Tri- and difluoromethoxylated N-based heterocycles – Synthesis and insecticidal activity of novel F3CO- and F2HCO-analogues of Imidacloprid and Thiacloprid

Grégory Landelle, Etienne Schmitt, Armen Panossian, Jean-Pierre Vors, Sergiy Pazenok, Peter Jeschke, Oliver Gutbrod, Frédéric Leroux

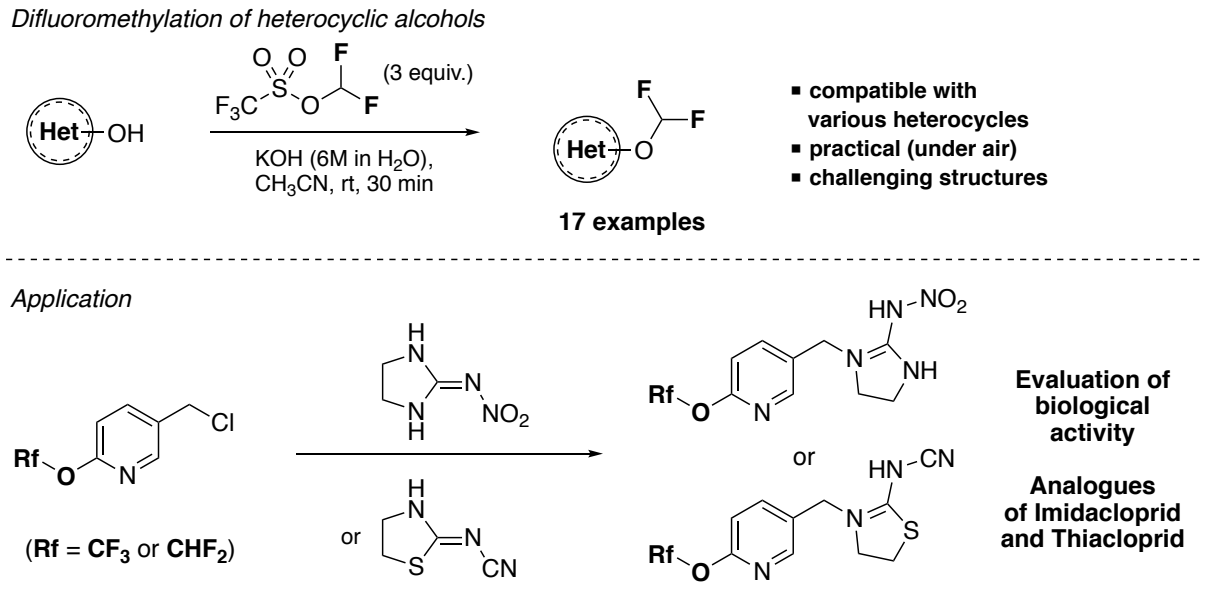
Tri- and difluoromethoxylated *N*-based heterocycles – Synthesis and insecticidal activity of novel F_3CO- and F_2HCO-analogues of Imidacloprid and Thiacloprid

Gregory Landelle[a], Etienne Schmitt[a], Armen Panossian[a], Jean-Pierre Vors[b], Sergiy Pazenok[c], Peter Jeschke[c], Oliver Gutbrod[c], and Frédéric R. Leroux[a,*]

[a] University of Strasbourg, CNRS, LCM, UMR 7509, 25 Rue Becquerel, 67087 Strasbourg, France
[b] Bayer S.A.S., Crop Science Division, 14 Impasse Pierre Baizet, BP99163, 69263 Lyon Cedex 09, France
[c] Bayer AG, Crop Science Division, Alfred-Nobel-Strasse 50, 40789 Monheim, Germany

Email: frederic.leroux@unistra.fr; http://coha.unistra.fr

Graphical abstract:



Synthesis of F_3CO- and F_2HCO-heterocyclic building blocks; preparation and evaluation of biological properties of novel analogues of Imidacloprid and Thiacloprid

Highlights:

- F_3CO- and F_2HCO-heterocyclic building blocks
- Difluoromethylation of hydroxylated heterocycles
- F_3CO- and F_2HCO-analogues of Imidacloprid & Thiacloprid

Abstract

The preparation of F_3CO- and F_2HCO-analogues of Imidacloprid and Thiacloprid and the evaluation of their biological activity have been performed. For this purpose, a first synthetic approach allowed the preparation of a desired F_3CO-containing key intermediate. To allow a facile access to the second F_2HCO-containing key intermediate, the difluoromethylation of hydroxylated *N*-based heterocycles has been developed using difluoromethyl triflate (a liquid non-ODS reagent) under air in aqueous conditions and with very short reaction time. The broad diversity of compatible heterocycles includes a large series of substituted hydroxy-pyridines, but also -pyrazoles, -pyrazine, -pyridazine, and -quinolines. The couplings of both key intermediates with the required 4,5-dihydro-*N*-nitro-1*H*-imidazol-2-amine and [*N*(*Z*)]-*N*-2-thiazolidinylidene-cyanamide were successfully achieved using literature conditions. This work enables the preparation of valuable building blocks, which could lead to the discovery of new bioactive entities.

Keywords:
Trifluoromethoxy; difluoromethoxy; difluorocarbene; heterocycles; agrochemicals

1. Introduction

Since some years ago, the electron-withdrawing trifluoromethoxy (F_3C-O) and difluoromethoxy (F_2HC-O) groups are becoming more and more important in modern crop protection but also in pharmaceutical chemistry[1-6], because they can protect an aromatic ring system against oxidative (or electrophilic) attacks. An increased stability towards degradation is observed for active ingredients or fragments containing this special substitution pattern. Based on its electronic properties, which are close to the halogen atoms chlorine and fluorine[7], the F_3C-O group has been referred as a super-[8] or a pseudo[9]-halogen. The fluorinated carbon adjacent to an oxygen atom increases lipophilicity as shown by the high value of the F_3C-O hydrophobic substituent parameter[10-12]. It appears that the F_3C-O substituent is far more lipophilic (π = +1.04) than the halogens and lies between a F_3C (π = +0.88) and a F_3C-S (π = +1.44) group. It may thus replace advantageously a fluorine atom (π = +0.14) in most molecules with the benefit of increased lipid solubility.
The trifluoromethoxy substituent can induce particular conformational changes due to its anisotropic character (in difference to the isotropic trifluoromethyl group)[13] and adopt an orthogonal orientation with respect to an arene plane, in contrast to the methoxy group, which normally lies in the plane of the arene[14, 15]. In fact, the electron density of the non-bonding p-orbitals at oxygen is very low. The electrons of the oxygen p-orbital are delocalized into the antibonding orbitals of the trifluoromethyl C–F bonds[16]. As a consequence, the oxygen non-bonding orbitals are not conjugated with the aromatic ring system; therefore the F_3C-group of F_3C-O lies out of the arene plane, and the rotational barrier is significantly lower than that for a methoxy group[17-19]. This behaviour can be used to tune the binding affinity in drug-target complexes. The use of the F_3C-O-motif in pharmaceuticals led to major

breakthroughs; Riluzole was the first drug approved for amylotropic lateral sclerosis treatment; Delamanid is included in the World Health Organization List for essential medicines as prodrug for tuberculosis treatment; Celikalim is a vasorelaxing agent protecting cardiac muscles. In addition, marketed agrochemicals bearing the F_3CO-motif display various possible MoAs; Indoxacarb is a Voltage-gated sodium channel (VgSoCh) blocker; Thifluzamide is a fungicide (SDH Complex II inhibitor); Flurprimidol is Plant Growth Regulator (or PGR) (Figure 1).

The difluoromethoxy group shares several key properties with its renowned trifluoromethoxy analogue (high electronegativity, excellent lipophilicity, specific electronic distribution, thermal/chemical stability), but is not as bulky and displays an additional H-bonding capacity. This combination of properties makes the F_2CH-O-group more and more popular. It is found in medicinally relevant compounds that include enzyme inhibitors (*e.g.*: Roflumilast, a selective and long-acting phosphodiesterase-4 inhibitor, anti-HIV agents and antimicrobial agents). Pantoprazole is a nice example of F_2CH-O-containing drug found in the top 100 selling drugs in 2013, as well as several cardiovascular medications, such as Riodipine (Figure 1)[1]. Surprisingly, most of marketed drugs are commonly bearing an aryl-$OCHF_2$ motif, but no example is known with heteroaryl-$OCHF_2$ motif.

Difluoromethoxy compounds are less described in marketed agrochemicals; only several examples containing a F_2CH-O-heteroaryl moiety are currently on the market: Diflumetorim is a fungicide (SDH Complex I inhibitor); Pyroxasulfone is a VLCFAs (Very Long Chain Fatty Acids) biosynthesis inhibitor; Flucythrinate, an insecticide acting as Voltage-gated sodium channel blocker, also contains this group (Figure 1)[2].

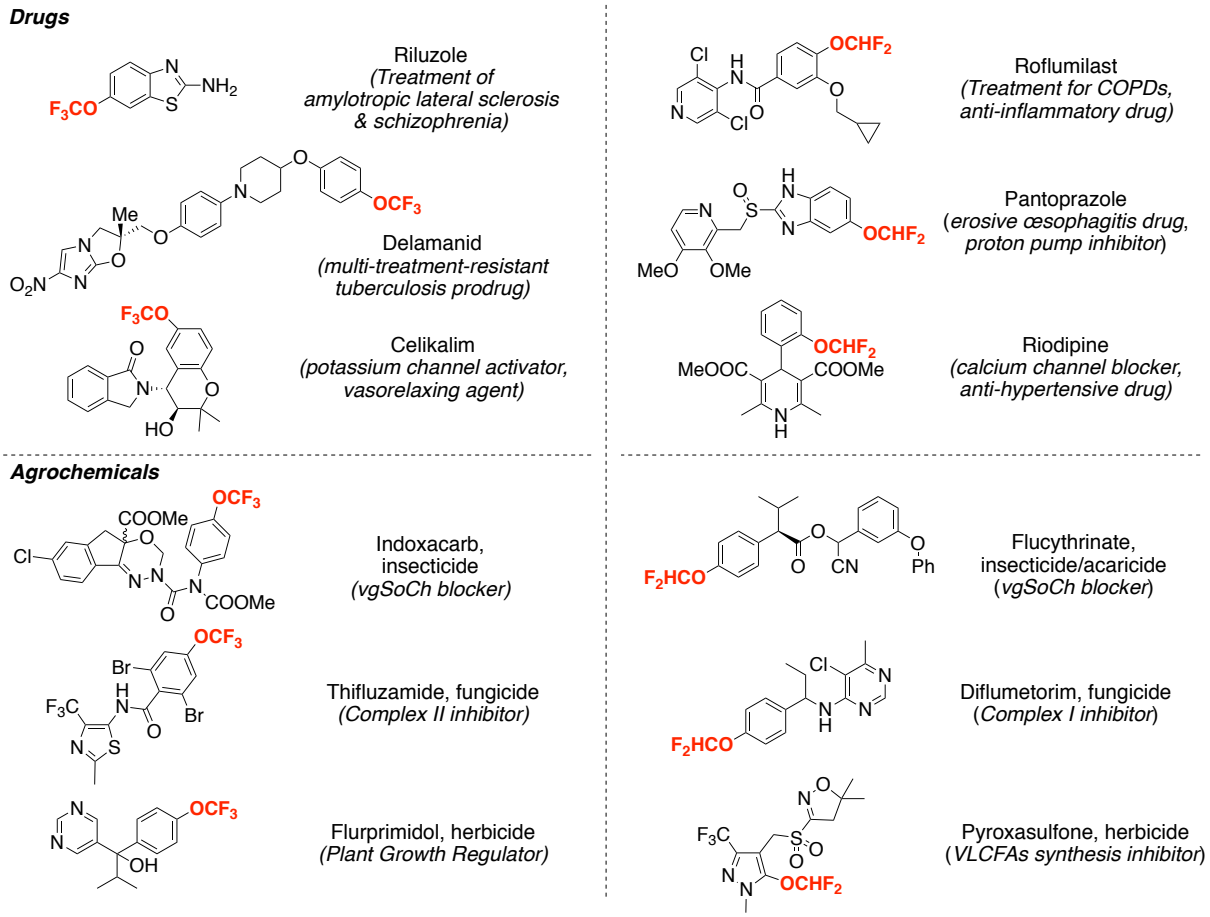


Figure 1. F_3CO- and F_2HCO-bearing drugs and agrochemicals.

