Synthesis of 3-Chloro-4-fluoro-7,8-dihydro-6*H*-isoquinolin-5-one and Its Derivatives

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Received 23 January 2010

Abstract: Synthesis of novel 3-chloro-4-fluoro-7,8-dihydro-6*H*-isoquinolin-5-one and its derivatives using sequential *ortho*-formylation/*ortho*-allylation reactions of 2-chloro-3-fluoropyridine and ring-closing metathesis is described.

Key words: *ortho*-lithiation, ring-closing metathesis, fluoro pyridine, isoquinolinone, fused-ring system

In the past decades, fluorine has become increasingly popular in the field of medicinal chemistry.[1] This trend has been fueled by the interesting properties of the fluorine atom, such as: (1) its ability to undergo weak hydrogen bonding (C–F···H–X)[1e] or electrostatic interactions (C–F···C=O)[2] with protein structures, thereby increasing their binding affinity to such proteins; (2) Its high electronegativity can be used to influence the pK_a of the proximal acidic or basic groups;[3] (3) Its small size, which is comparable to that of the hydrogen atom in terms of van der Waals radius, together with the high C–F bond energy, makes fluorine an excellent substitute for metabolically labile hydrogens.[1,4] The latter approach has been used, for example, in the development of EGFR tyrosine kinase inhibitor Gefitinib (**1**).[5] Other examples of successful applications of fluorine in drug discovery include the anticancer agent Fluorouracil (**2**), the cholesterol-lowering drug Fluvastatin (**3**) and the antibacterial agent Ciprofloxacin (**4**) (Figure 1).

Recently, we became interested in the preparation of fluorinated isoquinolinones such as **5**. However, although simple 7,8-dihydro-6*H*-isoquinolin-5-one can be prepared by oxidation of commercially available 5,6,7,8-tetrahydroisoquinoline[6,7a] and is a useful starting point for the synthesis of biologically active agents,[7] to best of our knowledge, no fluorine-containing analog of **5** is known in the literature; this prompted us to develop a synthetic route to such compounds and our results are described in this paper.

Since introduction of a fluorine atom into organic molecules[8] can still represent a quite challenging exercise, our strategy (Scheme 1) was based on the formation of the cyclohexyl ring of **5** starting from commercially available 2-chloro-3-fluoropyridine (**8**). A double allylation of this compound by means of a sequential *ortho*-lithiation[9] reaction was envisioned to provide the intermediate **7**. Ring-closing metathesis (RCM)[10] of such diallyl intermediates, followed by reduction/oxidation of RCM-product **6** was expected to lead to the target compound **5**.

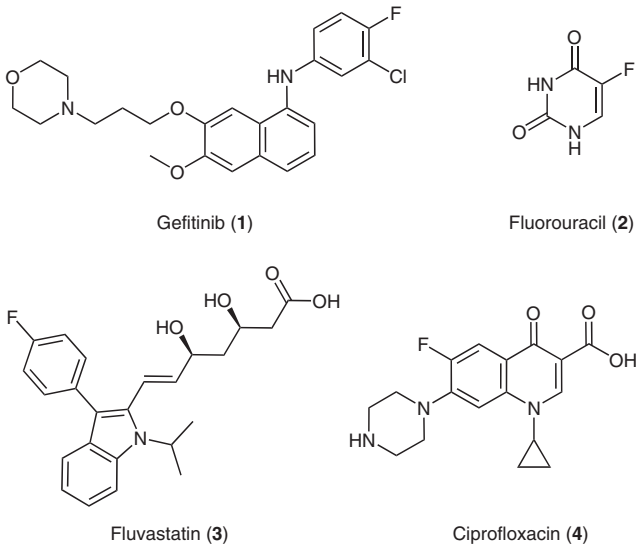
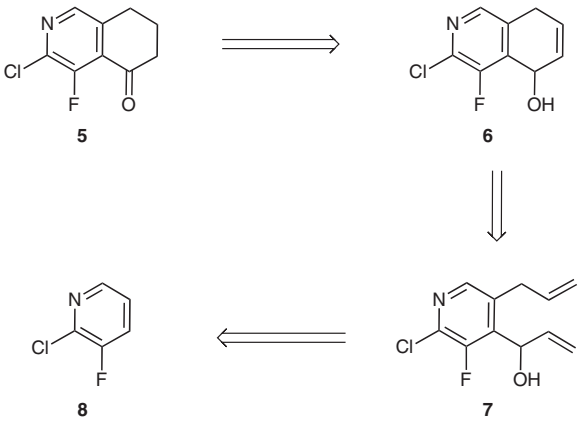


