, 151.0, 139.0, 130.9, 131.6, 121.7, 121.3, 116.5, 67.0, 53.4, 46.5, 29.6, 25.5. HRMS calcd. for C₁₃H₁₇N₂O⁺ ([M+H⁺]): 217.1335, found: 217.1341.

8-(Pyrrrolidin-1-yl)-3,4-dihydroisoquinoline (22b). A mixture of 23·HCl·H₂O (3.50 g, 17.2 mmol) and pyrrrolidine (4.23 mL, 3.66 g, 51.6 mmol) was stirred for 8 h at 80 °C in a sealed tube. After the reaction mixture was cooled, dichloromethane (60 mL) was added, and the resulting mixture was extracted with water (3 × 20 mL). The combined organic layer was dried over MgSO₄, and evaporated. The residue was purified by flash chromatography (0–5% methanol in dichloromethane) to afford the title compound (1.68 g, 49%) as an orange oil. IR (film): ν = 2945, 1608 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃), δ = 8.63 (brs, 1H), 7.19 (dd, J = 8.3, 7.3 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.59 (d, J = 7.3 Hz, 1H), 3.64 (brt, J ≈ 7 Hz, 2H), 3.39 (m, 4H), 2.67 (t, J = 7.2 Hz, 2H), 1.96 (m, 4H). ¹³C-NMR (150 MHz, CDCl₃), δ = 159.2, 148.7, 139.4, 131.1, 116.9, 112.8, 52.7, 46.0, 26.5, 25.6. HRMS calcd. for C₁₃H₁₅N₂⁺ ([M+H⁺]): 201.1386, found: 201.1393.

8-(Pyrrrolidin-1-yl)-3,4-dihydroisoquinoline hydrochloride (22b·HCl). Base 22b (1.68 g, 8.4 mmol) was dissolved in toluene (10 mL) and a solution of hydrochloric acid gas in isopropyl alcohol was added dropwise. The precipitate was filtered off to afford the title compound (1.98 g, 99%) as an orange solid. Mp 218–220 °C (ethanol/diethyl ether). IR (KBr): ν = 2858, 1612 cm⁻¹. ¹H-NMR (600 MHz, CDCl₃), δ = 13.68 (brs, 1H), 9.00 (d, J = 8.4 Hz, 1H), 7.40 (dd, J = 8.8, 7.1 Hz, 1H), 6.72 (brd, J = 8.8 Hz, 1H), 6.57 (brd, J = 7.1 Hz, 1H), 3.84 (td, J_CH₂-CH₂ = 7.5 Hz, J_CH₂-NH = 3.0 Hz, 2H), 3.60 (m, 4H), 3.04 (t, J = 7.5 Hz,
1.73 mL, 4.31 mmol) was added to a suspension of 1-Hexyl-8-(pyrrolidin-1-yl)-1,2,3,4-tetrahydroisoquinoline (1-Butyl-8-(pyrrolidin-1-yl)-1,2,3,4-tetrahydroisoquinoline (4b)). A solution of MeLi (1.6 M in diethyl ether, 2.67 mL, 4.28 mmol) was added to a suspension of 22b · HCl (506 mg, 2.14 mmol) in THF (15 mL) at −78 °C. The mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 8 mL). The combined organic layer was dried over MgSO$_4$. The solvents were evaporated, the residue was purified by flash chromatography (3–6% methanol in dichloromethane) to afford the title compound (291 mg, 63%) as a pale brown oil. IR (film): $\nu$ = 2935, 1583 cm$^{-1}$. $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ = 158.0, 152.6, 133.4, 126.2, 123.0, 116.0, 51.8, 48.9, 38.8, 30.3, 21.2, 19.9. HRMS calcd. for C$_{14}$H$_{21}$N$_2^+$ ([M + H]+): 215.1543, found: 215.1549.

