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Synthesis of New Fluorinated Tebufenpyrad Analogs with Acaricidal Activity Through Regioselective Pyrazole Formation

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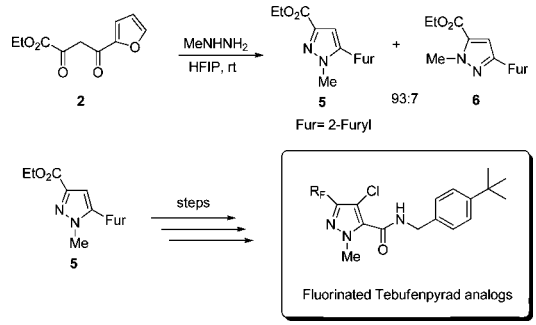

In previous studies, our group has shown that the use of fluorinated alcohols such as trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) as solvents dramatically increases the regioselectivity in the pyrazole formation from 1,3-diketone with methylhydrazine. We have now applied this synthetic method to the preparation of new fluorinated pyrazoles, which have then been used as synthetic intermediates in the preparation of fluorinated analogs of Tebufenpyrad, a commercial acaricide. These compounds display a strong acaricidal activity that is either comparable to or better than that of the commercial compound.

Introduction

In the past few years, the interest in pyrazole derivatives has increased due to their proven usefulness as intermediates in the preparation of new biological materials. Specifically, the pyrazole moiety is present in many agrochemically important compounds, such as the pesticides Cyenopyrafen,[1] Tebufenpyrad,[2] Tolfenpyrad,[3] and Fenpyroximate[4] (Figure 1).

Tebufenpyrad is a commercial *N*-methylpyrazole derivative with important acaricidal activity against the two-spotted spider mite *Tetranychus urticae* Koch, which causes significant yield losses worldwide in many field and greenhouse crops.[5] This mite infests over 200 species of plants, including common ornamental plants such as azaleas, camellias, or roses; fruits such as blackberries, blueberries, and strawberries; vegetables such as tomatoes and cucumbers; and trees, including elms, orange trees, and lemon trees. The mite affects crops through direct feeding, which reduces the area available for photosynthetic activity and, in severe infestations, can cause leaf abscission. Unfortunately, *T. urticae* is difficult to control because of its ability to quickly develop resistance to acaricides.[6] This resistance has resulted in a demand for new, resistant-free acaricides with novel modes of action.

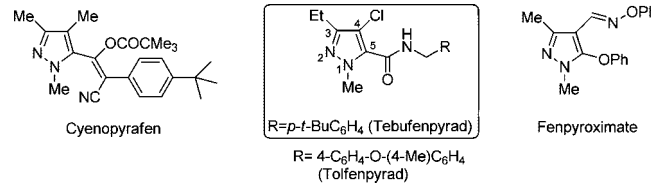

FIGURE 1. Some representative examples of pesticides with an *N*-methylpyrazole unit.

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(1) Murakami, H.; Masuzawa, S.; Takii, S.; Ito, T. Jpn. Patent 2003201280 A 20030718.
(2) Marcic, D. *Experim. Appl. Acarology* **2005**, *36*, 177–185.
(3) Nonata, N. *Agrochem. Jpn.* **2003**, *83*, 17–19.
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(5) Kim, M.; Shin, D.; Suh, E.; Cho, K. *Appl. Entomol. Zool.* **2004**, *39*, 401–409.
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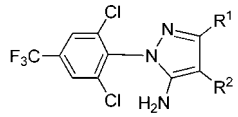


$R^1 = COCH_3$; $R^2 = SOCH_3$ (Acetoprole)
$R^1 = CN$; $R^2 = SOCF_3$ (Fipronil)
$R^1 = CN$; $R^2 = SOCH_2CH_3$ (Ethiprole)

FIGURE 2. Representative examples of *N*-[(trifluoromethyl)aryl]pyrazole derivatives with insecticidal/acaricidal activities.

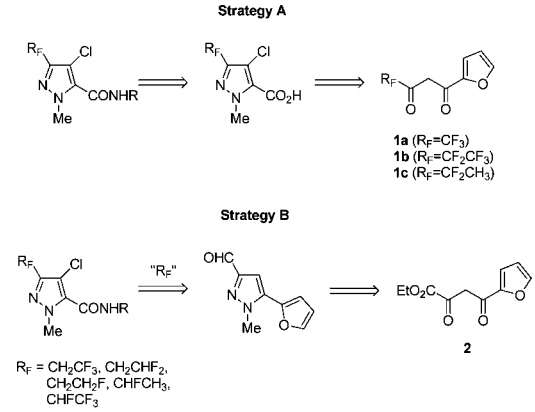
By varying the functional groups and structural elements of a model bioactive compound, the interaction of the latter with the active site of a given target molecule can be improved, as well as its physicochemical, pharmacokinetic, and dynamic properties. In this context, it is widely accepted that the introduction of fluorine atoms into organic molecules causes significant physicochemical and biological changes.[7] The so-called "fluorine factor" described in the literature several years ago stems from the unique combination of properties associated with the fluorine atom itself. The introduction of fluorine into bioactive compounds has thus become an important tool in the quest for modern crop protection products in terms of improving efficacy, environmental safety, user friendliness, and economic viability. Indeed, the number of active ingredients in modern crop protection products that contain fluorine-substituted moieties has steadily increased over the past 30 years. A survey of all halogenated commercial products available between 1940 and 2003 shows that fluorine products account for more than 28%. Moreover, about 27% of all fluoroorganic agrochemicals on the market today are insecticides/acaricides,[8] including the *N*-[(trifluoromethyl)aryl]pyrazole derivatives Acetoprole, Fipronil, and Ethiprole (Figure 2).

In a previous paper we reported on the synthesis of a series of fluorinated analogs of the commercial acaricide Tebufenpyrad,[9] two of which displayed acaricidal activity within the same order of magnitude as that of the commercial product. We have now used a different synthetic strategy for the introduction of the desired fluorine atoms, one that again makes use of the regioselective synthesis of key pyrazole intermediates. In this case, however, a different pyrazole functionalization is employed to access other pyrazoles that are partially fluorinated on the C-3 ethyl group of Tebufenpyrad (Figure 1). This has allowed us to prepare new Tebufenpyrad analogs with a different fluorination pattern and improved acaricidal activity.

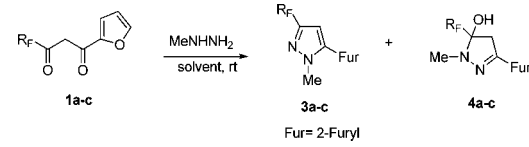
Results and Discussion

A. Synthesis. The aim of our work was to prepare new fluorinated pyrazoles derived from Tebufenpyrad and which incorporate several different fluorinated substitution patterns (R_F) on the C-3 ethyl group of the heterocyclic ring. For those pyrazoles in which $R_F = CF_3$, CF_3CF_2, or CH_3CF_2, we have very recently developed strategy **A** (Scheme 1), taking into account that the fluorinated 1,3-diketones **1a-c** were either commercially available or easily synthesized from the appropriate fluorinated esters and ketones.[10] In contrast, when $R_F = CF_3CH_2$, CHF_2CH_2, CH_2FCH_2, CH_3CHF, or CF_3CHF, the starting fluorinated 1,3-diketone analogs were not easily available. We thus developed strategy **B** (Scheme 1), in which ethyl 4-(2-furyl)-2,4-dioxobutanoate **2** is used as the key 1,3-dicarbonylic starting material, with the fluorine atoms being incorporated at a later stage of the sequence. Compound **2** can be easily prepared in 92% yield through the condensation of 2-acetylfurane and diethyl oxalate with *t*-BuOK as a base and THF:DME as a solvent.[10]