Figure 1 Examples of fluorine-containing drugs on the market

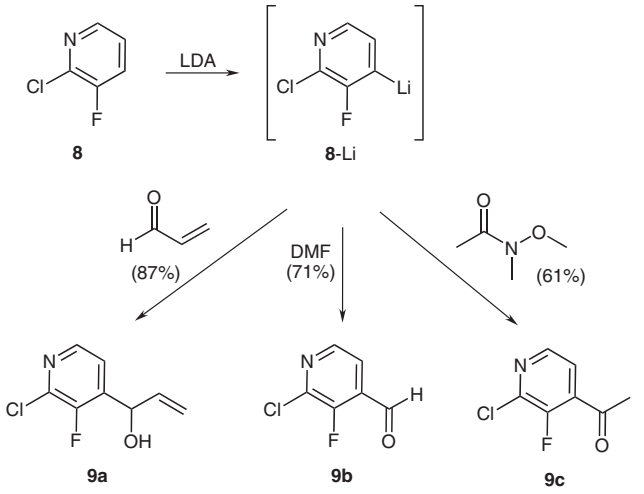


Scheme 1 Synthetic strategy towards tetrahydroisoquinolinone (**5**)

The synthesis began with the preparation of the substrate for RCM, **7** (Scheme 2). Lithiation of 2-chloro-3-fluoropyridine (**8**) occurred, as expected, at the 4-position (*ortho*- to fluorine atom)[11] as evidenced by the formation of products **9a–c**, which were isolated in good yields after quenching the lithium species **8**-Li with acrolein, *N*,*N*-dimethylformamide (DMF) or *N*-methoxy-*N*-methylacetamide.[12]

SYNLETT 2010, No. 9, pp 1397–1401
Advanced online publication: 13.04.2010
DOI: 10.1055/s-0029-1219818; Art ID: G01710ST

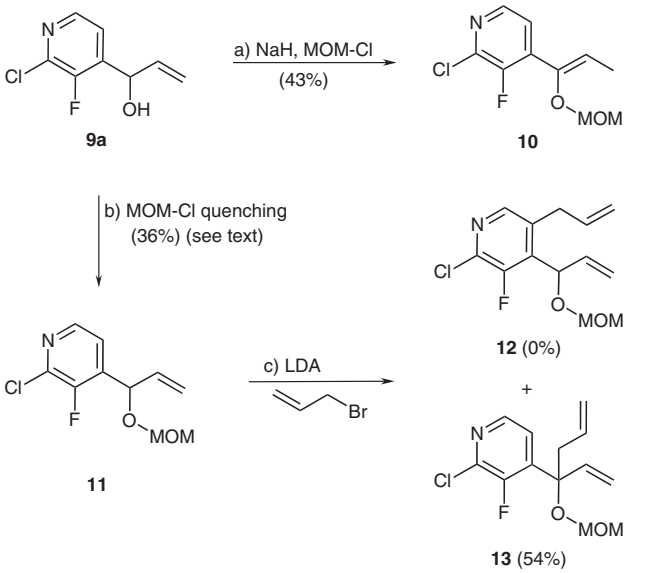
Next, we planned to use a second *ortho*-lithiation/allylation sequence with hydroxyallyl intermediate **9a** (Scheme 3). In order to achieve this task, we believed that it would be advantageous to attach an *ortho*-directing group,[13] such as methoxymethyl (MOM),[14] to the alcohol functionality of **9a**. Unexpectedly, all attempts to introduce the MOM-group under standard conditions failed; while weak bases such as Hünig's base afforded no product even at 50 °C, use of sodium hydride at 10 °C led to the isomerized enol ether **10** instead of desired MOM-protected alcohol **11**.



Scheme 2 Reagents and conditions: LDA (1.7 equiv), THF, –78 °C, 30 min, then electrophile (2 equiv), –78 °C to r.t., 2 h.