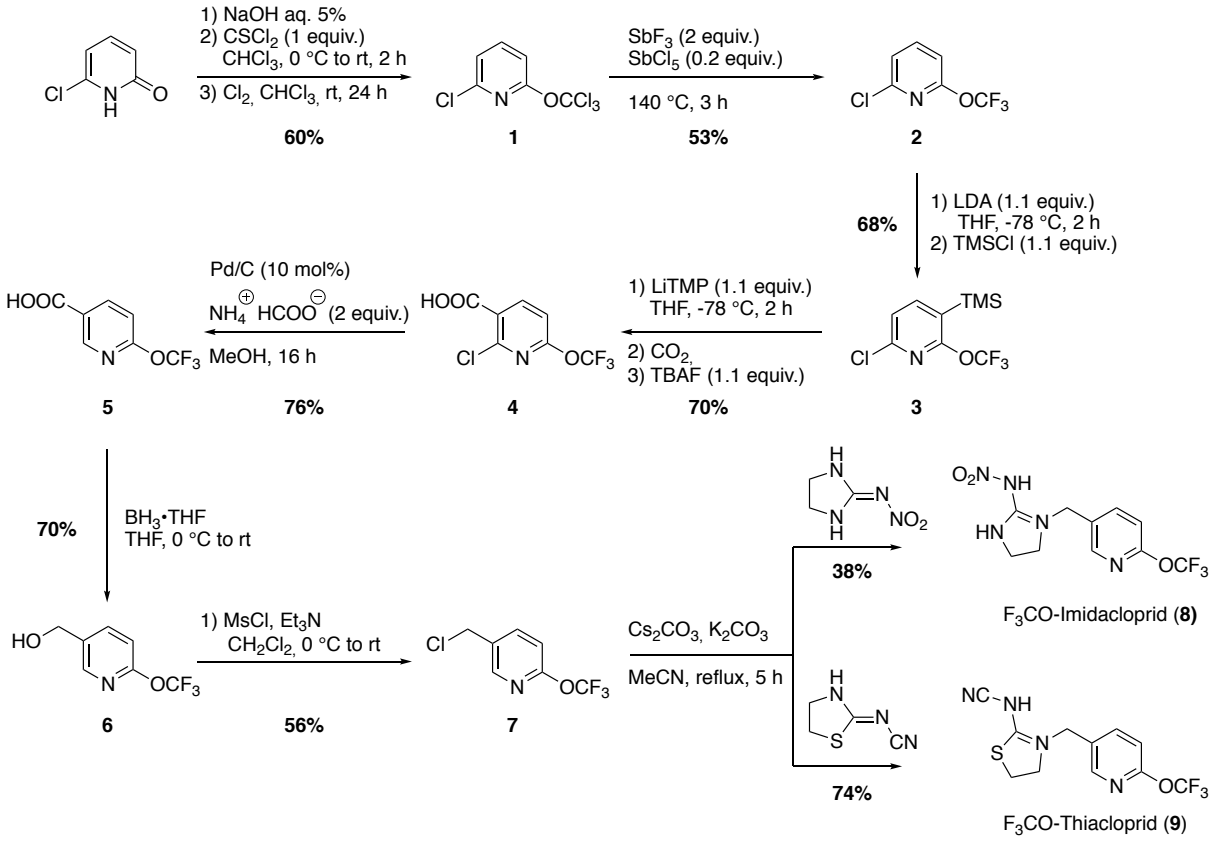
These examples clearly illustrate the large potential of both F_3CO- and F_2HCO-substituents for the development of new bioactive ingredients. Therefore, we became interested in preparing new analogues of pyridine-containing neonicotinoid insecticides Imidacloprid and Thiacloprid, containing either 6-trifluoromethoxy- or 6-difluoromethoxy-pyridin-3-yl-methyl moieties.

2. Results and discussion

2.1. *Trifluoromethoxy-derivatives*

Our group was the first to report on the modular synthesis of a library of trifluoromethoxylated pyridines[17]. This approach has been applied in the synthesis of F_3CO-analogues of Imidacloprid and Thiacloprid.

According to our procedure, 2-chloro-6-hydroxypyridine was converted *in situ* into the corresponding chlorothionoformate and submitted to a chlorination with elemental chlorine in chloroform at room temperature yielding the corresponding trichloromethyl ether **1** in 60% yield (Scheme 1). Subsequent fluorination in the presence of antimony trifluoride and catalytic antimony pentachloride provided 2-chloro-6-trifluoromethoxypyridine **2** in 53% yield. Next, pyridine **2** was protected in the 3-position with a TMS group by metalation with lithium diisopropyl amide (LDA) and subsequent trapping with trimethylsilyl chloride (TMSCl). The nicotinic acid **4** was then prepared by metalation of **3** with lithium tetramethyl piperidide (LiTMP) followed by trapping with carbon dioxide and direct deprotection of the TMS group. Palladium-catalysed dechlorination to afford the 2-(trifluoromethoxy)nicotinic acid **5** was performed with 76% yield. The reduction of the acid into the corresponding primary alcohol was performed with 70% yield with BH_3·THF. The expected chlorinated product **7** was obtained by an *in situ* mesylation-chlorination in 56% yield. This product was further coupled with 4,5-dihydro-*N*-nitro-1*H*-imidazol-2-amine or *N*-(4,5-dihydro-2-thiazolyl) cyanamide, to provide the two desired trifluoromethoxy analogues of Imidacloprid and Thiacloprid (**8** and **9**) in 38% and 74 % yield respectively (Scheme 1).



Scheme 1. Synthesis of F_3CO-Imidacloprid (**8**) and Thiacloprid (**9**).

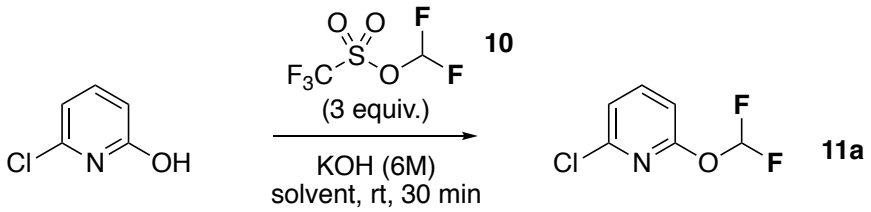
2.2. *Difluoromethoxy-precursors*

The synthesis of F_2HCO-compounds was reported either by the use of ozone-depleting CHF_2Cl gas, or by means of many other difluorocarbene precursors. The generated difluorocarbene is reacted with an alkoxide/phenoxide to provide the corresponding F_2HCO-product. Elevated temperatures or poor functional group tolerance were sometimes important drawbacks of these approaches[20]. Hartwig reported a new approach for the preparation of difluoromethoxylated aromatics by means of a non-ODS-based reagent, namely difluoromethyl triflate (TfO-CHF_2), which displays difluorocarbene reactivity[21]. This reagent can be conveniently prepared from the Ruppert-Prakash reagent ($TMSCF_3$) and triflic acid, and can be used as an air-stable liquid. The difluoromethylation of a diversity of phenols (and sulphides) was reported with good to excellent yields within minutes in aqueous solvent. A broad functional group tolerance and mild reaction conditions enabled the difluoromethylation of phenols generated *in situ* by catalytic and oxidative processes (from aryl boronic acids, arenes or aryl halides), despite slightly lower yields. Surprisingly, only two examples of hydroxychromenones and that of 8-hydroxyquinoline (i.e. where the OH group is borne by the benzo ring, not the pyrido one) were included into this report; the difluoromethylation of other hydroxylated heterocycles thus remained untapped, and it seemed important to complete the study. Therefore, we developed the difluoromethylation of a variety of hydroxylated heterocycles, including pyridines, pyridazines, pyrazines, pyrazoles or quinolines.

Our first model substrate, 6-chloropyridone, was submitted to Hartwig *et al.*'s reaction conditions (3 equiv. of **10**, 12 equiv. of KOH in MeCN at room temperature), affording the

desired product in 85% yield (Table 1, entry 8). Attempts to deviate from these conditions, in terms of solvent, base or amount of base could not provide any improvement (Table 1). Difluoromethyl triflate was prepared using Dilman's procedure[22].
After this first study, the scope extension was achieved using a selection of hydroxy-pyridines, -pyrazoles, -pyrazine, -pyridazine and -quinoline (**11a-o**, Table 2). The difluoromethylation reaction of these substrates using difluoromethyl triflate was achieved with moderate to good yields. Interestingly, all heterocycles used to illustrate this study were successfully difluoromethylated, showing the versatility of this method. The possibility of using difluoromethyl-nonaflate (F_2HC-ONf) to avoid the formation of aryl triflate side-products was not investigated in this case (as previously achieved by Hartwig's group). The low yields observed in the cases of light substrates can be explained by the volatility of the corresponding products (*e.g.*: entries 7, 8, 12, Table 2).

Table 1: Optimization of the reaction conditions for the difluoromethylation of 6-chloropyridin-2-ol using difluoromethyl triflate.