SCHEME 1. Two Synthetic Strategies for the Preparation of Fluorinated Analogs of *Tebufenpyrad*



SCHEME 2. Reaction of Fluorinated 1,3-Diketones (1a−c) with Methylhydrazine



In both strategies, the first step is the formation of the pyrazole ring through condensation of methylhydrazine and the appropriate 1,3-dicarbonyl compound (**1a−c, 2**). Recently, we reported on the results of the regioselective condensation between fluorinated 1,3-diketones **1a−c** and methylhydrazine.[9] The results showed that mixtures of 5-furylpyrazoles **3a−c** and 5-hydroxypyrazolines **4a−c** in ca. 1:1 to 2:1 ratios were formed when EtOH was used as a solvent at room temperature (Scheme 2), but that the regioselectivities were considerably enhanced when the fluorinated solvents 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) were used instead. The targeted 5-furylpyrazoles **3a−c** were thus obtained almost exclusively when reactions were carried out in HFIP.[9]

However, to access pyrazoles with other partially fluorinated groups, we needed a different, more flexible synthetic approach. We therefore decided to introduce the ethoxycarbonyl group as a synthetic precursor of the target groups. In this new strategy **B**, the reaction of the 1,3-diketoester **2** with methylhydrazine in ethanol at room temperature afforded an almost 1:1 mixture of the two 5-furyl **5** and 3-furyl **6** regioisomers in high yield; these were then easily separated with the aid of flash chromatography. In contrast to the lack of regioselectivity observed in EtOH, when the condensation reaction was carried out with the fluorinated solvents TFE and HFPI, the ratio increased to 93:7 in favor of the desired regioisomer **5**, which was obtained in almost quantitative yield (Scheme 3).

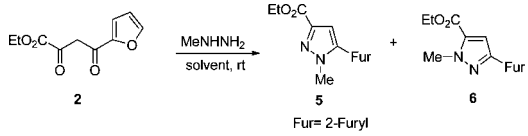
(7) (a) Baasner, B.; Hagemann, H.; Tatlow, J. C. In *Houben-Weyl Organo-Fluorine Compounds Volume E 10a−c*; Thieme Stuttgart: New York, 2000. (b) Banks, R. E.; Smart, B. E.; Tartlow, J. C. Ed. In *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (c) Schlosser, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1496–1513.

(8) Jeschke, P. *ChemBioChem* **2004**, *5*, 570–589.

(9) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Cuñat, A. C.; Villanova, S.; Murguía, M. *J. Org. Chem.* **2008**, *73*, 3523–3529.

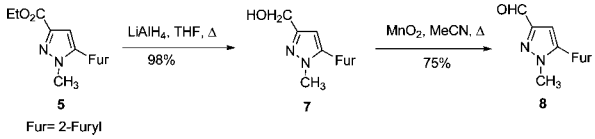
(10) Jiang, X.-H.; Song, L.-D.; Long, Y.-Q. *J. Org. Chem.* **2003**, *68*, 7555–7558.

SCHEME 3. Reaction of Ethyl 4-(2-Furyl)-2,3-dioxobutanoate (2) with Methyl-hydrazine

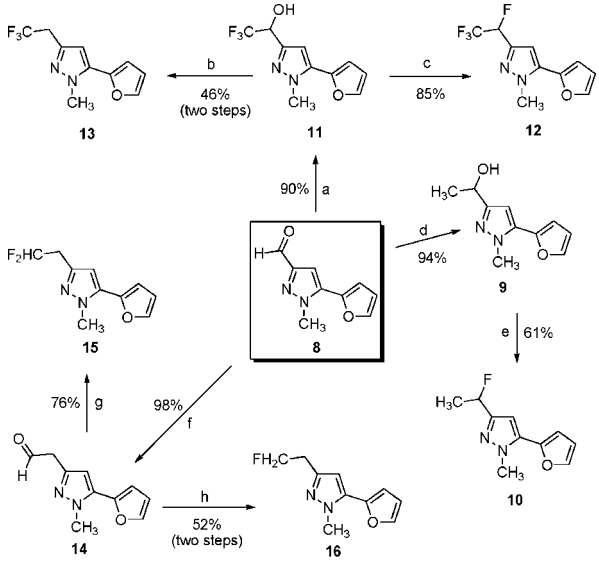


Solvent	Yield (%)	ratio **5**:**6**
EtOH	86	44:56
TFE	99	89:11
HFIP	98	93:7

SCHEME 4. Preparation of 3-Formyl-5-(2-furyl)-1-methylpyrazole (8)



SCHEME 5. Synthesis of Fluorinated *N*-Methylpyrazoles (10,12,13,15,16)



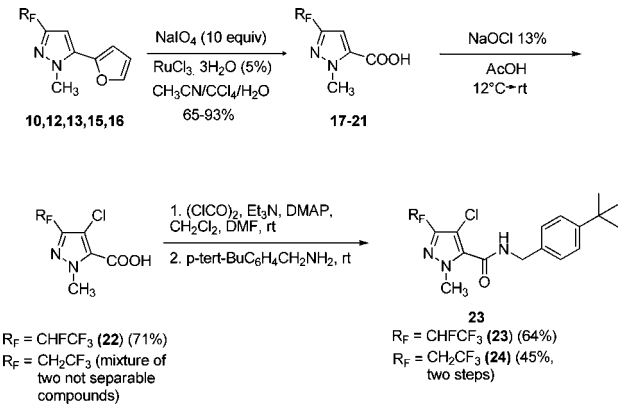
(a) i) CF_3SiMe_3, THF, TBAF cat., rt. ii) HCl, H_2O. (b) i) PhOCSCl, DMAP, Tol, 50-60°C. ii) Bu_3SnH, AIBN cat., Tol, 80°C. (c) Deoxofluor, CH_2Cl_2, rt. (d) MeMgBr, THF, 0°C. (e) Deoxofluor, CH_2Cl_2, rt. (f) i) $MeOCH{=}PPh_3$, NaHMDS, THF, rt. ii) 12N HCl, CH_2Cl_2, rt. (g) Deoxofluor, CH_2Cl_2, rt. (h) i) $NaBH_4$, MeOH, 0°C to rt. ii) Deoxofluor, CH_2Cl_2, rt.

3-(Ethoxycarbonyl)-5-(2-furyl)-*N*-methylpyrazole **5** was then converted into the aldehyde **8**, obtained in 74% combined yield through a two-step sequence involving $LiAlH_4$ reduction to the corresponding alcohol **7** and subsequent oxidization with MnO_2 (Scheme 4). This two-step process afforded much higher yields than the direct reduction of the ester to the aldehyde with DIBALH.

Compound **8** was then used as the key intermediate for the preparation of the rest of the fluorinated analogs of Tebufenpyrad in this work (Scheme 5). Reaction of **8** with MeMgBr afforded the 1-hydroxyethyl derivative **9** in 94% yield. Subsequent treatment of **9** with Deoxofluor provided the monofluorinated derivative **10** ($R_F = CH_3CHF$) in 61% yield. In a similar fashion,

(11) Singh, R. P.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1999**, *64*, 2579–2581.

SCHEME 6. Preparation of Carboxylic Acids 17−21 and Synthesis of the Fluorinated Analogs of Tebufenpyrad 23 and 24



treatment of **8** with Ruppert-Prakash's reagent[11] (CF_3SiMe_3) followed by acid hydrolysis afforded the 1-hydroxy-2,2,2-trifluoroethyl derivative **11** in 90% yield. This was then converted into the tetrafluorinated derivative **12** ($R_F = CF_3CHF$) in 85% yield through treatment with Deoxofluor. Alternatively, **11** was dehydroxylated via its thiocarbonate, which was reduced with Bu_3SnH to provide the trifluoroethyl derivative **13** ($R_F = CF_3CH_2$) in 46% yield (two steps).[12] Likewise, Wittig reaction of **8** with a basic solution of (methoxymethyl)triphenylphosphonium chloride followed by acid hydrolysis afforded the homologous aldehyde **14** in 98% yield, which then gave rise to the difluorinated derivative **15** ($R_F = CHF_2CH_2$) in 76% yield through treatment with Deoxofluor. Finally, sodium borohydride reduction of **14** and subsequent treatment with Deoxofluor afforded the monofluorinated derivative **16** ($R_F = CH_2FCH_2$) in 52% yield (two steps).