1-Methyl-8-(pyrrolidin-1-yl)-1,2,3,4-tetrahydroisoquinoline (4a). A solution of MeLi (1.6 M in diethyl ether, 2.67 mL, 4.28 mmol) was added to a suspension of 22b · HCl (502 mg, 2.12 mmol) in THF (15 mL) at −78 °C. The mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 8 mL). The combined organic layer was dried over MgSO$_4$. The solvents were evaporated, the residue was purified by flash chromatography (3–6% methanol in dichloromethane) to afford the title compound (537 mg, 98%) as a pale brown oil. IR (film): $\nu$ = 2935, 1620 cm$^{-1}$. $^{1}$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 7.09 (dd, $J$ = 7.9, 7.5 Hz, 1H), 6.92 (br d, $J$ = 7.9 Hz, 1H), 6.74 (br d, $J$ = 7.5 Hz, 1H), 4.47 (q, $J$ = 6.7 Hz, 1H), 3.35–3.23 (m, 1H), 3.09 (dt, $J_{gem}$ = 12.8 Hz, $J$ = 5.4 Hz, 1H), 2.97–2.78 (m, 4H), 2.03–1.79 (m, 4H), 1.47 (d, $J$ = 7.1 Hz, 3H). $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ = 148.0, 135.7, 133.4, 126.2, 123.0, 116.0, 51.8, 48.9, 38.8, 30.3, 21.2, 19.9. HRMS calcd. for C$_{14}$H$_{21}$N$_2^+$ ([M + H]+): 217.1699, found: 217.1705.

1-Butyl-8-(pyrrolidin-1-yl)-1,2,3,4-tetrahydroisoquinoline (4b). A solution of BuLi (1.6 M in hexane, 2.65 mL, 4.25 mmol) was added to a suspension of 22b · HCl (502 mg, 2.12 mmol) in THF (15 mL) at −78 °C. The mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 8 mL). The combined organic layer was dried over MgSO$_4$. The solvents were evaporated, the residue was purified by flash chromatography (3–6% methanol in dichloromethane) to afford the title compound (291 mg, 63%) as a pale brown oil. IR (film): $\nu$ = 2935, 1583 cm$^{-1}$. $^{1}$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 7.07 (dd, $J$ = 8.1, 7.5 Hz, 1H), 6.94 (dd, $J$ = 8.1, 1.4 Hz, 1H), 6.75 (dd, $J$ = 7.5, 1.4 Hz, 1H), 4.21 (dd, $J$ = 9.8, 2.5 Hz, 1H), 3.29 (m, 2H), 3.21 (m, 1H), 3.00 (dt, $J_{gem}$ = 12.6 Hz, $J$ = 5.2 Hz, 1H), 2.91–2.82 (m, 3H), 2.76 (dt, $J_{gem}$ = 16.4 Hz, $J$ = 5.2 Hz, 1H), 2.00–1.78 (m, 5H), 2.10 (br s, 1H), 1.60 (m, 1H), 1.49 (m, 1H), 1.43–1.27 (m, 3H), 0.91 (t, $J$ = 7.1 Hz, 3H). $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ = 148.1, 134.7, 131.1, 126.9, 123.4, 117.1, 53.1, 52.2, 38.2, 32.5, 28.6, 28.4, 25.0, 22.4, 13.8. HRMS calcd. for C$_{14}$H$_{27}$N$_2^+$ ([M + H]+): 259.2169, found: 259.2171.