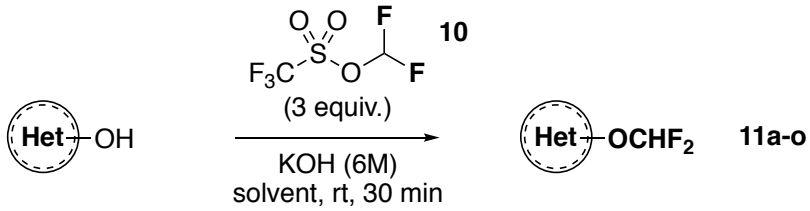


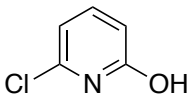
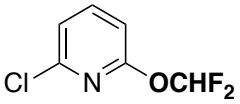
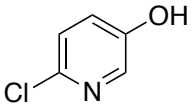
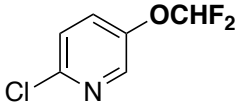
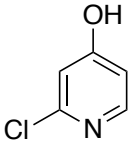
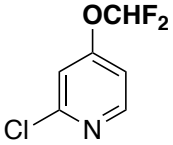
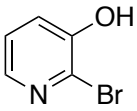
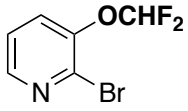
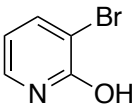
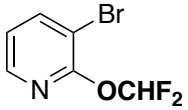
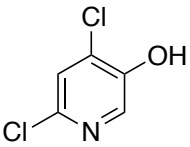
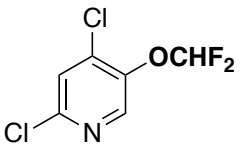
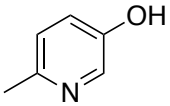
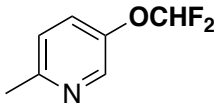
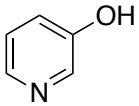
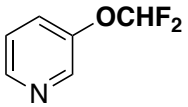
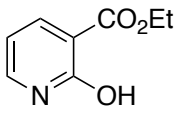
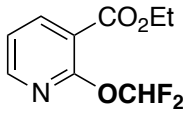
Entry	Base	Solvent	Yield [11a]
1	KOH	DMSO	6%
2	KOH	DMF	8%
3	KOH	*i*PrOH	34%
4	KOH	acetone	67%
5	KOH	DME	66%
6	KOH	dioxane	76%
7	KOH	THF	83%
8	**KOH**	**MeCN**	**85%**
9	KOH[a]	MeCN	71%
10	LiOH	MeCN	36%
11	NaOH	MeCN	55%

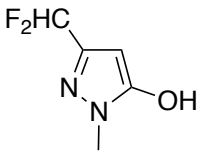
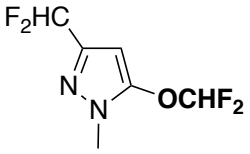
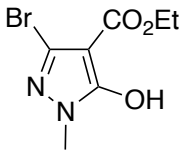
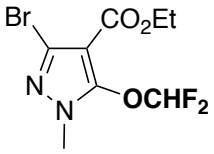
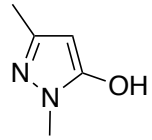
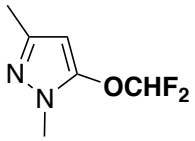
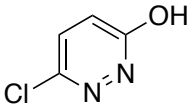
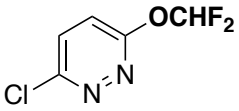
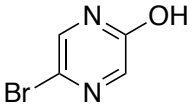
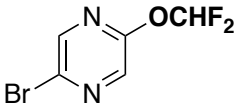
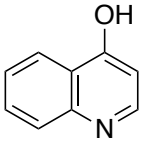
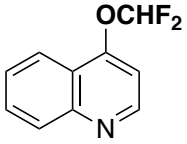
Reactions were performed on a 0.5 mmol scale and the yields were determined by ^{19}F NMR spectroscopic analysis on the crude product using $PhCF_3$ as internal standard. a: 0.5mL KOH instead of 1.0 mL.

It is important to note that several reports have recently described the preparation of difluoromethoxylated heterocycles using different difluorocarbene precursors ($[Cu(phen)_2][O_2CCF_2Cl]$ or fluoroform). In the majority of cases, the reported yields were lower, heating the reaction mixture was required, as well as the use of less environmentally friendly organic solvents[23, 24].

Table 2: Difluoromethylation of various *N*-based heterocycles using difluoromethyl triflate.



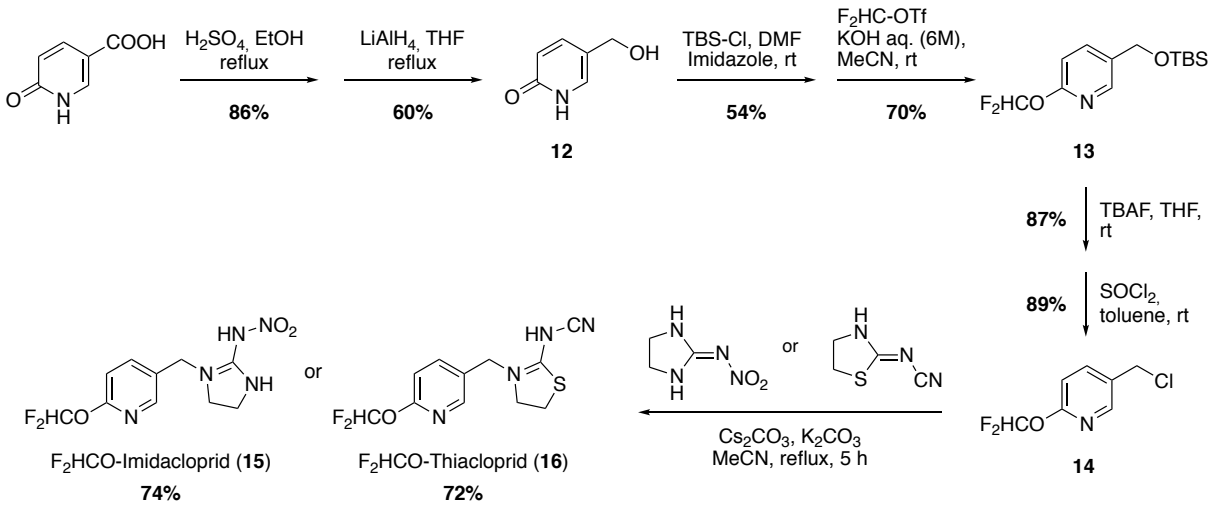
Entry	Substrate	Product	Yield
1		**11a** 	**72%**
2		**11b** 	**74%**
3		**11c** 	**41%**
4		**11d** 	**76%**
5		**11e** 	**45%** **(+ 50% N-CHF_2)**
6		**11f** 	**66%**
7		**11g** 	**31%**
8		**11h** 	**32%**
9		**11i** 	**28%** **(+ 15% N-CHF_2)**

10		**11j**		**75%**
11		**11k**		**40%**
12		**11l**		**35%**
13		**11m**		**59%**
14		**11n**		**53%**
15		**11o**		**51%**[a]

The reactions were performed on a 1 mmol scale.
a: yield measured by ^{19}F NMR spectroscopic analysis on the crude product using $PhCF_3$ as internal standard.

As previously mentioned, the F_2HC-O-group possesses similar electronic properties to those of F_3C-O, but with specific features (H-bonding capacity, different conformational behaviour, size). Therefore, we decided to apply this approach to the synthesis of F_2HC-O-analogues of Imidacloprid and Thiacloprid.

For this purpose, the key intermediate **14** was prepared starting from readily available 6-hydroxynicotinic acid. First, this starting material was converted into 5-(hydroxymethyl)pyridin-2(1*H*)-one (**12**) after esterification in acidic medium followed by ester reduction. The resulting product **12** was then *O*-protected *via* a TBS group, in order to successfully achieve the *O*-difluoromethylation of the pyridine core providing intermediate **13**. After a TBAF-mediated *O*-desilylation, the chlorination of the resulting primary alcohol using thionyl chloride was performed providing the desired product **14**. This product was further coupled with 4,5-dihydro-*N*-nitro-1*H*-imidazol-2-amine or *N*-(4,5-dihydro-2-thiazolyl) cyanamide, to provide the two desired difluoromethoxy analogues of Imidacloprid and Thiacloprid (**15** and **16**) in 74% and 72 % yield respectively (Scheme 2).



Scheme 2. Synthesis of F_2HCO-Imidacloprid (**15**) and Thiacloprid (**16**).

2.3. *F_3CO- and F_2HCO-analogues of Imidacloprid and Thiacloprid – Biological evaluation*

The activity of neonicotinoids towards inhibition of an enzymatic reaction can be approximately evaluated as the pI_{50} index (I_{50} = quantity of neonicotinoid required for 50% inhibition)[25]. Both 6-difluoromethoxy- (**15**; log*P*-value = 1.59) and 6-trifluoromethoxy-analogues (**8**; log*P*-value = 1.82) of Imidacloprid have the same low pI_{50}-values (5.3 vs 5.2) *in vitro*, which are significantly lower than the one measured for Imidacloprid (log*P*-value = 0.6; pI_{50} = 9.1). Despite the fact that **15** (100 g a.i. ha^{-1}) is 5 times more active *in vivo* against green-peach aphid (*M. persicae*) than **8** (500 g a.i. ha^{-1}), both derivatives are much less active (by a factor of 625) than Imidacloprid (0.16 g a.i. ha^{-1}). A similar result was obtained for the two Thiacloprid analogues (**9** and **16**). Both 6-difluoromethoxy- (**16**; log*P*-value = 1.92) and 6-trifluoromethoxy-analogues (**9**; log*P*-value = 2.08) have the same low pI_{50}-values (4.9 vs 4.8) *in vitro*, which are significantly lower than the one measured for Thiacloprid (log*P*-value = 1.6; pI_{50} = 9.2). Contrary to the case of Imidacloprid and of its derivatives **8** and **15**, the OCF_3-Thiacloprid analogue **9** (100 g a.i. ha^{-1}) is 5 times more active *in vivo* against *M. persicae* than the $OCHF_2$- one (**16**; 500 g a.i. ha^{-1}); however —as for **8** and **15** compared to Imidacloprid— both derivatives **9** and **16** are much less active (by a factor of 125) than Thiacloprid (0.8 g a.i. ha^{-1}) (Table 3).

Table 3. Biological evaluation of the F_3CO- and F_2HCO-analogues of imidacloprid (**8**, **15**) and thiacloprid (**9**, **16**).