The oxidation of the furyl ring of the fluorinated *N*-methylpyrazoles thus obtained with sodium periodate in the presence of a catalytic amount of $RuCl_3 \cdot 3H_2O$ at room temperature provided the corresponding carboxylic acids **17**−**21** in good to excellent yields.[13] However, the next step, which involved chlorination of C-4 at the pyrazole ring, presented several unexpected difficulties. For example, while the reaction was successful with the carboxylic acid **18** ($R_F = CF_3CHF$) (Scheme 6), providing the corresponding chlorinated derivative **22** in good yield, the carboxylic acid analog **19** ($R_F = CF_3CH_2$) afforded a mixture of two nonseparable compounds (one of them being the desired C-4 chlorinated derivative). Furthermore, with the rest of the compounds (**17**, **20**, and **21**), only complex mixtures were obtained. Nevertheless, both the chlorinated derivative **22** and the chlorinated carboxylic acid found in the mixture of compounds from the chlorination of **19** were subsequently converted into the fluorinated carboxamide analogs of Tebufenpyrad **23** and **24**, respectively (Scheme 6).

To avoid the aforementioned inconvenience in the chlorination reaction, we modified our strategy slightly and performed

(12) Jiang, Z.-X.; Qin, Y.-Y.; Ping, F.-L. *J. Org. Chem.* **2003**, *68*, 7544–7547.

(13) Danishefsky, S. J.; DeNinno, M. P.; Chen, S. H. *J. Am. Chem. Soc.* **1988**, *110*, 3929–3940.

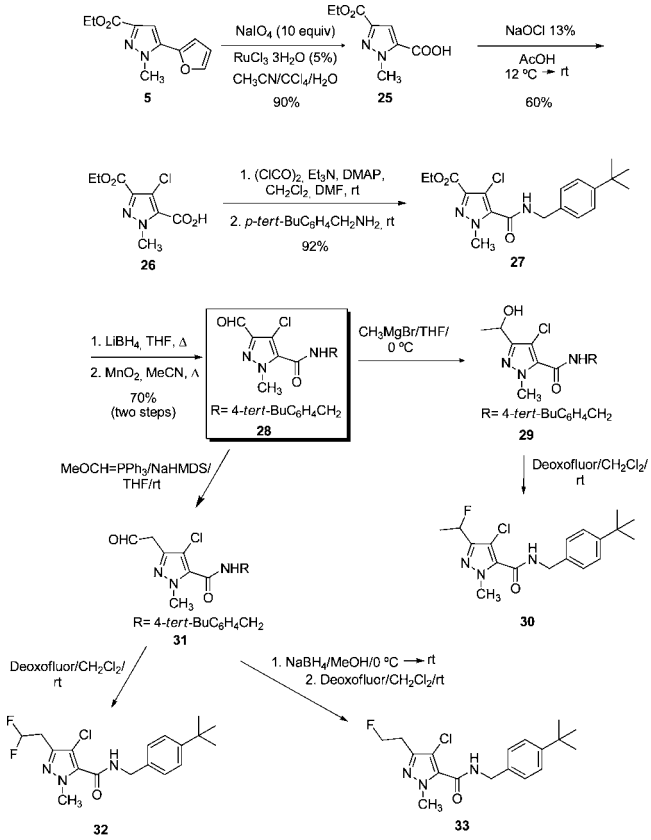
(14) Preliminary assays were carried out using the non-chlorinated carboxamide analogs of Tebufenpyrad **30′** ($R_F = CHFCH_3$) and **32′** ($R_F = CH_2CHF_2$), which were obtained by amidation of the corresponding carboxylic acids **17** and **21**, respectively. Under the same reaction conditions described above, chlorination of **30′** and **32′** afforded complex mixtures of products. Likewise, the desired results were not obtained when other chlorination agents such as NCS, Chloramine-T, and *tert*-butyl hypochlorite were used in the reaction with the carboxylic acids **17**−**21**.

TABLE 1. Biological Activity of the Fluorinated Tebufenpyrad Analogs on *Tetranychus urticae*

		% mortality[a]			% fertility inhibition[a]		
entry	compound [R_F]	24 h	4 days	6 days	24 h	4 days	6 days
1	**23** [CHF-CF_3]	10	10	60	53	60	65
2	**24** [CH_2−CF_3]	25	30	70	97	98	98
3	**30** [CHF-CH_3]	70 (48)	75 (44)	100 (66)	100 (95)	100 (95)	100 (96)
4	**30′** [CHF-CH_3]	70 (16)	70 (10)	80 (10)	100 (68)	96 (91)	100 (94)
5	**32** [CH_2−CF_2H]	100 (80)	100 (71)	100 (75)	100 (100)	100 (100)	100 (100)
6	**32′** [CH_2−CF_2H]	100 (59)	100 (14)	100 (10)	100 (96)	100 (100)	100 (98)
7	**33** [CH_2−CH_2F]	100 (96)	100 (100)	100 (100)	100 (100)	100 (100)	100 (100)
8	Tebufenpyrad	100 (92)	100 (100)	100 (100)	100 (84)	100 (100)	100 (100)

[a] Concentration of active principle in the assay: 5 g/L; the numbers in parentheses show the results for an active principle concentration in the assay of 0.16 g/L.

SCHEME 7. Synthesis of Fluorinated Analogs of Tebufenpyrad 30, 32, and 33



the chlorination at an earlier stage.[14] The furyl ring of 3-(ethoxycarbonyl)-5-(2-furyl)-*N*-methylpyrazole **5** was thus oxidized in 90% yield and the resulting carboxylic acid **25** was successfully chlorinated in 60% yield (Scheme 7). Conversion of **26** into the amide **27** took place without difficulty and was followed by chemoselective reduction of the ester group with $LiBH_4$. The resulting primary alcohol was easily oxidized with MnO_2 to afford aldehyde **28** in 70% combined yield. This compound, in turn, constituted the key intermediate for the preparation of the target molecules. The subsequent steps were similar to those previously described (see Scheme 5) and provided the fluorinated Tebufenpyrad analogs **30**, **32**, and **33** (Scheme 7).

B. Acaricidal Activity. A standard method was used to test the fluorinated analogs of Tebufenpyrad **23**, **24**, **30**, **32**, and **33** and the nonchlorinated carboxamides **30′** and **32′** as acaricides against *Tetranychus urticae* Koch.[15] The activity of the fluorinated compounds was then compared to that of the commercial product Masai, the active principle of which is Tebufenpyrad.[16] The effects of applying the assayed compounds as adulticides and fertility inhibitors was evaluated for each compound 24 h, 4 days, and 6 days after application. Preliminary tests were carried out with a solution of 5 g/L for each compound. Table 1 lists the obtained results.

The results indicate that, except for **23**, all the fluorinated derivatives tested —both chlorinated and nonchlorinated —exert complete (100%) or nearly complete (96%) fertility inhibition early within the 24 h period, as was also observed for Tebufenpyrad. In contrast, whereas **32**, **32′**, **33**, and Tebufenpyrad all cause 100% mortality within 24 h, **30** and **30′** display slightly lower activity (70%), while both **23** and **24** exhibit a very low adulticide activity within the same time period.