Interestingly, while no reaction was observed with NaH at –78 °C, the enol ether **10** was formed again simply by allowing the reaction temperature to reach 23 °C. We further observed that the formation of compound **10** already occurred at –20 °C, demonstrating the ease of such isomerization. The required intermediate **11** could finally be obtained by direct MOM-Cl quenching of the **9a**-alcoholate formed by addition of 4-pyridyl anion (**8**-Li) to acrolein (Scheme 3). Nevertheless, the expected second *ortho*-lithiation of **11** failed because LDA deprotonated this material at the benzylic position, leading to the formation of compound **13** by quenching with allyl bromide, instead of forming the anticipated product **12**.

Due to the observed high acidity of the benzylic position in **11**, we changed our initial strategy and, instead, tried to reach the desired intermediate **7a** starting from aldehyde **9b** (Scheme 4). This task could be achieved using Comins' method for the in situ protection/*ortho*-lithiation of aromatic aldehydes.[15a] The requisite allylaldehyde **15** was obtained in 30% yield (on a 120 mmol scale) after transmetallation of 5-pyridyl lithium species **14** with CuBr and subsequent nucleophilic substitution with allyl bromide. Despite further optimization of this reaction, no increase in the yield of intermediate **15** could be achieved. For example, direct reaction of allyl bromide with 5-pyridyl lithium **14** was extremely messy, while varying the temperature or using CuCN instead of CuBr also proved to be ineffective. It is worth mentioning that no *ortho*-lithiation of 4-pyridinyl carboxaldehyde of any kind has been reported in the literature. In addition, allylation of a close analog (3-pyridinyl carboxaldehyde), as reported by Zhai,[16a] also proved to be difficult (44% yield), as did its iodination, as reported by Gronowitz (18% yield).[16b]

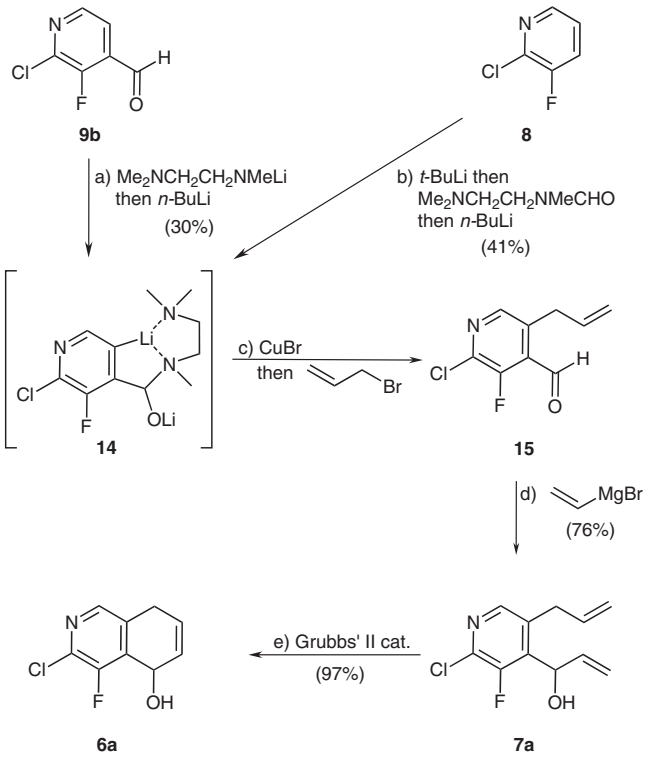


Scheme 3 *Reagents and conditions*: (a) NaH (1.5 equiv), 10 °C, 10 min, MOM-Cl (1.3 equiv), THF, 10 °C to r.t., 2 h; (b) MOM-Cl (1.1 equiv *cf.* LDA) added 2 h after acrolein addition to **8**-Li; (c) LDA (1.5 equiv), THF, –78 °C, 30 min, then electrophile (1.5 equiv), –78 °C to r.t., 2 h.