Compound	Activity in vitro (pI_{50}-value)	Activity in vivo (Myzus persicae) [in g a.i. ha^{-1}]
Imidacloprid	9.1	0.16
8	5.2	500
9	4.8	100
Thiacloprid	9.2	0.8
15	5.3	100
16	4.9	500

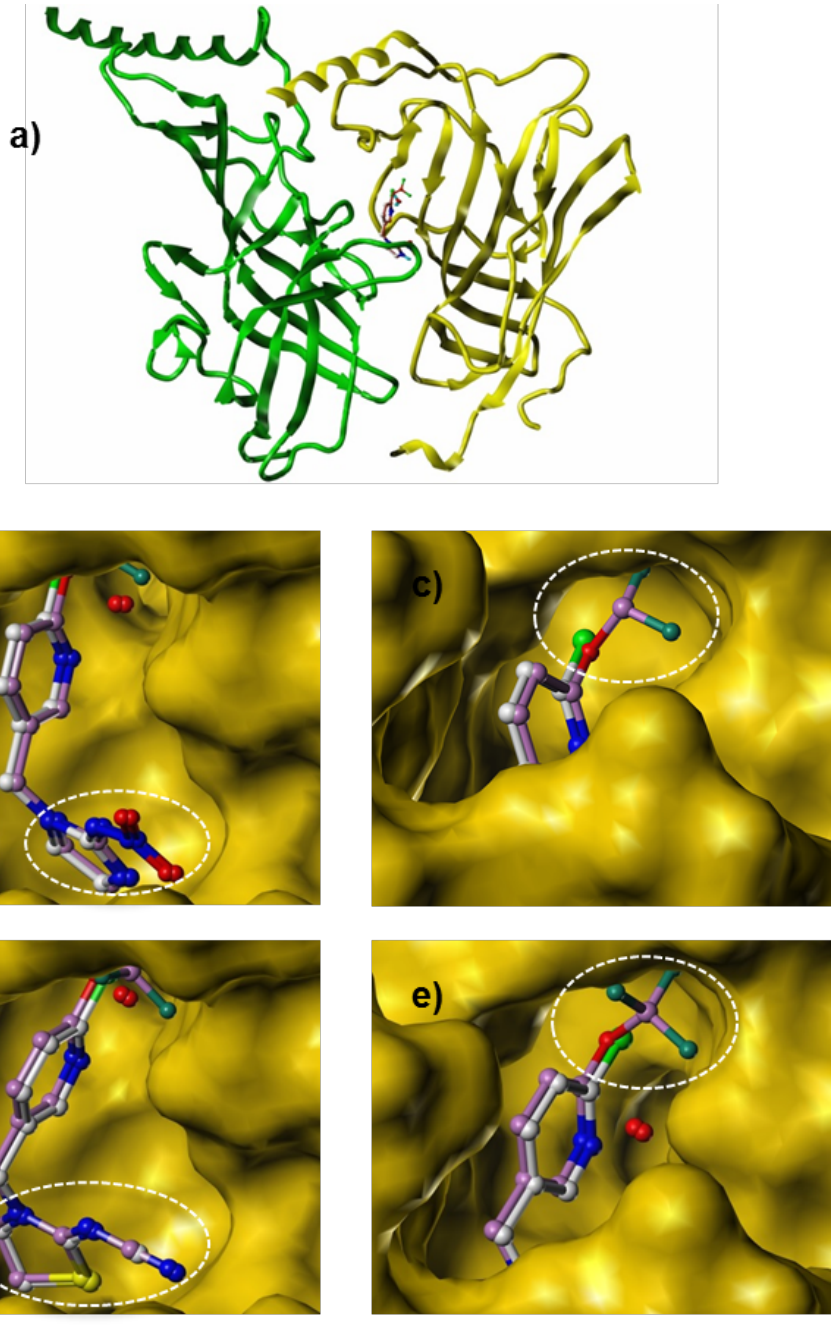


Figure 2. Binding modes of Imidacloprid and Thiacloprid to *Ac*-AChBP. a) Overlay of two neighbouring monomers generated from PDB entry 3C79. The remaining panels zoom into the respective structures, but adopt similar perspectives. b) Overlay of Imidacloprid and its 6-trifluoromethoxy-analogue (**8**) with the focus on the [O_2N-N=]-pharmacophores. c) Overlay of Imidacloprid and its 6-difluoromethoxy-analogue (**15**) with the focus on 6-F_2HC-O- and 6-Cl-pyridin-3-yl residues. d) Overlay of Thiacloprid and its 6-difluoromethoxy-analogue (**16**) with the focus on the [NC-N=]-pharmacophores. e) Overlay of Thiacloprid and its 6-trifluoromethoxy-analogue (**9**) with the focus on 6-F_3C-O- and 6-Cl-pyridin-3-yl residues. Parts of the cysteine loop covering the active site were undisplayed to allow a complete view on the ligand orientations. The images shown above were generated using the molecular modeling software suite SYBYLx2.2.[26]

While it has been difficult to obtain crystals of any *n*AChR of sufficient quality to conduct high-resolution X-ray crystallography, both the crystal structure of a soluble homopentameric acetylcholine binding protein isolated from the seawater mollusc *Aplysia californica* (*Ac*-AChBP) and the only recently added crystal structure of the human α4β2 acetylcholine receptor[27] can be used to provide considerable support to the understanding of ligand–receptor interactions[28]. Figure 2 compares the mode of binding of Imidacloprid and its 6-difluoromethoxy-analogue (**15**) as well as Thiacloprid and its 6-trifluoromethoxy-analogue (**9**) to *Ac*-AChBP from *A. californica*. The Figure 2 has been created from PDB entry 3C79 (Imidacloprid in complex with *Ac*-AChBP)[29] following the procedure described by Beck *et al*.[30]. In both cases, the positively polarized *N*-nitroguanidine and *N*-cyano-amidine π-systems of Imidacloprid and **15** as well as Thiacloprid and **9** demonstrate a perfect overlay as shown in Figures 2b and 2d.

In addition, a strikingly conserved water molecule mediates a hydrogen bridge between the pyridine nitrogen atoms of all neonicotinoids and the loop D backbone, which is known to be important for ligand binding. However, the overlay of Imidacloprid and **15** with the focus on 6-F_2HC-O- and 6-Cl-pyridin-3-yl residues (Figure 2c) as well as Thiacloprid and **9** with the focus on 6-F_3C-O- and 6-Cl-pyridin-3-yl residues (Figure 2e) clearly demonstrates the differences between the two commercial neonicotinoids and their fluoroalkoxy-containing analogues. Both the F_2HCO- and F_3CO-groups in 6-position of the pyridine are much larger (see dotted circles in Figure 2c and 2e) compared to a chlorine atom and therefore disruptive for the ligand-receptor interaction. In addition, the groups tend to adopt perpendicular position as described for (hetero)aromatic ring systems[31, 32]. As a consequence of these structural modifications the insecticidal activity of **15** and **9** decreased remarkably.

3. Conclusion

To illustrate the potential of the F_3CO- and F_2HCO-groups as emergent fluorinated substituents (EFS), analogues of Imidacloprid and Thiacloprid displaying a replacement of the key chlorine atom by these two groups have been prepared and evaluated. For the preparation of the key intermediates, we have developed an efficient synthetic route to prepare the desired F_3CO-intermediate; in a second hand, we have developed a novel strategy to prepare F_2HCO-substituted heterocycles, and this strategy was applied to the preparation of the desired F_2HCO-intermediate. With both key intermediates, F_3CO- and F_2HCO-analogues of Imidacloprid and Thiacloprid were prepared. While the *in-vitro* activity of these analogues is promising, their *in-vivo* activity revealed to be much less elevated. However, this

investigation opens the route to a new access to analogues of bioactive ingredients and their further evaluation, which could possibly lead to large activity enhancements.

4. Experimental

4.1. *General*

All reactions were performed in flame-dried glassware using sealed tube or Schlenk tube. Liquids and solutions were transferred with syringes. Air- and moisture- sensitive materials were stored protected and handled under an atmosphere of argon, with appropriate glassware. Solvents were purified and dried following standard procedures: tetrahydrofuran (THF) was distilled from sodium or sodium + benzophenone prior to use. Anhydrous MeCN was used from commercial source and was stored under Argon. Technical grade solvents for extraction and chromatography (cyclohexane, dichloromethane, *n*-pentane, ether, toluene, and ethyl acetate) were used without purification. All reagents were purchased from standard suppliers (Sigma Aldrich, ABCR, Alfa Aesar and Apollo scientific). Starting materials, if commercial, were purchased and used as such, provided that adequate checks (NMR) had confirmed the claimed purity. Analytical thin-layer chromatography (TLC) was performed on silica gel. Flash column chromatography was performed on silica gel 60 (40–63 μm, 230–400 mesh, ASTM) by Merck using the indicated solvents. ^{1}H, ^{13}C, and ^{19}F-NMR spectra were recorded in $CDCl_3$ on Bruker AV 400 instruments (^{1}H: 400MHz, ^{19}F: 376MHz, ^{13}C: 100MHz, ^{11}B: 128MHz). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual solvent resonance as the internal standard (chloroform (δ [^{1}H] 7.26 and accordingly δ [^{13}C] 77.16 ppm), CD_3CN (δ [^{1}H] 1.94 and accordingly δ [^{13}C] 1.32 ppm, MeOD-d^4 (δ [^{1}H] 3.31 and accordingly δ [^{13}C] 49.00 ppm), DMSO-d^6 (δ [^{1}H] 2.50 and accordingly δ [^{13}C] 39.52 ppm) or Acetone-d^6 (δ [^{1}H] 2.05 and accordingly δ [^{13}C] 29.84 ppm). Data are reported as follows: chemical shift, multiplicity (br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br d = broad doublet), coupling constant (Hz) and integration. Fluorobenzene (δ [^{19}F] -113.15 ppm) was used as internal standard to measure yields *in-situ*. The spectra were processed with the program NMR Notebook (Version 2.70, NMRtec). Experiments under microwave irradiation were carried out on an Initiator™ apparatus from Biotage, exact parameters are given with the procedures. Melting points (M.p.) were determined for crystalline or solid compounds with a Melting Point Apparatus M-560 and are not corrected. High resolution mass spectrometry (HRMS) analysis and elemental analysis (Anal.) were performed by the analytical facility at the University of Strasbourg (measurement accuracy ≤ 15 ppm). Spectral data were recorded from samples purified by Hickmann distillation when necessary.

4.2. *F_3CO-Imidacloprid and F_3CO-Thiacloprid*

4.2.1. *2-Chloro-6-trichloromethoxypyridine (**1**)*

Thiophosgene (3.0 mL, 39 mmol, 1 equiv.) in dichloromethane (24 mL) was added dropwise to a solution of 2-chloro-6-hydroxypyridine (5.0 g, 39 mmol) in aqueous sodium hydroxide (5%, 34 mL) at 0 °C. The reaction mixture was vigorously stirred for 2 h at 0 °C before being extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with 1M HCl (20 mL) and water (20 mL) and dried with sodium sulphate before being evaporated. The crude product was taken up in chloroform (40 mL) and the reaction mixture was then saturated with chlorine at 25 °C until the reaction mixture began to warm up. After 2 h at 25 °C, excess chlorine was again added until a yellow solution was obtained. After 24 h at 25 °C,

excess chlorine was removed with a stream of argon and the solution was concentrated. The crude pale-yellow oil was distilled under reduced pressure to afford pure 2-chloro-6-trichloromethoxypyridine (**1**). Colourless oil (5.7 g, 60% yield), b.p. = 80–82 °C (1 mbar); ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ 7.70 (t, 1 H, J = 7.9 Hz, H-4), 7.19 (d, 1 H, J = 7.9 Hz, H-5), 7.02 (d, J = 7.9 Hz, 1 H, H-3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ 151.8 (C), 149.0 (C), 141.7 (CHarom), 122.2 (CHarom), 112.7 (CHarom), 109.1 ($OCCl_3$). Spectroscopic data were in agreement with literature values[17].