Solutions of **30**, **30′**, **32**, **32′**, **33**, and Tebufenpyrad at 1.50, 0.67, and 0.16 g/L were then prepared to evaluate and compare their acaricidal activity at concentrations lower than 5 g/L (Figure 3).[17]

Interestingly, the results indicate that only **33** (R_F = CH_2CH_2F) causes complete (100% at a concentration of 1.5 g/L) or nearly complete (96% at a concentration of 0.67 and 0.16 g/L) adult mortality within the first 24 h, with its effect being slightly higher than that of Tebufenpyrad at the same concentration. Within the same time period, the only other compound to cause 100% mortality is **32** at a concentration of 1.5 g/L. Like Tebufenpyrad, the chlorinated derivatives **30**, **32**, and **33** cause complete mortality at 1.5 g/L within the first 4 days. In contrast, the nonchlorinated carboxamides **32′** and particularly **30′** display significantly lower adulticide activities than the chlorinated analogs at both 0.67 and 0.16 g/L. These results show the relation between the adulticide activity of fluorinated analogs of Tebufenpyrad and the presence of the chlorine atom in the pyrazole moiety.

The fertility inhibition of *Tetranychus urticae* is thus clearly increased by several of our new fluorinated analogs. While **30**, **30′**, **32**, **32′**, **33**, and Tebufenpyrad all display 100% fertility inhibition after 24 h, significant differences appear at lower concentrations. Indeed, at the lowest concentration assayed (0.16 g/L), while the inhibitory activity for Tebufenpyrad is 84%, compounds **32** and **33** still display 100% activity, with the nonchlorinated analog **32′** still exerting a somewhat higher activity (96%) than the reference compound (Figure 3).

(15) García-Marí, F.; Roca, D.; Fonbuena, P.; Ferragut, F.; Costa-Comelles, *J. Bol. San. Veg. Plagas* **1988**, *14*, 163–169.

(16) Masai is commercialized by BASF.

(17) The concentration of Tebufenpyrad in solution for standard field treatment varies between 200 mg/L (pumpkin, eggplant, tomato), 130 mg/L (cotton), and 70 mg/L (citrus fruits).

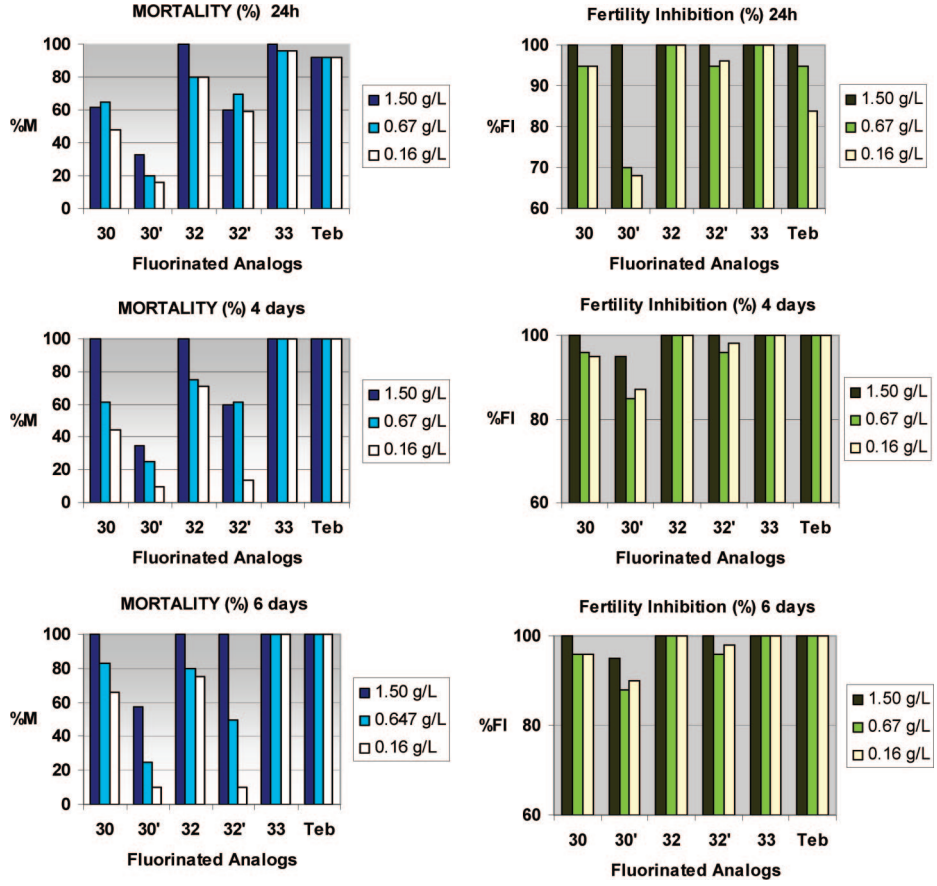


FIGURE 3. Adult mortality and fertility inhibition of fluorinated analogs of Tebufenpyrad on *Tetranychus urticae*.

Conclusions

In summary, the use of the fluorinated alcohols TFE and HFIP allows for the regioselective synthesis of pyrazole **5**, a compound that constitutes a versatile synthetic intermediate for the preparation of biologically active compounds with a pyrazole moiety. As an example, we have successfully synthesized a small set of Tebufenpyrad analogs with several fluorination patterns on the ethyl group that were for the most part highly active as acaricides against *Tetranychus urticae*, in some cases displaying an even higher acaricidal activity than Tebufenpyrad, which was used as a reference. In fact, two of these compounds (**32** and **33**) display a fertility inhibition superior to that of Tebufenpyrad.

Experimental Section

Ethyl 4-(2-Furyl)-2,4-dioxobutanoate (2). A solution containing 2-acetylfurane (27 mmol, 2.9 g) and diethyl oxalate (54 mmol, 7.9 g) in dimethoxyethane (DME) (50 mL) was added slowly to a suspension of *t*-BuOK (54 mmol, 6.0 g) in THF (50 mL) at room temperature and the resulting reaction mixture was stirred for two hours. Solvents were removed *in vacuo* and the residue was hydrolyzed with HCl 1 M (20 mL) until acid pH was reached. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the organic phase was washed with brine, dried over anh. Na_2SO_4, and filtered. The solvent was removed to give a brown solid, which was then purified with the aid of column chromatography on silica gel that had previously been deactivated through treatment with 2% acetic acid. Flash chromatography [*n*-hexane-EtOAc (2:1)] (R_f = 0.30) afforded **2** as a brownish solid (92%, 5.2 g); mp 72−5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, J = 5.3 Hz, 3H; CH_3), 4.32 (q, J = 5.3, 2H; CH_2), 6.56 (dd, J_1= 2.8 Hz, J_2= 1.2 Hz, 1H; C*H*), 6.87 (s, 1H; C*H*), 7.28 (dd, J_1= 2.8 Hz, J_2= 0.5 Hz, 1H; C*H*); 7.62 (dd, J_1= 1.2 Hz, J_2= 0.5 Hz, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.9, 62.4, 98.8, 113.0, 118.4, 147.6, 150.7, 161.8, 165.9, 180.7 ppm. HRMS: calcd for $C_{10}H_{10}O_5$ (M^+): 210.0523; found 210.0528.