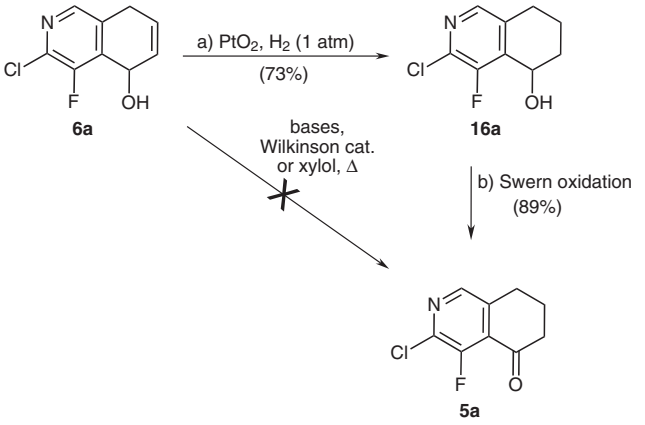
Finally, Comins' modified method[15b,c] was tried for the preparation of intermediate **15** directly from pyridine **8**. Thus, **8**-Li (formed using *t*-BuLi in this case) was added to *N*-formyl-*N*,*N*′,*N*′-trimethylethylene-1,2-diamine leading directly to the intermediate **14** upon a second deprotonation with *n*-BuLi. Subsequent transmetallation with CuBr and quenching of the cuprate with allyl bromide provided compound **15** in moderate yield (41%) directly from pyridine **8**.[17] The advantage of this approach over the aldehyde route is not only the higher yields of **15** obtained this way, but also that it avoids the need to isolate the intermediate aldehyde **9b**.

The highly functionalized pyridine **15** could easily be converted further into the required RCM precursor **7a** by addition of vinyl Grignard reagent[18] (Scheme 4). As expected, the planned RCM of diallyl compound **7a** with Grubbs' II catalyst[18] proceeded smoothly, providing the desired cyclized product **6a** in excellent isolated yield (97%). Grubbs' I catalyst[18] worked as well, but the product **6a** was obtained in lower yield (71%).

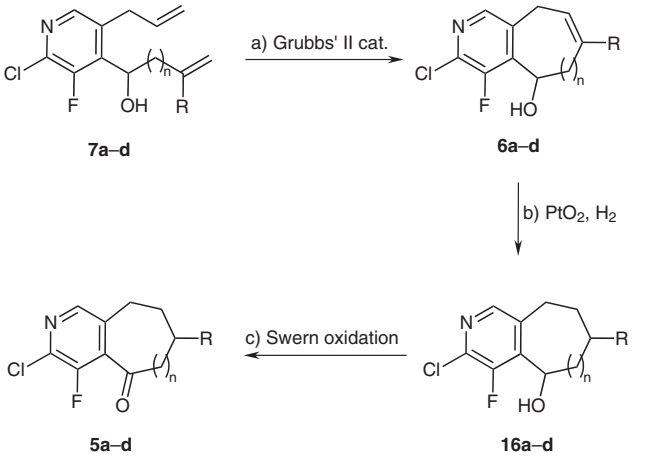
Further transformation of the alcohol **6a** into ketone **5a** was planned to be achieved by an isomerization of allylic alcohol to the corresponding ketone[19] (Scheme 5). In contrast to the conversion of **9a** into the enol ether **10**, which



Scheme 4 Reagents and conditions: (a) *N*,*N*,*N*′-trimethylethylene-1,2-diamine (1.4 equiv), *n*-BuLi (1.5 equiv), THF, –40 °C, 30 min then –10 °C, 30 min; **9b** (1 equiv), THF, –40 °C, 30 min; *n*-BuLi (1.5 equiv), –40 °C to –30 °C, 2 h; (b) *t*-BuLi (1.05 equiv), –78 °C, 1 h; *N*-formyl-*N*,*N*′,*N*′-trimethylethylene-1,2-diamine (1.05 equiv), *n*-BuLi (1.5 equiv), THF, –40 °C to –30 °C, 3 h; (c) CuBr (1.3 equiv), –30 °C to 0 °C, 1 h; allyl bromide (1.6 equiv), –30 °C to –10 °C, 1 h; (d) vinylmagnesium bromide (1.5 equiv), THF, 0 °C, 1 h; (e) Grubbs' II cat. (5 mol%), CH_2Cl_2, r.t., 1 h.



Scheme 5 *Reagents and conditions*: (a) PtO_2 (10 wt-%), H_2 (1 atm), MeOH, r.t., 1 h; (b) $(ClCO)_2$ (1.1 equiv), DMSO (2.2 equiv), Et_3N (5 equiv), CH_2Cl_2, –60 °C to r.t., 4 h.