1-Hexyl-8-(pyrrolidin-1-yl)-1,2,3,4-tetrahydroisoquinoline (4c). A solution of hexyllithium (2.5 M in hexane, 1.73 mL, 4.31 mmol) was added to a suspension of 22b · HCl (510 mg, 2.16 mmol) in THF (15 mL) at −78 °C. The mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 8 mL). The combined organic layer was dried over MgSO$_4$. The solvents were evaporated, the residue was purified by flash chromatography (1–5% methanol in dichloromethane) to afford the title compound (427 mg, 69%) as a pale brown oil. IR (film): $\nu$ = 2924, 1583 cm$^{-1}$. $^{1}$H-NMR (600 MHz, CDCl$_3$): $\delta$ = 7.06 (dd, $J$ = 8.0, 7.4 Hz, 1H), 6.93 (br d, $J$ = 8.0 Hz, 1H), 6.75 (dd, $J$ = 7.4, 1.1 Hz, 1H), 4.16 (dd, $J$ = 9.9, 2.5 Hz, 1H), 3.28 (m, 2H), 3.17 (m, 1H), 2.96 (m, 1H), 2.96 (ddd, $J_{gem}$ = 12.7 Hz, $J$ = 5.7, 4.7 Hz, 1H), 2.87–2.80 (m, 3H), 2.72 (dt, $J_{gem}$ = 16.4 Hz, $J$ = 4.9 Hz, 1H), 1.98–1.91 (m, 2H), 1.89–1.80 (m, 3H), 1.57 (m, 1H), 1.49 (m, 1H), 1.43–1.37 (m, 3H), 0.91 (t, $J$ = 7.1 Hz, 3H). $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ = 158.0, 152.6, 133.4, 126.2, 123.0, 116.0, 51.8, 48.9, 38.8, 30.3, 21.2, 19.9. HRMS calcd. for C$_{14}$H$_{21}$N$_2^+$ ([M + H]+): 215.1543, found: 215.1549.
1-Phenyl-8-(pyrrolidin-1-yl)-1,2,3,4-tetrahydroisoquinoline (4d). A solution of PhLi (1.9 M in dibutyl ether, 2.24 mL, 4.25 mmol) was added to a suspension of 22b·HCl (503 mg, 2.13 mmol) in THF (15 mL) at −78 °C. The mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 8 mL). The combined organic layer was dried over MgSO₄. The solvents were evaporated, the residue was purified by flash chromatography (1–5% methanol in dichloromethane) to afford the title compound (396 mg, 67%) as a pale brown oil. IR (film): ν = 2999, 1584 cm⁻¹. ¹¹B-NMR (600 MHz, CDCl₃): δ = 7.22 (m, 2H), 7.17 (m, 2H), 7.11 (m, 2H), 6.93 (br d, J = 8.0 Hz, 1H), 6.87 (br d, J = 7.5 Hz, 1H), 5.37 (br s, 1H), 3.03 (m, 1H), 2.94–2.87 (m, 4H), 2.79 (m, 1H), 2.56 (m, 2H), 1.93 (br s, 1H), 1.66 (m, 2H), 1.53 (m, 2H). ¹³C-NMR (150 MHz, CDCl₃): δ = 148.5, 144.9, 136.9, 132.8, 127.9, 127.7, 126.9, 126.3, 123.6, 117.5, 57.3, 52.0, 38.7, 29.6, 24.7. HRMS calcd. for C₁₉H₂₁N₂⁺ ([M + H⁺]⁺): 279.1856, found: 279.1860.

8-Fluoro-1,2,3,4-tetrahydroisoquinoline (30). Sodium borohydride (153 mg, 4.04 mmol) was added to a solution of 23 (502 mg, 3.37 mmol) in methanol (10 mL), and the reaction mixture was cooled with an ice/water bath. After stirring for 1 h at room temperature, water (5 mL) was added, and the resulting mixture was extracted with dichloromethane (3 × 8 mL). The combined organic layer was dried over MgSO₄, and evaporated to afford the title compound (73% yield). IR (film): ν = 2924, 1468 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 8.2, 7.6 Hz, J₉ = 5.7 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.83 (dd, J = 9.7 Hz, 1H), 4.03 (br s, 2H), 3.11 (t, J = 5.9 Hz, 2H), 2.79 (br t, J = 5.9 Hz, 1H), 1.77 (br s, 1H). ¹³C-NMR (150 MHz, CDCl₃): δ = 159.5 (d, J_CF = 244 Hz), 137.4 (d, J_CF = 5.0 Hz), 126.8 (d, J_CF = 8.6 Hz), 124.6 (d, J_CF = 3.1 Hz), 123.4 (d, J_CF = 17.1 Hz), 112.0 (d, J_CF = 21.3 Hz), 43.3, 42.2 (d, J_CF = 5.1 Hz), 28.8 (d, J_CF = 2.8 Hz). ¹⁹F-NMR (564.7 MHz, CDCl₃): δ = −121.2 (d, J_FH = 9.7, 5.7 Hz). HRMS calcd. for C₉H₁₁FN⁺ ([M + H⁺]⁺): 152.0870, found: 152.0874.