3-(Ethoxycarbonyl)-5-(2-furyl)-1-methylpyrazole (5). Methylhydrazine (36 mmol, 1.6 g) was added slowly to 1,3-diketone **2** (28 mmol, 5.9 g) dissolved in HFIP (60 mL) at 0 °C under nitrogen atmosphere and the resulting mixture was stirred at room temperature for 45 min. The solvent was evaporated and the residue was taken up in EtOAc, washed with water and brine, dried over anh Na_2SO_4, filtered, and concentrated *in vacuo* to afford pyrazole **5**, which was then purified with the aid of column chromatography on silica gel. Flash chromatography [*n*-hexane-EtOAc (8:1)] (R_f = 0.30) afforded **5** as a pale-yellow solid (93% yield) (mp: 50−52 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (t, J = 7.2 Hz, 3H; CH_3), 4.06 (s, 3H; CH_3), 4.35 (q, J = 7.2 Hz, 2H; CH_2), 6.46 (dd, J_1 = 3.5 Hz, J_2= 1.4 Hz, 1H; C*H*), 6.51 (d, J = 3.5 Hz, 1H; C*H*), 6.94 (s, 1H; C*H*), 7.47 (d, J = 1.4 Hz, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.8, 39.9, 61.5, 108.1, 109.8, 111.9, 135.9, 143.0, 143.6, 144.2, 162.5 ppm. HRMS: calcd for $C_{11}H_{12}N_2O_3$ (M^+) 220.0818; found 220.0805.

3-Formyl-5-(2-furyl)-1-methylpyrazole (8). Step 1: Reduction of the Ethoxycarbonyl Group of 5 to Afford Compound 7. A solution of 3-(ethoxycarbonyl)-5-(2-furyl)-1-methylpyrazole (**5**) (9 mmol, 2.0 g) in THF (30 mL) was added to a solution of $LiAlH_4$ (27 mmol, 1.1 g) in THF (30 mL) at 0 °C under nitrogen atmosphere and the resulting mixture was stirred at 50−60 °C until **5** was no longer detectable through TLC (ca. 1 h). Three milliliters of water were then added to the mixture at 0 °C, followed by 3 mL of 15% aqueous solution of NaOH and 8 mL of water. The mixture was stirred at room temperature for 30 min and then 30 mL of Cl_2CH_2 were added. The organic phase was then separated

and the mixture was dried over anh Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil, which was purified by means of column chromatography on silica gel to afford pure compound **7**. Flash chromatography [*n*-hexane-EtOAc (3:1)] (R_f = 0.30) afforded **7** as a pale-yellow oil (98%, 1.6 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 3H; CH_3), 4.58 (s, 2H; CH_2), 6.38 (s, 1H; CH), 6.42 (dd, J_1= 3.4 Hz, J_2= 1.7 Hz, 1H; CH), 6.46 (dd, J_1= 3.4 Hz, J_2= 0.6 Hz, 1H; CH), 7.42 (dd, J_1= 1.7 Hz, J_2= 0.6 Hz, 1H; CH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 38.7, 58.7, 103.9, 109.0, 111.8, 135.4, 143.1, 145.0, 151.7 ppm. HRMS: calcd for $C_9H_{10}N_2O_2$ (M^+) 178.0739; found 178.0742.

Step 2: Oxidation of the Hydroxymethyl Group of 7. Activated MnO_2 (60 mmol, 6.1 g) was added to a solution of **7** (10 mmol, 1.8 g) in CH_3CN (60 mL). The reaction mixture was refluxed until **7** was no longer detectable through TLC (ca. 4 h). The mixture was then cooled to room temperature, filtered through celite *in vacuo*, extracted with ethyl acetate, dried over anh Na_2SO_4, and concentrated *in vacuo* to give a brown solid, which was purified by means of column chromatography on silica gel to give compound **8**. Flash chromatography [*n*-hexane-EtOAc (4:1)] (R_f = 0.40) afforded pure **8** as a pale-yellow solid (75%, 1.3 g) (mp: 55−57 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.08 (s, 3H; CH_3), 6.47 (dd, J_1= 3.5 Hz, J_2= 1.9 Hz, 1H; C*H*), 6.58 (d, J = 3.5 Hz, 1H; C*H*), 6.90 (s, 1H; C*H*), 7.48 (dd, J_1= 1.9 Hz, J_2= 0.5 Hz, 1H; C*H*), 9.87 (s, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 40.0, 104.9, 110.2, 112.1, 136.6, 143.8, 143.9, 150.6, 186.6 ppm. HRMS: calcd for $C_9H_8N_2O_2$ (M^+) 176.0586; found 176.0585.

3-(1-Fluoroethyl)-5-(2-furyl)-1-methylpyrazole (10). Step 1: Addition of Methylmagnesium Bromide to 8 to Afford Compound 9. A 1 M solution of CH_3MgBr (4.5 mmol) in THF was slowly added to a solution of **8** (3 mmol, 0.5 g) in THF (11 mL) under nitrogen atmosphere at 0 °C. The mixture was stirred overnight at room temperature. The reaction mixture was then hydrolyzed with a saturated solution of NH_4Cl (5 mL), extracted with EtOAc (3 × 10 mL), washed with brine, dried over anh Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil, which was purified by means of column chromatography on silica gel. Flash chromatography [*n*-hexane-EtOAc (2:1)] (R_f = 0.30) afforded **9** as a pale-yellow oil (94%, 0.54 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (d, J = 4.9 Hz, 3H; CH_3), 2.31 (broad, 1H; O*H*), 3.93 (s, 3H; CH_3), 4.87 (q, J = 4.9 Hz, 1H; C*H*), 6.35 (s, 1H; C*H*), 6.43 (dd, J_1= 2.5 Hz, J_2= 1.4 Hz, 1H; C*H*), 6.47 (dd, J_1= 2.5 Hz, J_2= 0.5 Hz, 1H; C*H*), 7.43 (dd, J_1= 1.4 Hz, J_2= 0.5 Hz, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 1.4, 23.7, 30.1, 38.8, 65.2, 101.8, 108.9, 111.8, 143.1 ppm. HRMS: calcd for $C_{10}H_{12}N_2O_2$ (M^+) 192.0899; found 192.0887.

Step 2: Fluorination of 9 with Deoxofluor. Deoxofluor (3 mmol, 50% in toluene) was added slowly to a solution of **9** (2 mmol) in CH_2Cl_2 (5 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred overnight at room temperature. The reaction mixture was then cooled to 0 °C, hydrolyzed with saturated sodium bicarbonate solution until neutral pH was reached, and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was washed with brine, dried over anh Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil, which was purified by means of column chromatography on silica gel. Flash chromatography [*n*-hexane-EtOAc (8:1)] (R_f = 0.40) afforded **10** as a pale-yellow oil (61%, 0.24 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (dd, J_1^{HF}= 24.0 Hz, J_2= 6.6 Hz, 3H; CH_3), 3.95 (d, J_{HF}= 1.1 Hz, 3H; C*H*), 5.63 (dq, J_1^{HF}= 48.3 Hz, J_2= 6.6 Hz, 1H; C*H*), 6.43 (dd, J_1= 3.4 Hz, J_2= 1.8 Hz, 1H; C*H*), 6.46 (s, 1H; C*H*), 6.49 (dd, J_1= 3.4 Hz, J_2= 0.6 Hz, 1H; C*H*), 7.44 (dd, J_1= 1.8 Hz, J_2= 0.6 Hz, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.3 (d, $^2J_{CF}$= 24.7 Hz), 38.9, 86.1 (d, $^1J_{CF}$= 162.7 Hz), 102.9 (d, $^3J_{CF}$= 2.9 Hz), 109.1, 111.8, 135.4, 143.2, 144.9, 151.6 (d, $^2J_{CF}$= 24.2 Hz) ppm. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −166.1 (qd, J_1^{FH}= 48.3 Hz, J_2^{FH}= 24.0, 1F; C*F*) ppm. HRMS: calcd for $C_{10}H_{11}FN_2O$ (M^+) 194.0855; found 194.0852.