4.2.2. *2-Chloro-6-trifluoromethoxypyridine (**2**)*

2-Chloro-6-trichloromethoxypyridine (**1**, 5.9 g, 24 mmol, 1 equiv.) was added dropwise at 120 °C to a mixture of SbF_3 (8.7 g, 48 mmol, 2 equiv.) and $SbCl_5$ (0.60 mL, 4.8 mmol, 0.2 equiv.) and the mixture was stirred for 3 h at 140 °C. GC monitoring indicated 100% conversion and disappearance of the -OCF_2Cl byproduct. The mixture was then cooled to room temperature and dissolved in dichloromethane (100 mL). The solution was washed with 2M HCl (150 mL) and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over sodium sulphate and the solvent was evaporated at atmospheric pressure. The crude product was distilled under reduced pressure to afford pure 2-chloro-6-trifluoromethoxypyridine (**2**). Colourless oil (2.5 g, 53% yield), b.p. = 42–44 °C (20 mbar); ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ 7.67 (t, 1 H, J = 7.9 Hz, H-4), 7.18 (d, 1 H, J = 7.9 Hz, H-5), 6.87 (d, 1 H, J = 7.9 Hz, H-3) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ 155.6 (C), 149.3 (C), 142.0 (CHarom), 122.2 (CHarom), 119.8 (q, $J_{C\text{-}F}$ = 262.1 Hz, OCF_3), 111.1 (CH); ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ -57.2 ppm. Spectroscopic data were in agreement with literature values[17].

4.2.3. *2-Chloro-6-(trifluoromethoxy)-5-(trimethylsilyl)pyridine (**3**)*

Butyllithium (1.56 M in hexanes, 5.7 mL, 8.9 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of diisopropylamine (1.2 mL, 8.9 mmol, 1.1 equiv.) in THF (15 mL). A solution of 2-chloro-6-(trifluoromethoxy)pyridine **2** (1.6 g, 8.1 mmol, 1 equiv.) in THF (5 mL) was added dropwise at -78 °C, and the reaction mixture was stirred for 2 h at this temperature. Chlorotrimethylsilane (1.0 g, 1.13 mL, 8.9 mmol, 1.1 equiv.) was then added dropwise and the mixture was allowed to reach 25 °C before being neutralised with water (20 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. The crude product was distilled under reduced pressure to afford pure 2-chloro-6-(trifluoromethoxy)-5-(trimethylsilyl)pyridine (**3**). Colourless oil (1.5 g, 68%), b.p. = 89–93 °C (14 mbar); ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ 7.78 (d, 1 H, J = 7.6 Hz, H-3), 7.22 (d, 1 H, J = 7.6 Hz, H-4), 0.34 (s, 9 H, $SiMe_3$) ppm. Spectroscopic data were in agreement with literature values[17].

4.2.4. *2-Chloro-6-trifluoromethoxynicotinic acid (**4**)*

Butyllithium (1.56 M in hexanes, 3.7 mL, 5.7 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of 2,2,6,6-tetramethylpiperidine (1.0 mL, 5.7 mmol, 1.1 equiv.) in THF (10 mL). A solution of 2-chloro-6-(trifluoromethoxy)-5-(trimethylsilyl)pyridine **3** (1.4 g, 5.2 mmol, 1 equiv.) in THF (5 mL) was added dropwise at -78 °C, and the reaction mixture was stirred for 2 h at this temperature. The mixture was then poured onto an excess of freshly crushed dry ice before being treated with an aqueous solution of sodium hydroxide (5%, 10 mL). The resulting aqueous layer was collected, washed with diethyl ether (10 mL), and acidified to pH = 1 by dropwise addition of 6M HCl (4 mL). After extraction with ethyl acetate (3 x 10 mL), the combined organic layers were dried over sodium sulphate and evaporated. The crude oil was treated with tetrabutylammonium fluoride (1M in THF, 5.7 mL, 5.7 mmol, 1.1 equiv.) for 20 h at 25 °C. The mixture was then neutralised by addition of 2M HCl (10 mL) and extracted

with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulphate and evaporated to afford pure 2-chloro-6-(trifluoromethoxy)nicotinic acid (**4**). Colourless powder (0.92 g, 70%); ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ 8.44 (d, 1H, J = 8.3 Hz, H-4), 7.21 (d, 1 H, J = 8.3 Hz, H-5) ppm. Spectroscopic data were in agreement with literature values[17].

4.2.5. *6-Trifluoromethoxynicotinic acid (**5**)*

Palladium (10% on charcoal, 2.1 g, 2.0 mmol, 10 mol%) was added at 25 °C with stirring to a solution of 2-chloro-6-trifluoromethoxynicotinic acid **4** (4.8 g, 20 mmol, 1 equiv.) and ammonium formate (2.5 g, 40 mmol, 2 equiv.) in methanol (40 mL). The reaction mixture was stirred for 16 h at room temperature before being filtered on Celite®, the filtrate was concentrated and the residue was taken up in ethyl acetate (50 mL). The organic layer was washed with 2M HCl (2 x 20 mL) and water (20 mL). The organic layer was dried over sodium sulphate and evaporated *in vacuo* to afford pure 6-(trifluoromethoxy)nicotinic acid (**5**). Colourless powder (3.2 g, 76%); ^{1}H NMR (CD_3OD, 300 MHz, 25 °C): δ 8.91 (d, 1 H, *Jm* = 2.3 Hz, H-2), 8.48 (dd, 1 H, *Jo* = 8.4, *Jm* = 2.3 Hz, H-4), 7.24 (d, 1 H, *Jo* = 8.4 Hz, H-5) ppm. Spectroscopic data were in agreement with literature values[17].

4.2.6. *(6-(Trifluoromethoxy)pyridin-3-yl)methanol (**6**)*

BH_3·THF (1M in THF, 36 mL, 36 mmol, 5 equiv.) was added dropwise to 6-trifluoromethoxy nicotinic acid **5** (1.5 g, 7.3 mmol, 1 equiv.) in solution in THF (25 mL) at 0 °C. The reaction mixture was stirred 30 min at this temperature, and allowed to reach room temperature overnight. It was quenched with methanol (25 mL), diluted with diethyl ether (100 mL) and the organic layer was washed with brine (2 x 100 mL). The combined organic layers were dried with sodium sulphate and the solvent was distilled off. The crude product was purified by column chromatography on silica gel with pentane/diethyl ether (6:4 to 3:7) as eluent, which afforded **6.** Colourless oil (1.0 g, 70%); ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ 8.28 (d, J = 2.4 Hz, 1 H, H-2), 7.82 (dd, 1 H, *Jo* = 8.4 Hz, *Jm* = 2.4 Hz, H-4), 7.03 (d, 1 H, J = 8.4 Hz, H-5), 4.73 (s, 2H, CH_2), 2.36 (brs, 1H, -OH) ppm.; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ 156.5 (C-6), 146.7 (C-2), 139.7 (C-4), 135.6 (C-3), 120.6 (q, $J_{C\text{-}F}$ = 259.2 Hz, OCF_3), 62.1 (CH_2) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ -56.7 ppm; HRMS (ESI Positive) for $C_7H_7F_3NO_2$ [M+H]: calcd. 194.043; found 194.044.

4.2.7. *3-(Chloromethyl)-6-(trifluoromethoxy) pyridine (**7**)*

Mesyl chloride (0.28 mL, 3.6 mmol, 1.5 equiv.) was added dropwise to a solution of (6-(trifluoromethoxy)pyridin-3-yl)methanol **6** (0.50 g, 2.4 mmol, 1 equiv.) in dichloromethane (8 mL) in presence of triethylamine (0.60 g, 0.79 mL, 5.7 mmol, 2.4 equiv.) at 0 °C. The reaction mixture was allowed to reach room temperature overnight. It was then poured into a saturated solution of sodium hydrogen carbonate (10 mL). The aqueous layer was extracted with dichloromethane (3 x 15 mL) and washed with water (2 x 10 mL). The combined organic layers were dried over sodium sulphate and the solvent was distilled off. The crude product was purified by column chromatography on silica gel with pentane/diethyl ether (9:1) as eluent, which afforded **7.** Pale yellow oil (0.31 g, 56%);^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ 8.32 (d, 1 H, J = 2.4 Hz, H-2), 7.85 (dd, 1 H, *Jm* = 2.4 Hz, *Jo* = 8.4 Hz, H-4), 7.03 (d, 1 H, J = 8.4 Hz, H-5), 4.59 (s, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ 156.5 (C-6), 147.4 (C-2), 140.6 (C-4), 131.6 (C-3), 120.0 (q, OCF_3, $J_{C\text{-}F}$ = 260.1 Hz), 42.0 (CH_2) ppm; ^{19}F NMR ($CDCl_3$, 282 MHz, 25 °C): δ -56.6 ppm; MS (EI): m/z = 211.1 [M^+], 176.0 [M^+-Cl].

4.2.8. *N-(1-((6-(Trifluoromethoxy)pyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)nitramide (**8**)*

3-(Chloromethyl)-6-(trifluoromethoxy)pyridine **7** (0,15 g, 0.69 mmol, 0.90 equiv.) was added dropwise to a solution of 4,5-dihydro-*N*-nitro-1*H*-imidazol-2-amine (0,10 g, 0.76 mmol, 1 equiv.), potassium carbonate (0.10 g, 0.73 mmol, 0.96 equiv.) and caesium chloride (5.0 mg, 0.030 mmol, 0.03 equiv.) in acetonitrile (5 mL) at room temperature. The reaction mixture was stirred 5 hours at room temperature. It was then filtrated and the solvent was distilled off. The crude product was purified by HPLC on reverse phase with water/acetonitrile gradient, which afforded **8** (89.0 mg, 38% yield); ^{1}H NMR (DMSO-d_6, 150 MHz): δ 3.50 (m, 2H, CH_2), 3.63 (m, 2H, CH_2), 4.50 (s, 2H, CH_2), 7.31 (d, 2H, C-H, Py, J = 8.4 Hz), 7.96 (dd, 1H, C-H, Py, J = 8.4 Hz, J = 2.5 Hz), 8.32 (d, 1H, C-H, Py, J = 2.5 Hz), 9.00 (s, 1H, NH); ^{13}C NMR (proton-decoupled) (DMSO-d_6, 150 MHz): δ 41.8, 44.6, 45.3 (CH_2), 113.4 (C-H, Ph), 119.9 (OCF_3), 131.5 (C, Ph), 141.3, 147.3 (C-H, Ph), 155.5 (C-O, Ph), 160.5 (C=N) ppm; ^{19}F NMR (DMSO-d_6, 566 MHz): δ = -54.7 ppm. HRMS (ESI) calcd for $C_{10}H_{11}F_3N_5O_3$ $[M+H]^+$: 306.0814. Found: 306.0816.