Scheme 6 Reagents and conditions: (a) Grubbs' II cat. (5 mol%), CH_2Cl_2, r.t., 2 h (18 h for **7b** and **7d**); (b) PtO_2 (10 wt.%), H_2 (1 atm.), MeOH, r.t., 1 h; (c) $(ClCO)_2$ (1.1 equiv), DMSO (2.2 equiv), Et_3N (5 equiv), CH_2Cl_2, –60 °C to r.t., 4 h; for yields, see Table 1.

was easily performed, the basic isomerization of cyclic compound **6a** failed due to prevailing aromatization of the cyclohexene ring, leading to 3-chloro-4-fluoro-isoquinoline (e.g., NaH, MeI, THF, 10→23 °C, 2 h, 61%). Since thermal isomerization (heating in xylene)[19b] and isomerization catalyzed by rhodium catalyst (Wilkinson)[19c] also failed, we decided to explore a two-step process (oxidation/reduction).

In order to avoid possible aromatization of **6a** by oxidation, we started with reduction of the allylic double bond. Interestingly, Pd/C catalyzed hydrogenation (1 atm. of H_2) of allylic alcohol **6a** led predominantly to aromatization rather than reduction. Using Raney-Ni as a catalyst, the reaction was not only very slow but became also messy with time. Finally, PtO_2 was found to be the catalyst of choice, affording the saturated alcohol **16a** in good yield (73%) under 1 atm. of H_2 (Scheme 5). Oxidation of benzylic alcohol **16a** to ketone **5a**[20] was successfully achieved by Swern oxidation (89%) while, quite surprisingly, the initially applied MnO_2 was found to be too weak to oxidize this benzylic alcohol.

To apply the developed synthesis for the preparation of other derivatives, dienols **7b–d** were prepared by addition of appropriate Grignard reagents[18] to the aldehyde **15** (Table 1). The RCM worked well for all derivatives and afforded the cyclized products **6b–d** in good yields (Scheme 6, Table 1), although the cyclization of substituted derivatives **7b** and **7d** were slower and thus required longer reaction times (18 h). The last two steps also worked smoothly for the unsubstituted derivative **6c**, providing ketone **5c**[20] in good yield. Hydrogenation of substituted intermediates **6b** and **6d** afforded the corresponding saturated alcohols in somewhat lower yields as a separable mixture of *syn*/*anti* diastereomers (2.6:1 for **16b** and 1:2 for **16d**). Interestingly, the hydrogenation took place from two different sides, depending on the ring size. While the six-membered alcohol **6b** was predominantly hydrogenated from the side opposite to the hydroxyl group, the seven-membered ring in **6d** was hydrogenated from the same side as the hydroxyl group. Both outcomes can, however, be explained by conformational analysis of six- versus seven-membered rings, assuming that the hydroxyl group adopts a pseudo-equatorial position and that the hydrogenation occurs from convex side of the ring

(which is different in these two ring systems). Mixtures of both diastereomers were easily oxidized to provide the final products[20] **5b** and **5d** in good yields.

Table 1 Yields of Compounds **5** (see Scheme 6)[a]

Compound	**a**	**b**	**c**	**d**
n	0	0	1	1
R	H	Me	H	Me
7	76	51	59	58
6	97	74	71	75
16	73	50 (2.6:1)[b]	80	63 (1:2)[b]
5	89	73	75	86

[a] Isolated yield (%).
[b] Diastereomeric ratio (*syn*/*anti*).

In summary, we have developed a short synthesis of novel fluorinated 5-isoquinolinones such as **5a** and its seven-membered or substituted derivatives. The key diallyl precursor **7** was prepared in one step starting from commercially available 2-chloro-3-fluoropyridine by Comins' sequentional *ortho*-formylation/substitution protocol. Ring-closing metathesis of diallyl derivative **7a** worked well, and the product **5a** was reached from the RCM intermediate **6a** by a reduction/oxidation sequence. Keto- and chloro-substituents contained in these molecules are useful functional groups that can serve for further derivatization of such compounds leading to more complex molecules containing the 3-fluoro-pyridine motif for use as pharmaceuticals or agrochemicals. In addition, the described methodology could also potentially be applied for the introduction of a cyclohexenone ring (or of other ring sizes) into different aromatic compounds allowing for (*ortho*)lithiation.

Acknowledgment

We would like to thank Roland Steiner for the preparation of compound **9c**. We are also grateful to Susanne Osswald from the analytical department for NMR determination of the *cis*/*anti* stereochemistry of compounds **16b** and **16d**.