3-(1,2,2,2-Tetrafluoroethyl)-5-(2-furyl)-1-methylpyrazole (12). Step 1: Addition of (Trifluoromethyl)trimethylsilane (CF_3SiMe_3) to 8 to Afford Compound 11. (Trifluoromethyl)trimethylsilane (7.6 mmol, 1.1 g) and tetrabutylamonium fluoride (0.09 mmol) were added in succession to a solution of **8** (4.5 mmol, 0.8 g) in THF (15 mL) at room temperature under nitrogen atmosphere and the resulting mixture was stirred until **8** was no longer detectable through TLC (ca. 3.5 h). A 6N solution of HCl (5 mL) was then added and the reaction mixture was stirred for 1 h. Next, water (5 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL), washed with brine (2 × 5 mL), dried over anh Na_2SO_4, and concentrated *in vacuo* to give a yellow solid, which was purified by means of column chromatography on silica gel. Flash chromatography [*n*-hexane-EtOAc (3:1)] (R_f = 0.30) afforded **11** as a pale-yellow solid (90%, 1.0 g) (mp: 82−84 °C).^{1}H NMR (300 MHz, $CDCl_3$): δ 3.98 (s, 3H; CH_3), 5.01 (q, J_{HF} = 6.7 Hz, 1 H; C*H*), 6.45 (dd, J_1 = 3.4 Hz, J_2 = 1.8 Hz, 1H; C*H*), 6.47 (s, 1H; C*H*), 6.53 (d, J = 3.4 Hz, 1H; C*H*), 7.46 (dd, J_1 = 1.8 Hz, J_2 = 0.8 Hz, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 39.1, 68.1 (q, $^2J_{CF}$= 33.3 Hz), 103.6 (q, $^4J_{CF}$ = 1.7 Hz), 109.6, 111.9, 124.5 (q, $^1J_{CF}$ = 231.7 Hz), 136.3, 143.4, 144.4, 145.5 (q, $^3J_{CF}$ = 1.2) ppm. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −78.9 (d, J_{FH} = 6.7 Hz, 3F; CF_3) ppm. HRMS: calcd for $C_{10}H_9F_3N_2O_2$ (M^+) 246.0606; found 246.0586.

Step 2: Fluorination of 11 with Deoxofluor (see above, "Fluorination of 9 with Deoxofluor" for the Procedure). Flash chromatography [*n*-hexane-EtOAc (10:1)] (R_f = 0.40) afforded **12** as a pale yellow oil (85%, 0.42 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.00 (d, J = 1.3 Hz, 3H; CH_3), 5.61 (qd, J_1^{HF} = 44.2 Hz, J_2^{HF} = 6.5, 1H; C*H*), 6.46 (dd, J_1 = 3.4 Hz, J_2 = 1.8 Hz, 1H; C*H*), 6.55 (dd, J_1= 3.4 Hz, J_2 = 0.5 Hz, 1H; C*H*), 6.63 (s, 1H; C*H*), 7.47 (dd, J_1 = 1.8 Hz, J_2 = 0.5 Hz, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 39.4, 84.6 (qd, $^1J_{CF}$ = 132.3 Hz, $^2J_{CF}$= 36.2 Hz), 104.6, 109.7, 111.9, 122.5 (qd, $^1J_{CF}$= 231.2 Hz, $^2J_{CF}$ = 29.9 Hz), 136.3, 141.8 (d, $^2J_{CF}$ = 24.7 Hz), 143.5, 144.2 ppm. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −78.8 (dd, J_1^{FF} = 14.3 Hz, J_2^{FH} = 6.5 Hz, 3F; CF_3), −189.4 (qd, J_1^{FH} = 44.2 Hz, J_2^{FF} = 14.3 Hz, 1F; C*F*) ppm. HRMS: calcd for $C_{10}H_8F_4N_2O$ (M^+) 248.0570; found 248.0573.

3-(2,2,2-Trifluoroethyl)-5-(2-furyl)-1-methylpyrazole (13). Molecular sieves (4 Å) (500 mg) and dimethylaminopyridine (DMAP) (3.4 mmol, 0.42 g) were added to a solution of **11** (1.7 mmol, 0.42 g) in toluene (25 mL) at room temperature under nitrogen atmosphere, and the resulting mixture was vigorously stirred magnetically. Phenyl chlorothioformiate (PHOCSCl) (3.4 mmol, 0.58 g) was then slowly added and the mixture was stirred at 50−60 °C until **11** was no longer detectable through TLC. The reaction mixture was cooled to room temperature, filtered over celite *in vacuo*, and washed with EtOAc. The filtrate was concentrated *in vacuo* to give a yellow oil, which was purified by means of column chromatography on silica gel. Flash chromatography [*n*-hexane-EtOAc (6:1)] (R_f = 0.30) afforded 3-(1-phenoxythiocarbonyloxy-2,2,2-trifluoro)ethyl-5-(2-furyl)-1-methyl pyrazole as a yellow oil (61%, 0.40 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.00 (s, 3H; CH_3), 6.45 (dd, J_1 = 3.4 Hz, J_2 = 1.7 Hz, 1H; C*H*), 6.54 (d, J = 3.4 Hz, 1H; C*H*), 6.65 (s, 1H; C*H*), 6.77 (q, J_{HF} = 6.7 Hz, 1 H; C*H*), 7.03 (d, J = 0.7 Hz, 1H; C*H*), 7.06 (d, J = 1.3 Hz, 1H; C*H*), 7.18−7.34 (m, 3H), 7.46 (dd, J_1 = 1.7 Hz, J_2 = 0.7 Hz, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 39.5, 75.9 (q, $^2J_{CF}$ = 34.6 Hz), 105.2, 109.6, 111.9, 122.1 (d, $^3J_{CF}$ = 12.1 Hz), 122.9 (q, $^1J_{CF}$ = 230.4 Hz), 127.3, 130.0 (d, $^3J_{CF}$ = 2.9 Hz), 136.1, 141.5, 143.5, 144.4, 153.9, 193.8 ppm. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −80.2 (d, J_{FH} = 6.7 Hz, 3F; CF_3) ppm. HRMS: calcd for $C_{17}H_{13}F_3N_2O_3S$ (M^+) 382.0640; found 382.0662.

A solution containing Bu_3SnH (5.36 mmol, 1.5 g) and α,α′-azobis(isobutyronitrile) (AIBN) (0.8 mmol, 0.13 g) in toluene (10 mL) was added to a solution of 3-(1-phenoxythiocarbonyloxy-2,2,2-trifluoro)ethyl-5-(2-furyl)-1-methylpyrazole (1.34 mmol; 0.51 g) in toluene (20 mL) at 80 °C under nitrogen atmosphere. The resulting mixture was stirred at this temperature until the starting material was no longer detectable through TLC. The reaction mixture was

then cooled to room temperature and concentrated *in vacuo*. Water (10 mL) was added to the residue, which was then extracted with EtOAc (3 × 15 mL), washed with brine, dried over anh Na_2SO_4, and concentrated *in vacuo* to give a yellow oil, which was purified by means of column chromatography on silica gel. Flash chromatography [*n*-hexane-EtOAc (9:1)] (R_f = 0.40) afforded **13** as a pale-yellow oil (75%, 0.23 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.37 (q, J_{HF} = 11.0 Hz, 2 H; CH_2), 3.95 (s, 3H; CH_3), 6.40 (s, 1H; C*H*), 6.43 (dd, J_1 = 3.4 Hz, J_2 = 1.9 Hz, 1H; C*H*), 6.49 (dd, J_1 = 3.4 Hz, J_2 = 0.7 Hz, 1H; C*H*), 7.43 (dd, J_1 = 1.9 Hz, J_2 = 0.7 Hz, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 33.9 (q, $^2J_{CF}$ = 31.1 Hz), 38.9, 105.4, 109.1, 111.8, 125.8 (q, $^1J_{CF}$ = 276.5 Hz), 135.7, 141.3 (q, $^3J_{CF}$ = 3.5 Hz), 143.2, 144.8 ppm. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −66.2 (t, J_{FH} = 11.0 Hz, 3F; CF_3) ppm. HRMS: calcd for $C_{10}H_9F_3N_2O$ (M^+) 230.0664; found 230.0667.