4.2.9. *N-(3-((6-(Trifluoromethoxy)pyridin-3-yl)methyl)thiazolidin-2-ylidene)cyanamide (**9**)*

3-(Chloromethyl)-6-(trifluoromethoxy)pyridine **7** (0.15 g, 0.69 mmol, 0.90 equiv.) was added dropwise to a solution of *N*-(4,5-dihydro-2-thiazolyl)cyanamide (98 mg, 0.76 mmol, 1 equiv.), potassium carbonate (0.10 g, 0.73 mmol, 0.96 equiv.) and caesium chloride (5.0 mg, 0.030 mmol, 0.03 equiv.) in acetonitrile (5 mL) at room temperature. The reaction mixture was stirred 5 hours at room temperature. It was then filtrated and the solvent was distilled off. The crude product was purified by HPLC on reverse phase with water/acetonitrile gradient, which afforded **9** (172.6 mg, 74% yield); ^{1}H NMR (CD_3CN, 150 MHz): δ 3.41 (m, 2H, CH_2), 3.85 (m, 2H, CH_2), 4.61 (s, 2H, CH_2), 7.12 (d, 2H, C-H, Py, J = 8.4 Hz), 7.87 (dd, 1H, C-H, Py, J = 8.4 Hz, J = 2.5 Hz), 8.23 (d, 1H, C-H, Py, J = 2.5 Hz); ^{13}C NMR (proton-decoupled) (CD_3CN, 150 MHz): δ 28.3, 47.4, 53.6 (CH_2), 114.1 (C-H, Py), 121.1 (OCF_3), 131.0 (C, Py), 142.0, 148.4 (C-H, Py), 157.1 (C-O, Py), 176.3 (C=N); ^{19}F NMR (CDCN, 566 MHz): δ = -55.8 ppm. HRMS (ESI) calcd for $C_{10}H_{10}F_3N_4OS$ $[M+H]^+$: 303.0527. Found: 303.0526.

4.3. *F_2HCO-Imidacloprid and F_2HCO-Thiacloprid*

4.3.1. *Preparation of 2-chloro-6-(difluoromethoxy)pyridine (**11a**). **General procedure for the difluoromethylation of hydroxyl-substituted heteroaromatics***

To a vigorously stirred solution of 2-chloro-6-hydroxypyridine (0.13 g, 1.0 mmol) in acetonitrile (2 mL) at room temperature was added a 6M aqueous solution of potassium hydroxide (2 mL). Difluoromethyltriflate (0.38 mL, 3.0 mmol, 3 equiv.) was added dropwise to the reaction mixture which was maintained at room temperature by means of a water bath (the reaction is exothermic), and the medium was stirred for 30 min. The mixture was diluted with water (20 mL) and extracted with diethyl ether (2 x 10 mL) and ethyl acetate (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 70:30) as eluent to afford the pure title compound (129 mg, 72% yield); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (t, 1H, J = 7.9 Hz), 7.37 (t, 1H, J = 72.2 Hz), 7.07 (d, 1H, J = 7.9 Hz), 6.76 (d, 1H, J = 8.0 Hz) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.3, 148.5, 142.1, 120.1, 113.8 (t, J = 259 Hz), 109.6 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -89.3 (d, 2F, J = 71.4 Hz) ppm. HRMS (ESI) calcd for $C_6H_5ClF_2NO$ $[M+H]^+$: 180.002. Found: 180.000. Spectroscopic data were in agreement with literature values[17].

4.3.2. *2-Chloro-5-(difluoromethoxy)pyridine (**11b**).*

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 70:30) as eluent to afford the pure title compound (133 mg, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.16 (d, 1H, J = 2.8 Hz), 7.37 (dd, 1H, J = 8.8 Hz, J = 2.8 Hz), 7.24 (d, 1H, J = 8.8 Hz), 6.44 (t, 1H, J = 72.2 Hz) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 147.8, 146.2, 141.9, 130.8, 124.9, 115.1 (t, J = 266 Hz) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -81.9 (d, 2F, J = 72.5 Hz) ppm. HRMS (ESI) calcd for $C_6H_5ClF_2NO$ $[M+H]^+$: 180.002. Found: 180.004. Spectroscopic data were in agreement with literature values[17].

4.3.3. *2-Chloro-4-(difluoromethoxy)pyridine (**11c**).*

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 70:30) as eluent to afford the pure title compound (74 mg, 41%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.36 (d, 1H, J = 5.6 Hz), 7.08 (s, 1H), 6.99 (m, 1H), 6.65 (t, 1H, J = 71.6 Hz) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.9, 152.9, 151.1, 114.6 (t, $J_{C\text{-}F}$ = 265.2 Hz), 113.7, 112.4 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -83.6 (d, 2F, J = 72.6 Hz) ppm. HRMS (ESI) calcd for $C_6H_5ClF_2NO$ $[M+H]^+$: 180.0022. Found: 180.0038.

4.3.4. *2-Bromo-3-(difluoromethoxy)pyridine (**11d**).*

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 70:30) as eluent to afford the pure title compound (170 mg, 76%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.28 (d, 1H, J = 4.6 Hz), 7.56 (d, 1H, J = 8.4 Hz), 7.31 (m, 1H), 6.60 (t, 1H, J = 73.0 Hz) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 146.7, 145.1, 135.9, 129.3, 123.5, 115.3 (t, $J_{C\text{-}F}$ = 264.5 Hz) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -82.0 (d, 2F, J = 72.6 Hz) ppm. HRMS (ESI) calcd for $C_6H_5BrF_2NO$ $[M+H]^+$: 223.952. Found: 223.952. Spectroscopic data were in agreement with literature values[17].

4.3.5. *3-Bromo-2-(difluoromethoxy)pyridine (**11e**).*

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 70:30) as eluent to afford the pure title compound (101 mg, 45%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.13 (d, 1H, J = 4.6 Hz), 7.94 (d, 1H, J = 7.7 Hz), 7.46 (t, 1H, J = 72.4 Hz), 7.01 (dd, 1H, J = 7.5 Hz, J = 4.8 Hz) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 155.5, 145.5, 143.2, 121.1, 114.2 (t, $J_{C\text{-}F}$ = 257.2 Hz), 106.8 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -89.3 (d, 2F, J = 72.1 Hz) ppm. HRMS (ESI) calcd for $C_6H_5BrF_2NO$ $[M+H]^+$: 223.952. Found: 223.952.

4.3.6. *2,4-Dichloro-5-(difluoromethoxy)pyridine (**11f**).*

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 70:30) as eluent to afford the pure title compound (141 mg, 66%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.47 (s, 1H), 6.60 (t, 1H, J = 72.1 Hz) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 148.5, 143.1, 138.8, 125.7, 115.0 (t, $J_{C\text{-}F}$ = 267.1 Hz), 110.2 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -81.8 (d, 2F, J = 72.0 Hz) ppm. HRMS (ESI) calcd for $C_6H_4Cl_2F_2NO$ $[M+H]^+$: 213.964. Found: 213.963.

4.3.7. *5-(Difluoromethoxy)-2-methylpyridine (**11g**).*

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 70:30) as eluent to afford the pure title compound (49 mg, 31%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.23 (m, 1H), 7.00 (d, 1H, J = 8.8 Hz), 6.35 (t, 1H, J = 73.0 Hz), 2.40 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 154.5, 143.9, 140.1, 126.8,

122.3, 114.1 (t, *J*C-F = 262.1 Hz), 22.4 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -81.2 (d, 2F, *J* = 74.8 Hz) ppm. HRMS (ESI) calcd for $C_7H_8F_2NO$ $[M+H]^+$: 160.057. Found: 160.058.

4.3.8. *3-(Difluoromethoxy)pyridine (**11h**).*

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 70:30) as eluent to afford the pure title compound (46 mg, 32%). Spectroscopic data were in agreement with literature values[17].

4.3.9. *Ethyl 2-(difluoromethoxy)nicotinate (**11i**).*

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 60:40) as eluent to afford the pure title compound (61 mg, 28%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.32 (dd, 1H, *J* = 4.8 Hz, *J* = 2.0 Hz), 8.27 (dd, 1H, *J* = 7.7 Hz, *J* = 2.0 Hz), 7.53 (t, 1H, *J* = 72.4 Hz), 7.19 (dd, 1H, *J* = 7.6 Hz, *J* = 4.8 Hz), 4.41 (q, 2H, *J* = 7.3 Hz), 1.41 (t, 3H, *J* = 7.2 Hz) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 163.9, 157.1, 150.2, 142.1, 119.7, 115.4, 114.0 (t, $J_{C\text{-}F}$ = 251.8 Hz), 61.8, 14.1 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -89.3 (d, 2F, *J* = 71.7 Hz) ppm. HRMS (ESI) calcd for $C_9H_9F_2NNaO_3$ $[M+Na]^+$: 240.0443. Found: 240.0414.

4.3.10. *5-(Difluoromethoxy)-3-(difluoromethyl)-1-methyl-1H-pyrazole (**11j**).*

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 60:40) as eluent to afford the pure title compound (149 mg, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.48 (t, 1H, *J* = 55.0 Hz), 6.47 (t, 1H, *J* = 71.9 Hz), 6.04 (s, 1H), 3.69 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 145.3, 145.1 (t, *J*C-F = 29.8 Hz), 114.9 (t, $J_{C\text{-}F}$ = 268.2 Hz), 111.0 (t, *J*C-F = 235.6 Hz), 89.4, 34.8 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -83.9 (d, 2F, *J* = 71.8 Hz), -112.3 (d, 2F, *J* = 55.0 Hz) ppm. HRMS (ESI) calcd for $C_6H_7F_4N_2O$ $[M+H]^+$: 199.049. Found: 199.050.

4.3.11. *Ethyl 3-bromo-5-(difluoromethoxy)-1-methyl-1H-pyrazole-4-carboxylate (**11k**).*

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 60:40) as eluent to afford the pure title compound (120 mg, 40%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.98 (t, 1H, *J* = 74.0 Hz), 4.34 (q, 2H, *J* = 7.5 Hz), 3.78 (s, 3H), 1.38 (t, 3H, *J* = 7.5 Hz) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 160.5, 146.8 (t), 126.9, 116.7 (t), 101.9, 61.1, 35.3, 14.1 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -83.3 (d, 2F, *J* = 74.7 Hz) ppm. HRMS (ESI) calcd for $C_8H_9BrF_2N_2NaO_3$ $[M+Na]^+$: 320.966. Found: 320.965.

4.3.12. *5-(Difluoromethoxy)-1,3-dimethyl-1H-pyrazole (**11l**).*

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 60:40) as eluent to afford the pure title compound (57 mg, 35%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.47 (t, 1H, *J* = 72.5 Hz), 5.65 (s, 1H), 3.66 (s, 3H), 2.21 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 147.3, 145.2, 115.1 (t, $J_{C\text{-}F}$ = 264.2 Hz), 90.8, 34.0, 14.3 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -83.6 (d, 2F, *J* = 72.3 Hz) ppm. HRMS (ESI) calcd for $C_6H_9F_2N_2O$ $[M+H]^+$: 163.0677. Found: 163.0674.