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(17) Preparation of compound **15**: *t*-BuLi (1.7 M in heptane, 14.1 mL, 24 mmol) was added within 15 min to a solution of 2-chloro-3-fluoropyridine (3 g, 22.8 mmol) in anhydrous THF (70 mL) at –78 °C. After stirring for 1 h at –78 °C, *N*-formyl-l-*N*,*N*′,*N*′-trimethylethylene-1,2-diamine (3.21 g, 24 mmol) was added slowly and the reaction mixture was left to warm to –40 °C, followed by addition of *n*-BuLi (1.6 M in hexane, 21.4 mL, 34.2 mmol). The red-brown solution was stirred for 3 h at –30 °C before CuBr (4.25 g, 29.6 mmol) was added. The reaction mixture was then allowed to reach 0 °C and was stirred at this temperature for 1 h. After cooling back to –30 °C, a solution of allylbromide (3.1 mL, 36.5 mmol) in anhydrous THF (50 mL) was added.

After stirring for 1 h at –10 °C, the mixture was quenched by addition of sat. aq NH_4Cl, filtered over Hyflo® and rinsed with diethyl ether. The organic layer was then washed with sat. aq NH_4Cl and brine. After drying over Na_2SO_4 and filtration, the mixture was concentrated under vacuum. The crude mixture was further purified by gradient MPLC (ethyl acetate–cyclohexane, 5→15%), followed by a second MPLC (diethyl ether–cyclohexane, 10→15%) to provide the product **15** (1.85 g, 41%) as a yellow oil. Spectral data for compound **15**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.31 (s, 1 H), 8.32 (s, 1 H), 5.97 (m, 1 H), 5.07 (dd, J = 10.2, 1.5 Hz, 1 H), 5.00 (dd, J = 17.2, 1.6 Hz, 1 H), 3.72 (d, J = 6.3 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 187.6, 153.0 (d, $J_{C,F}$ = 268 Hz), 146.3 (d, $J_{C,F}$ = 7 Hz), 136.4 (d, $J_{C,F}$ = 20 Hz), 135.2, 128.8 (d, $J_{C,F}$ = 6 Hz), 116.6, 32.2; ESI-HRMS: m/z [M + H]$^+$ calcd for C_9H_8ClFNO: 200.0278; found: 200.0274.

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(20) Characterization of final compounds. **5a**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.40 (s, 1 H), 2.97 (t, J = 6.1 Hz, 2 H), 2.66 (t, J = 6.3 Hz, 2 H), 2.06 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 193.6, 150.5 (d, $J_{C,F}$ = 273 Hz), 145.1 (d, $J_{C,F}$ = 8 Hz), 139.5, 135.8 (d, $J_{C,F}$ = 20 Hz), 126.9, 39.3, 25.0, 21.5; ESI-HRMS: m/z [M + H]$^+$ calcd for C_9H_8ClFNO: 200.0278; found: 200.0274; **5b**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.38 (s, 1 H), 3.03 (m, 2 H), 2.77 (m, 1 H), 2.14 (m, 1 H), 1.84 (m, 2 H), 1.12 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 197.1, 151.2 (d, $J_{C,F}$ = 274 Hz), 145.9 (d, $J_{C,F}$ = 8 Hz), 140.0, 136.4 (d, $J_{C,F}$ = 20 Hz), 127.5, 42.9, 29.8, 24.7, 14.8; ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{10}H_9ClFNO$: 214.0430; found: 214.0431; **5c**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.26 (s, 1 H), 2.86 (m, 2 H), 2.75 (m, 2 H), 1.79 (m, 4 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 201.6, 149.4 (d, $J_{C,F}$ = 264 Hz), 145.1, 136.3 (d, $J_{C,F}$ = 20 Hz), 135.9 (d, $J_{C,F}$ = 11 Hz), 135.1, 41.5, 28.3, 24.7, 22.3; ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{10}H_{10}ClFNO$: 214.0430; found: 214.0430; **5d**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.26 (s, 1 H), 2.91 (m, 1 H), 2.83 (m, 1 H), 2.71 (m, 1 H), 2.65 (m, 1 H), 2.02 (m, 1 H), 1.90 (m, 1 H), 1.48 (m, 1 H), 0.98 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 198.9, 148.5 (d, $J_{C,F}$ = 263 Hz), 144.5 (d, $J_{C,F}$ = 6 Hz), 135.6, 135.5, 135.1, 49.2, 33.1, 30.1, 27.5, 21.3; ESI-HRMS: m/z [M + H]$^+$ calcd for $C_{11}H_{12}ClFNO$: 228.0586; found: 228.0586