3-(2,2-Difluoroethyl)-5-(2-furyl)-1-methylpyrazole (15) and 3-(2-Fluoroethyl)-5-(2-furyl)-1-methylpyrazole (16). A 1 M solution of hexamethyldisylazane sodium salt (3.13 mmol) in THF was added dropwise to a suspension of (methoxymethyl)triphenylphosphonium chloride (3.13 mmol; 1.1 g) in THF (4 mL) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at this temperature for 45 min, after which a solution of **8** (2.61 mmol; 0.46 g) in THF (3 mL) was slowly added. The reaction mixture was stirred at room temperature until **8** was no longer detectable through TLC. The reaction mixture was then hydrolyzed with a saturated solution of NH_4Cl (3 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine (2 × 5 mL), dried over anh Na_2SO_4, and concentrated *in vacuo* to give a yellow oil, which was purified by means of column chromatography on deactivated silica gel. Flash chromatography [*n*-hexane-EtOAc (6:1)] afforded a nonseparable mixture of the *E* + *Z* diastereomers (R_f = 0.40) of 5-(2-furyl)-1-methyl-3-(2-methoxy)ethenylpyrazole as a pale-yellow oil (82%, 0.44 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.59 (s, 3H; CH_3), 3.71 (s, 3H; CH_3), 3.90 (s, 3H; CH_3), 3.92 (s, 3H; CH_3), 5.34 (d, J = 6.8 Hz, 1H; C*H*), 5.69 (d, J = 13.2 Hz, 1H; C*H*), 6.10 (d, J = 6.8 Hz, 1H; C*H*), 6.29 (s, 1H; C*H*), 6.41 (d, J = 1.0 Hz, 1H; C*H*), 6.42 (d, J = 0.8 Hz, 1H; C*H*), 6.45 (dd, J_1 = 5.6 Hz, J_2 = 0.8 Hz, 1H; C*H*), 6.46 (dd, J_1 = 5.6 Hz, J_2 = 0.6 Hz, 1H; C*H*), 6.73 (s, 1H; C*H*), 7.06 (d, J = 13.2 Hz, 1H; C*H*), 7.41 (dd, J_1 = 1.7 Hz, J_2 = 0.6 Hz, 1H; C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 38.7, 38.8, 56.6, 60.9, 97.3, 98.6, 100.7, 105.5, 108.6, 108.7, 111.7, 111.8, 134.8, 135.2, 142.8, 142.9, 145.3, 145.5, 147.1, 148.1, 148.7, 150.4 ppm; HRMS: calcd for (M^+) $C_{11}H_{12}N_2O_2$: 204.0899, found: 204.0896.

A 12 N solution of HCl (2.88 mmol) was slowly added to a solution of 5-(2-furyl)-1-methyl-3-(2-methoxy)ethenylpyrazole (*E* + *Z*) (1.44 mmol; 0.3 g) at 0 °C and then stirred at room temperature until the starting material was no longer detectable through TLC (ca. 16 h). The solvent was removed *in vacuo* and 2 mL of H_2O was added to the mixture. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the organic layer was washed with brine (2 × 2 mL), dried over anh Na_2SO_4, and concentrated *in vacuo* to give a yellow oil (98% yield), identified as the aldehyde **14**. The compound was not purified and was used as obtained in the subsequent reactions. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64 (d, J = 2.3 Hz, 2H; CH_2), 3.96 (s, 3H; CH_3), 6.33 (s, 1H; C*H*), 6.44 (dd, J_1 = 3.4 Hz, J_2= 1.9 Hz, 1H; C*H*), 6.48 (dd, J_1 = 3.4 Hz, J_2 = 0.7 Hz, 1H; C*H*), 7.44 (dd, J_1 = 1.9 Hz, J_2 = 0.7 Hz, 1H; C*H*), 9.73 (t, J = 2.3 Hz, 1H; C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 38.5, 43.1, 105.0, 108.7, 111.4, 135.4, 142.8, 144.6, 153.2, 198.7 ppm; HRMS: calcd for $C_{10}H_{10}N_2O_2$ (M^+) 190.0739; found 190.0742.

Fluorination of 14 (See Above: "Fluorination of 9 with Deoxofluor" for the Experimental Procedure). Flash chromatography [*n*-hexane-EtOAc (7:1)] (R_f = 0.40) afforded **15** as a pale-yellow oil (76% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.09 (td, J_1^{HF} = 17.0 Hz, J_2 = 4.5, 2H; CH_2), 3.91 (s, 3H; CH_3), 5.93 (tt, J_1^{HF} = 56.7 Hz, J_2 = 4.5, 1H; C*H*), 6.32 (s, 1H; C*H*), 6.40 (dd, J_1 = 3.4 Hz, J_2 = 1.8 Hz, 1H; C*H*), 6.44 (d, J = 3.4 Hz, 1H; C*H*), 7.41 (d, J = 1.8 Hz, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 34.2 (t, $^2J_{CF}$ = 23 Hz), 38.8, 105.4, 108.9, 111.8, 116.5 (t, $^1J_{CF}$ = 240.3 Hz), 135.6, 143.1, 143.4 (t, $^3J_{CF}$ = 7.0 Hz), 145.0 ppm. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −125.4 (dt, J_1^{FH} = 56.7 Hz, J_2^{FH} = 17.0 Hz, 2F; CF_2) ppm. HRMS: calcd for $C_{10}H_{10}F_2N_2O$ (M^+) 212.0751; found 212.0739.

Preparation of 16. Step 1: Reduction of 14. $NaBH_4$ (3.72 mmol, 0.14 g) was slowly added to a solution of **14** (1.24 mmol, 0.24 g) in MeOH (7 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature until **14** was no longer detectable through TLC (ca. 16 h). The reaction mixture was then concentrated *in vacuo*, hydrolyzed with a saturated NH_4Cl aq. solution (4 mL), and extracted with EtOAc (3 × 10 mL). The organic layers were pooled together and washed with brine (2 × 3 mL), dried over anh Na_2SO_4, and concentrated *in vacuo* to give a yellow oil, which was purified by means of column chromatography on silica gel. Flash chromatography [*n*-hexane-EtOAc (2:1)] (R_f = 0.20) afforded 5-(2-furyl)-3-(2-hydroxyethyl)-1-methylpyrazole as a pale yellow oil (64%, 0.15 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.79 (t, J = 5.9 Hz, 2H; CH_2), 3.8 (t, J = 5.9 Hz, 2H; CH_2), 3.93 (s, 3H; CH_3), 6.25 (s, 1H; C*H*), 6.43 (dd, J_1= 3.4 Hz, J_2= 1.8 Hz, 1H; C*H*), 6.47 (dd, J_1= 3.4 Hz, J_2= 0.8 Hz, 1H; C*H*), 7.43 (dd, J_1= 1.8 Hz, J_2= 0.8 Hz, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 31.4, 38.8, 62.3, 104.4, 108.8, 111.8, 135.1, 143.0, 145.2, 149.9 ppm. HRMS: calcd for $C_{10}H_{12}N_2O_2$ (M^+) 192.0899; found 192.0891.