8-Fluoro-2-methyl-3,4-dihydroisoquinolin-2-ium iodide (31). Methyl iodide (0.43 mL, 970 mg, 6.88 mmol) was added to a solution of 23 (513 mg, 3.44 mmol) in dichloromethane (10 mL). After stirring for 24 h at room temperature the reaction mixture was filtered to afford the title compound (87% yield). IR (film): ν = 2924, 1468 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 8.2, 7.6 Hz, J₉ = 5.7 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.83 (dd, J = 9.7 Hz, 1H), 5.37–7.27 (m, 2H), 4.11 (t, J = 8.1 Hz, 2H), 3.85 (s, 3H), 3.34 (t, J = 8.1 Hz, 2H). ¹³C-NMR (150 MHz, CDCl₃): δ = 164.1 (d, J_CF = 264 Hz), 162.6 (br s), 141.5 (d, J_CF = 9.9 Hz), 139.2, 125.5 (d, J_CF = 3.4 Hz), 116.2 (d, J_CF = 19.8 Hz), 115.0 (d, J_CF = 17.1 Hz), 51.2, 48.7, 25.9 (d, J_CF = 2.2 Hz). ¹⁹F-NMR (564.7 MHz, CDCl₃): δ = −114.7 (d, J_FH = 9.6, 5.8 Hz). HRMS calcd. for C₁₀H₁₁FN⁺ ([M + H⁺]⁺): 164.0870, found: 164.0876.

8-Fluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline (32). Sodium borohydride (80 mg, 2.09 mmol) was added to a solution of 31 (508 mg, 1.75 mmol) in methanol (14 mL), and the reaction mixture was cooled with an ice/water bath. After stirring for 1 h at room temperature, water (6 mL) was added, and the resulting mixture was extracted with dichloromethane (3 × 8 mL). The combined organic layer was dried over MgSO₄, and evaporated. The residue was triturated in hexane and filtered. The filtrate was evaporated to afford the title compound (251 mg, 87%) as a colorless oil. IR (film): ν = 2924, 1468 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 7.10 (d, J = 8.2, 7.7 Hz, J₉ = 5.8 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.83 (d, J₉ = 9.7 Hz, J₉H = 8.2 Hz, 1H), 3.59 (s, 3H), 2.93 (t, J = 5.9 Hz, 2H), 2.67 (t, J = 5.9 Hz, 2H), 2.49 (s, 3H). ¹³C-NMR (150 MHz, CDCl₃): δ = 159.4 (d, J_CF = 244 Hz), 136.5 (d, J_CF = 4.7 Hz), 126.9 (d, J_CF = 8.6 Hz), 124.0 (d, J_CF = 3.2 Hz), 122.5 (d, J_CF = 16.3 Hz), 111.9 (d, J_CF = 20.9 Hz), 52.2, 51.6 (d, J_CF = 5.5 Hz), 46.1, 29.0 (d, J_CF = 2.5 Hz). ¹⁹F-NMR (564.7 MHz, CDCl₃): δ = −121.3 (d, J_FH = 9.7, 5.8 Hz). HRMS calcd. for C₁₀H₁₁FN⁺ ([M + H⁺]⁺): 166.1027, found: 166.1032.
4. Conclusions

A simple, lithiation-based synthesis of 8-fluoro-3,4-dihydroisoquinoline, a versatile substrate for further transformations, is described. Starting from this, 1-alkyl(phenyl)-8-(cyclic amino)-1,2,3,4-tetrahydroisoquinolines were prepared by a fluorine–amine exchange reaction followed by the addition of alkyl(phenyl)lithium reagents to the C=N double bond. The synthetic route, based on simple model compounds, provides the basis for the preparation of a compound library containing more complex analogues as potential central nervous system drug candidates. 8-Fluoro-3,4-dihydroisoquinoline is also an advantageous precursor of some new 1,2,3,4-tetrahydroisoquinoline building blocks, optionally substituted at the nitrogen atom.

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Sample Availability: Samples of the compounds 4a–d, 22a–c, 23, 28–32 are available from the authors.

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