4.3.13. *3-Chloro-6-(difluoromethoxy)pyridazine (**11m**).*

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 60:40) as eluent to afford the pure title compound (107 mg, 59%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.52 (t, 1H, *J* = 71.1 Hz), 7.48 (d, 1H, *J* = 9.0 Hz), 7.06 (d, 1H, *J* = 9.0

Hz) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 160.9, 153.9, 132.4, 119.9, 113.4 (t, $J_{C\text{-}F}$ = 259.2 Hz) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -88.9 (d, 2F, J = 71.0 Hz) ppm. HRMS (ESI) calcd for $C_5H_4ClF_2N_2O$ $[M+H]^+$: 180.997. Found: 180.997.

4.3.14. *2-Bromo-5-(difluoromethoxy)pyrazine (**11n**)*.

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 60:40) as eluent to afford the pure title compound (119 mg, 53%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.19 (d, 1H, J = 1.2 Hz), 8.10 (d, 1H, J = 1.2 Hz), 7.25 (t, 1H, J = 71.8 Hz) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 155.0, 143.4, 135.2, 134.5, 113.8 (t) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -89.1 (d, 2F, J = 72.0 Hz) ppm. HRMS (ESI) calcd for $C_5H_4BrF_2N_2O$ $[M+H]^+$: 224.9470. Found : 224.9473.

4.3.15. *4-(Difluoromethoxy)quinoline (**11o**)*.

The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 60:40) as eluent to afford the pure title compound (61 mg, 31%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.73 (d, 1H, J = 4.8 Hz), 8.10 (d, 1H, J = 8.4 Hz), 8.02 (d, 1H, J = 8.4 Hz), 7.68 (t, 1H, J = 7.2 Hz), 7.50 (t, 1H, J = 7.8 Hz), 6.93 (s, 1H), 6.75 (t, 1H, J = 72.2 Hz) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 154.4, 150.7, 149.8, 130.5, 129.2, 127.0, 121.5, 120.8, 115.3 (t, $J_{C\text{-}F}$ = 261.1 Hz), 105.8 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -82.9 (d, 2F, J = 72.6 Hz) ppm. HRMS (ESI) calcd for $C_{10}H_8F_2NO$ $[M+H]^+$: 196.057. Found: 196.058.

4.3.16. *5-(Hydroxymethyl)pyridin-2-ol or 5-(hydroxymethyl)pyridin-2(1H)-one (**12**)*.

To a stirred solution of 6-hydroxynicotinic acid (10 g, 72 mmol) in absolute ethanol (500 mL) was added sulfuric acid (4 mL) at room temperature. The mixture was heated to reflux for 48 h. After cooling down to room temperature, water (50 mL) was added and the reaction mixture was neutralized to pH = 6-7 by portionwise addition of sodium hydrogen carbonate (caution: gas evolution). The mixture was evaporated under reduced pressure (most of ethanol was removed), and the residue was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure leading to the pure ethyl 6-hydroxynicotinate[30] (10 g, 86%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 13.07 (s, 1H), 8.14 (s, 1H), 7.94 (d, 1H, J = 9.9 Hz), 6.51 (d, 1H, J = 9.4 Hz), 4.25 (q, 2H, J = 7.1 Hz), 1.29 ppm.

To a stirred solution of lithium aluminium hydride (1.4 g, 37 mmol, 1.2 equiv.) in anhydrous THF (20 mL) at room temperature was added dropwise over 1 h a solution of ethyl 6-hydroxynicotinate (5.1 g, 31 mmol) in anhydrous THF (150 mL) at the same temperature. The mixture was stirred at room temperature for 2 h and then heated to reflux for 30 min. The reaction mixture was cooled down to 0 °C and quenched with ethyl acetate (12 mL) and water (6 mL). The solvents were removed and the residue was taken up in refluxing ethanol (200 mL). The solution was filtered through Celite® and ethanol was evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel with ethyl acetate/methanol (75:25) as eluent to afford the pure title compound **12** (2.3 g, 60%). ^{1}H-NMR (400 MHz, DMSO-d^6): δ 11.56 (s, 1H), 7.43 (dd, 1H, J = 9.1 Hz, J = 2.5 Hz), 7.25 (d, 1H, J = 2.5 Hz), 6.30 (d, 1H, J = 9.1 Hz), 5.22 (t, 1H, J = 5.6 Hz), 4.20 (d, 2H, J = 5.6 Hz) ppm. ^{13}C-NMR (101 MHz, DMSO-d^6): δ 162.6, 142.0, 133.0, 120.1, 119.6, 60.1 ppm. HRMS (ESI) calcd for $C_6H_8NO_2$ $[M+H]^+$: 126.056. Found: 126.055.

4.3.17. *5-(((tert-Butyldimethylsilyl)oxy)methyl)-2-(difluoromethoxy)pyridine (**13**)*.

To a stirred solution of 5-(hydroxymethyl)pyridin-2-ol (1.3 g, 10 mmol) and imidazole (1.7 g, 25 mmol, 2.5 equiv.) in DMF (2.5 mL) was added *tert*-butyldimethylsilyl chloride (1.8 g, 12 mmol, 1.2 equiv.) at room temperature, and the reaction medium was stirred overnight. Water (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 80:20) as eluent to afford pure 5-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridin-2-ol (1.3 g, 54%). ^{1}H-NMR (400 MHz, DMSO-d^6): δ 11.36 (s, 1H), 7.31 (dd, 1H, J = 9.4 Hz, J = 2.7 Hz), 7.20 (m, 1H), 6.27 (d, 1H, J = 9.4 Hz), 4.36 (s, 2H), 0.81 (s, 9H), 0.00 (s, 6H) ppm. ^{13}C-NMR (101 MHz, DMSO-d^6): δ 162.5, 141.3, 133.0, 120.4, 118.2, 61.8, 26.3, 18.4, -4.7 ppm. HRMS (ESI) calcd for $C_{12}H_{22}NO_2Si$ $[M+H]^+$: 240.142. Found: 240.141.

To a vigorously stirred solution of 5-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridin-2-ol (0.48 g , 2 mmol) in acetonitrile (4 mL) at room temperature was added a 6M aqueous solution of potassium hydroxide (4 mL). Difluoromethyltriflate (0.76 mL, 6 mmol, 3 equiv.) was added dropwise to the reaction mixture which was maintained at room temperature by means of a water bath (the reaction is exothermic), and the medium was stirred for 30 min. The mixture was diluted with water (20 mL) and extracted with diethyl ether (2 x 10 mL) and ethyl acetate (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel with pentane/diethyl ether (100:0 to 90:10) as eluent to afford the pure title compound **13** (0.40 g, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.02 (m, 1H), 7.59 (dd, 1H, J = 8.1 Hz, J = 2.5 Hz), 7.35 (t, 1H, J = 73.1 Hz), 6.73 (d, 1H, J = 8.4 Hz), 4.60 (s, 2H), 0.82 (s, 9H), 0.00 (s, 6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.3, 144.8, 138.5, 133.2, 114.1 (t, $J_{C\text{-}F}$ = 255.4 Hz), 111.1, 62.2, 25.9, 18.3, -5.3 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -88.6 (d, 2F, J = 72.9 Hz) ppm. HRMS (ESI) calcd for $C_{13}H_{22}F_2NO_2Si$ $[M+H]^+$: 290.139. Found: 290.138.

4.3.18. *5-(Chloromethyl)-2-(difluoromethoxy)pyridine (**14**).*

To a stirred solution of 5-(((*tert*- butyldimethylsilyl)oxy)methyl)-2-(difluoromethoxy)pyridine **13** (1.4 g, 5 mmol) in THF (10 mL) was added a solution of TBAF (1.0 M solution in THF, 10 mmol, 2 equiv.) at room temperature, and the mixture was stirred for 4 h. The reaction was quenched with saturated ammonium chloride and brine, and extracted with ethyl acetate (3x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel with ethyl acetate/pentane (60:40) as eluent to afford pure (6-(difluoromethoxy)pyridin-3-yl)methanol (761 mg, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.15 (d, 1H, J = 2.5 Hz), 7.76 (dd, 1H, J = 8.5 Hz, J = 2.5 Hz), 7.45 (t, 1H, J = 73.7 Hz), 6.90 (d, 1H, J = 8.5 Hz), 4.68 (m, 2H), 2.04 (m, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.7, 145.6, 139.4, 132.5, 114.1 (t, $J_{C\text{-}F}$ = 253.9 Hz), 111.4, 62.1 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ -88.7 (d, 2F, J = 73.5 Hz) ppm. HRMS (ESI) calcd for $C_7H_8F_2NO_2$ $[M+H]^+$: 176.0518. Found: 176.0530.

To a stirred solution of thionyl chloride (0.16 mL, 2.2 mmol, 1.1 equiv.) in toluene (1 mL) at room temperature was added dropwise a solution of (6-(difluoromethoxy)pyridin-3-yl)methanol (0.35 g, 2 mmol) in toluene (2 mL). After 1 h at room temperature, vacuum was applied leading to the pure title compound **14** (0.34 g, 89%) without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.18 (d, 1H, J = 2.6 Hz), 7.78 (dd, 1H, J = 8.5 Hz, J = 2.6 Hz), 7.46 (t, 1H, J = 72.8 Hz), 6.92 (d, 1H, J = 8.5 Hz), 4.56 (s, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.9, 146.7, 140.6, 129.8, 114.0 (t, $J_{C\text{-}F}$ = 256.7 Hz), 111.4, 42.5 ppm. ^{19}F-NMR

(376 MHz, $CDCl_3$): δ -89.1 (d, 2F, J = 72.5 Hz) ppm. HRMS (ESI) calcd for $C_7H_7ClF_2NO$ $[M+H]^+$: 194.018. Found: 194.018.

4.3.19. *N-(1-((6-(Difluoromethoxy)pyridin-3-yl)methyl)-4,5-dihydro-1H-imidazol-2-yl)nitramide (**15**)*

5-(Chloromethyl)-2-(difluoromethoxy)pyridine **14** (0.13 g, 0.69 mmol, 0.90 equiv.) was added dropwise to a solution of 4,5-dihydro-*N*-nitro-1*H*-imidazol-2-amine (0.10 g, 0.76 mmol, 1 equiv.), potassium carbonate (0.10 g, 0.73 mmol, 0.96 equiv.) and caesium chloride (5.0 mg, 0.030 mmol, 0.03 equiv.) in acetonitrile (5 mL) at room temperature. The reaction mixture was stirred 5 hours at room temperature. It was then filtrated and the solvent was distilled off. The crude product was purified by HPLC on reverse phase with water/acetonitrile gradient, which afforded **15** (163.9 mg, 74%); ^{1}H (DMSO-d_6, 150 MHz): δ 3.47 (m, 2H, CH_2), 3.62 (m, 2H, CH_2), 4.45 (s, 2H, CH_2), 7.10 (d, 2H, C-H, Py, J = 8.4 Hz), 7.70 (t, 1H, $OCHF_2$, $J_{C\text{-}F}$ = 72.8 Hz), 7.86 (dd, 1H, C-H, Py, J = 8.4 Hz, J = 2.5 Hz), 8.22 (d, 1H, C-H, Py, J = 2.5 Hz); 8.96 (s, 1H, NH); ^{13}C NMR (proton-decoupled) (DMSO-d_6, 150 MHz): δ 41.7, 44.6, 45.1 (CH_2), 111.5 (C-H, Ph), 114.9 ($OCHF_2$), 128.9 (C, Ph), 141.0, 146.7 (C-H, Ph), 158.1 (C-O, Ph), 160.5 (C=N); ^{19}F NMR (DMSO-d_6, 566 MHz): δ = -86.8 (d, 2F, J = 72.9 Hz) ppm. HRMS (ESI) calcd for $C_{10}H_{12}F_2N_5O_3$ $[M+H]^+$: 288.0908. Found: 288.0917.