Step 2: Fluorination of 5-(2-Furyl)-3-(2-hydroxyethyl)-1-methylpyrazole (See Above: "Fluorination of 9 with Deoxofluor" for the Experimental Procedure). Flash chromatography [*n*-hexane-EtOAc (7:1)] (R_f = 0.30) afforded **16** as a yellow oil (81% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (dt, J_1^{HF}= 23.7 Hz, J_2= 6.5, 2H; CH_2), 3.91 (s, 3H; CH_3), 4.61 (dt, J_1^{HF}= 50.4 Hz, J_2= 6.5, 2H; CH_2), 6.29 (s, 1H; C*H*), 6.41 (dd, J_1= 3.4 Hz, J_2= 1.8 Hz, 1H; C*H*), 6.45 (dd, J_1= 3.4 Hz, J_2= 0.6 Hz, 1H; C*H*), 7.41 (dd, J_1= 1.8 Hz, J_2= 0.6 Hz, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 29.9 (d, $^2J_{CF}$= 21.3 Hz), 38.7, 83.4 (d, $^1J_{CF}$= 167.9 Hz), 104.7, 108.9, 111.8, 135.4, 143.0, 145.1, 147.7 (d, $^3J_{CF}$= 7.0 Hz) ppm. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −216.7 (tt, J_1^{FH} = 50.4 Hz, J_2^{FH}= 23.7 Hz, 1F; C*F*) ppm. HRMS: calcd for $C_{10}H_{11}FN_2O$ (M^+) 194.0855; found 194.0857.

General Procedure for Oxidation of the Furane Ring to the Carboxylic Acid. $RuCl_3$·3H_2O (0.55 mol) was added to a solution of the 5-(2-furyl)pyrazole derivative **10**, **12**, **13**, **15**, or **16** (0.011 mol) and $NaIO_4$ (0.110 mol) in CCl_4 (70 mL), CH_3CN (70 mL), and H_2O (105 mL). The mixture was then stirred at room temperature and monitored with the aid of TLC. The starting material disappeared within 5 min, after which the reaction mixture was filtered and the organic phase of the filtrate was separated. The aqueous phase was acidified with HCl 1 M until pH = 3 and extracted with EtOAc (3 × 20 mL). The organic layers were collected, washed with brine, dried over anh Na_2SO_4, and filtered. The solvent was concentrated to give a solid, which could be purified either by means of column chromatography over silica gel with HOAc (2%) or through crystallization.

3-(1,2,2,2-Tetrafluoroethyl)-1-methyl-1H-pyrazole-5-carboxylic acid (18). Pale-yellow solid crystallized from *n*-hexane/ethyl acetate (93% yield); mp 150−2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.06 (s, 3H; CH_3), 6.01 (qd, J_1^{HF}= 42.0 Hz, J_2^{HF} = 6.2 Hz, 1H; C*H*), 7.00 (s, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 40.4, 84.9 (qd, $^1J_{CF}$= 179,9 Hz, $^2J_{CF}$= 35.6 Hz), 111.5 (q, $^3J_{CF}$= 1.8 Hz), 123.5 (dq, $^1J_{CF}$= 150.0 Hz, $^2J_{CF}$= 29.3 Hz), 135.6, 141.7 (d, $^2J_{CF}$= 21.8 Hz), 160.5 ppm. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −190.8 (qd, J_1^{FH} = 42.0 Hz, J_2^{FF}= 13.8 Hz, 1F; C*F*), −79.5 (dd, J_1^{FF} = 13.8 Hz, J_2^{FH}= 6.2 Hz, 3F; CF_3) ppm. HRMS: calcd for $C_7H_6F_4N_2O_2$ (M^+) 226.0365; found 226.0362.

General Procedure for Pyrazole Ring Chlorination. The pyrazole derivative **17**−**21** (18 mmol) was dissolved in HOAc (45 mL) and the resulting solution was cooled to 10−12 °C. An aq solution of NaOCl 13% (45 mmol) was then slowly added and the mixture was stirred at room temperature for 16 h, after which HOAc

was removed *in vacuo*. The residue was hydrolyzed with HCl 1 M (15 mL), extracted with EtOAc (3 × 20 mL), washed with brine, and dried over anh Na_2SO_4. The solvent was removed to afford a solid, which was purified either by means of column chromatography over silica gel with HOAc (2%) or through crystallization.

4-Chloro-3-(1,2,2,2-tetrafluoroethyl)-1-methyl-1H-pyrazole-5-carboxylic acid (22). Pale-yellow solid crystallized from *n*-hexane/ethyl acetate (93% yield); mp 135−7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.21 (s, 3H; CH_3), 6.21 (qd, J_1^{HF}= 43.6 Hz, J_2^{HF} = 6.2 Hz, 1H; C*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 46.6, 87.7 (qd, $^1J_{CF}$= 137.9 Hz, $^2J_{CF}$= 27.5 Hz), 120.3, 128.2 (dq, $^1J_{CF}$= 151.1 Hz, $^2J_{CF}$= 22.5 Hz), 136.2, 142.9 (d, $^2J_{CF}$= 16.5 Hz), 163.6 ppm. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −196.5 (qd, J_1^{FH} = 43.6 Hz, J_2^{FF}= 13.8 Hz, 1F; C*F*), −77.9 (dd, J_1^{FF} = 13.8 Hz, J_2^{FH}= 6.2 Hz, 3F; CF_3) ppm. HRMS: calcd for $C_7H_5ClF_4N_2O_2$ (M^+) 259.9976; found 259.9964.

General Procedure for the Preparation of Carboxamides. A 2 M solution of oxalyl dichloride (3.96 mmol) in THF was added dropwise to a solution of the carboxylic acid (3.6 mmol) and DMF (0.18 mmol) in CH_2Cl_2 (30 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 30 min, after which Et_3N (9 mmol), 4-*tert*-butylbencylamine (4.7 mmol), and DMAP were added at 0 °C. The resulting mixture was stirred at room temperature until the carboxylic acid was no longer detectable through TLC (approximately 18 h) and then hydrolyzed with a saturated aq. solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The aqueous phase was acidified with 3N H_2SO_4 and extracted again with CH_2Cl_2 (2 × 10 mL). The organic layers were collected, dried over anh Na_2SO_4, and filtered. The solvent was removed *in vacuo* to give the carboxamides, which were purified by means of column chromatography over silica gel.

***N*-(4-tert-Butylbenzyl)-4-chloro-3-(1,2,2,2-tetrafluoroethyl)-1-methyl-1H-pyrazole-5-carboxamide (23).** Flash chromatography [*n*-hexane-EtOAc (6:1)] (R_f = 0.40) afforded **23** as a pink oil (64% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 9H; (CH_3)$_3$), 4.17 (s, 3H; CH_3), 4.56 (d, J = 5.7 Hz, 2H; CH_2), 5.69 (qd, J_1^{HF}= 43.7 Hz, J_2^{HF} = 6.0 Hz, 1H; C*H*), 6.88 (br, 1H; N*H*), 7.22 (d, J = 8.3 Hz, 2H; Ar-*H*), 7.34 (d, J = 8.3 Hz, 2H; Ar-*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 31.7, 34.9, 42.1, 43.8, 82.8 (qd, $^1J_{CF}$ = 187.4 Hz, $^2J_{CF}$= 37.4 Hz), 110.3, 122.1 (dq, $^1J_{CF}$= 282.3 Hz, $^2J_{CF}$ = 29.3 Hz), 126.3, 127.8, 133.1, 134.3, 137.8 (d, $^2J_{CF}$ = 23.0 Hz), 151.4, 157.9 ppm. ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ −197.2 (qd, J_1^{FH} = 43.7 Hz, J_2^{FF} = 14.3 Hz, 1F; C*F*), −77.5 (dd, J_1^{FF} = 14.3 Hz, J_2^{FH} = 6.0 Hz, 3F; CF_3) ppm. HRMS: calcd for $C_{18}H_{20}ClF_4N_3O$ (M^+) 405.1231; found 405.1238.

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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