4.3.20. *N-(3-((6-(Difluoromethoxy)pyridin-3-yl)methyl)thiazolidin-2-ylidene)cyanamide (**16**)*

5-(Chloromethyl)-2-(difluoromethoxy)pyridine **14** (0.13 g, 0.69 mmol, 0.90 equiv.) was added dropwise to a solution of *N*-(4,5-dihydro-2-thiazolyl)cyanamide (98 mg, 0.76 mmol, 1 equiv.), potassium carbonate (0.10 g, 0.73 mmol, 0.96 equiv.) and caesium chloride (5.0 mg, 0.030 mmol, 0.03 equiv.) in acetonitrile (5 mL) at room temperature. The reaction mixture was stirred 5 hours at room temperature. It was then filtrated and the solvent was distilled off. The crude product was purified by HPLC on reverse phase with water/acetonitrile gradient, which afforded of **16** (158.5 mg, 72%); ^{1}H (DMSO-d_6, 150 MHz): δ 3.49 (m, 2H, CH_2), 3.90 (m, 2H, CH_2), 4.62 (s, 2H, CH_2), 7.11 (d, 2H, C-H, Py, J = 8.4 Hz), 7.71 (t, 1H, $OCHF_2$, $J_{C\text{-}F}$ = 72.7 Hz), 7.85 (dd, 1H, C-H, Py, J = 8.4 Hz, J = 2.5 Hz), 8.23 (d, 1H, C-H, Py, J = 2.5 Hz); ^{13}C NMR (proton-decoupled) (DMSO-d_6, 150 MHz): δ 27.5, 46.4, 52.9 (CH_2), 111.5 (C-H, Py), 114.9 ($OCHF_2$), 128.0 (C, Py), 141.2, 147.0 (C-H, Py), 158.2 (C-O, Py), 174.8 (C=N); ^{19}F NMR (DMSO-d_6, 566 MHz): δ = -86.88 (d, 2F, J = 72.8 Hz) ppm. HRMS (ESI) calcd for $C_{11}H_{11}F_2N_4OS$ $[M+H]^+$: 285.0622. Found: 285.0618.

4.4. *Receptor binding studies (pI_{50}-values in vitro)*

Radioligand [^{3}H]imidacloprid displacement studies were conducted according to established protocols by using membranes isolated from frozen (−80 °C) housefly (*Musca domestica* L.) heads.[33, 34] Briefly, 5 g heads were homogenised in 100 mL of 0.1 MK-phosphate buffer, pH 7.4, 320 mM of sucrose and 1 mM of EDTA using an Ultra Turrax at 4 °C. After centrifugation for
15 min at 1200 × g and 4 °C, the pellet was resuspended and centrifuged again. Both supernatants were combined and filtered through Miracloth, and the filtrate was subsequently centrifuged at 105.000 × g for 60 min at 4 °C. The resulting pellet was resuspended in buffer and adjusted to approximately 0.5 mg protein mL^{-1}. The assay was conducted in a total volume of 1 mL,

consisting of 850 µL of homogenate and 50 µL of [^{3}H]imidacloprid (25.000 dpm; 1.406 GBq µmol^{-1}) in 0.1 MK-phosphate buffer, pH 7.4, containing 1 g L^{-1} of BSA and 5% ethanol (0.25% final concentration). After 5 min, different concentrations of the F_3CO- and F_2HCO-analogues of imidacloprid (**8**, **15**) and thiacloprid (**9**, **16**) were added (1000, 100, 10, 3, 1, 0.3, 0.1 and 0.01 nM, containing up to 0.1% DMSO). After incubation for 60 min at 22 °C while shaking, the samples were filtered through prewetted Whatman GF/C glass fibre filters, followed by two rinseswith 3 mL of ice-cold 0.1 MK-phosphate buffer (pH 7.4). Subsequently, the filters were dried (55 °C, 40 min), and 3.5 mL of scintillation cocktail was added. After 16 h at room temperature, the samples were subjected to liquid scintillation counting.

Myzus persicae* – spray test *(in vivo)

Solvent:	78.0	parts by weight acetone
	1.5	parts by weight *N,N*-dimethylformamide
Emulsifier:	alkylarylpolyglycol ether	

To produce a suitable preparation of active compound, 1 part by weight of the F_3CO- and F_2HCO-analogues of imidacloprid (**8**, **15**) and thiacloprid (**9**, **16**) is mixed with the stated amount of solvents and is diluted with water, containing an emulsifier concentration of 1000 ppm, to the desired concentration. Further test concentrations are prepared by dilution with emulsifier containing water.

Chinese cabbage (*Brassica pekinensis*) leaf disks infected with all instars of the green peach aphid (*Myzus persicae*), are sprayed with a preparation of the active ingredient of the desired concentration.

After 5-6 days mortality in % is determined. 100 % means all aphids have been killed and 0 % means none of the aphids have been killed.

In this test, for example, the compounds **8** and **16** from the preparation examples showed good activity of 100 % at an application rate of 500 g ha^{-1} and the compounds **9** and **15** from the preparation examples showed good activity of 100 % at an application rate of 100 g ha^{-1}.

Acknowledgment

The authors thank the Centre National de la Recherche Scientifique (CNRS) France and are very much grateful to Bayer for grants to E. S. and G. L. The French Fluorine Network (GIS Fluor) is also acknowledged. The authors thank the analytical platform (GDS3648) and the mass spectroscopy service of the Chemistry Institute of Strasbourg for both microanalysis and HRMS results.

References

[1] P. Jeschke, E. Baston, F.R. Leroux, Mini-Rev. Med. Chem. 7 (2007) 1027-1034.
[2] F. Leroux, P. Jeschke, M. Schlosser, Chem. Rev. 105 (2005) 827-856.
[3] B. Manteau, S. Pazenok, J.-P. Vors, F.R. Leroux, J. Fluorine Chem. 131 (2010) 140-158.

[4] A. Tlili, F. Toulgoat, T. Billard, Angew. Chem. Int. Ed. 55 (2016) 11726-35.
[5] F.R. Leroux, B. Manteau, J.P. Vors, S. Pazenok, Beilstein J. Org. Chem. 4 (2008) 13.
[6] T. Besset, P. Jubault, X. Pannecoucke, T. Poisson, Org. Chem. Front. 3 (2016) 1004-1010.
[7] G.A. Olah, T. Yamato, T. Hashimoto, J.G. Shih, N. Trivedi, B.P. Singh, M. Piteau, J.A. Olah, J. Am. Chem. Soc. 109 (1987) 3708-3713.
[8] W.A. Sheppard, J. Am. Chem. Soc. 85 (1963) 1314-18.
[9] A. Haas, Adv. Inorg. Chem. Radiochem. 28 (1984) 167-202.
[10] C. Hansch, A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology, John Wiley and Sons1979.
[11] A. Leo, P.Y.C. Jow, C. Silipo, C. Hansch, J. Med. Chem. 18 (1975) 865-8.
[12] C. Hansch, A. Leo, S.H. Unger, K.H. Kim, D. Nikaitani, E.J. Lien, J. Med. Chem. 16 (1973) 1207-16.
[13] F. Leroux, ChemBioChem 5 (2004) 644-649.
[14] G. Landelle, A. Panossian, F.R. Leroux, Curr. Top. Med. Chem. 14 (2014) 941-951.
[15] K. Muller, C. Faeh, F. Diederich, Science 317 (2007) 1881-1886.
[16] O. Marrec, T. Billard, J.-P. Vors, S. Pazenok, B.R. Langlois, J. Fluorine Chem. 131 (2010) 200-207.
[17] B. Manteau, P. Genix, L. Brelot, J.-P. Vors, S. Pazenok, F. Giornal, C. Leuenberger, F.R. Leroux, Eur. J. Org. Chem. (2010) 6043-6066.
[18] J. Klocker, A. Karpfen, P. Wolschann, Chem. Phys. Lett. 367 (2003) 566-575.
[19] I.W. Serfaty, T. Hodgins, E.T. McBee, J. Org. Chem. 37 (1972) 2651-2655.
[20] C. Ni, J. Hu, Synthesis 46 (2014) 842-863.
[21] P.S. Fier, J.F. Hartwig, Angew. Chem. Int. Ed. 52 (2013) 2092-5.
[22] V.V. Levin, A.D. Dilman, P.A. Belyakov, M.I. Struchkova, V.A. Tartakovsky, J. Fluorine Chem. 130 (2009) 667-670.
[23] X. Lin, C. Hou, H. Li, Z. Weng, Chem. Eur. J. 22 (2016) 2075-2084.
[24] C.S. Thomoson, L. Wang, W.R. Dolbier, J. Fluorine Chem. 168 (2014) 34-39.
[25] D. Kulhavy, A. Cegan, K. Komers, J. Mindl, Z. Naturforsch. C 57 (2002) 496-499.
[26] SYBYLx2.2 L.P. Certara St. Louis, MO, 2015.
[27] C.L. Morales-Perez, C.M. Noviello, R.E. Hibbs, Nature 538 (2016) 411-415.
[28] Z. Alamiddine, B. Selvam, J.P. Ceron-Carrasco, M. Mathe-Allainmat, J. Lebreton, S.H. Thany, A.D. Laurent, J. Graton, J.Y. Le Questel, J. Comp.-Aid. Mol. Des. 29 (2015) 1151-1167.
[29] T.t. Talley, M. Harel, R.E. Hibbs, Z. Radic, M. Tomizawa, J.E. Casida, P. Taylor, Proc. Natl. Acad. Sci. USA 105 (2008) 7606-7611.
[30] M.E. Beck, O. Gutbrod, S. Matthiesen, ChemPhysChem 16 (2015) 2760-2767.
[31] D. Federsel, A. Herrmann, D. Christen, S. Sander, H. Willner, H. Oberhammer, J. Mol. Struc. 567 (2001) 127-136.
[32] J. Klocker, A. Karpfen, P. Wolschann, J. Phys. Chem. A 107 (2003) 2362-2368.
[33] M.Y. Liu, J.E. Casida, Pestic. Biochem. Physiol. 46 (1993) 40-46.
[34] R. Nauen, K. Tietjen, K. Wagner, A. Elbert, Pest Manag. Sci. 52 (1998) 53-57.