Organic Process Research & Development

Article

pubs.acs.org/OPRD

Synthesis of Fluorinated and Nonfluorinated Tebufenpyrad Analogues for the Study of Anti-angiogenesis MOA

Raquel Román,[†,§] Antonio Navarro,[∥,§] Dariusz Wodka,[∥] Maria Alvim-Gaston,[∥,⊥] Saba Husain,[∥] Natalie Franklin,[⊥] Antonio Simón-Fuentes,[†] and Santos Fustero*[,†,‡]

[†]Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain

[‡]Laboratorio de Moléculas Orgánicas, Centro de Investigación Príncipe Felipe, E-46012 Valencia, Spain

[∥]Discovery Chemistry Research and Technologies, [⊥]Open Innovation Drug Discovery, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285, United States

Supporting Information

ABSTRACT: In this contribution we report the synthesis of fluorinated and nonfluorinated tebufenpyrad analogues to explore potential druglike properties through the phenotypic screening as part of the Lilly Open Innovation Drug Discovery (OIDD) program.

INTRODUCTION

Pyrazoles are well-known and important nitrogen-containing five-membered heterocyclic compounds, found in a number of small molecules[1] that possess a wide range of agricultural and pharmaceutical activities; some representative examples are the acaricide tebufenpyrad,[2] the selective COX-2 inhibitor celecoxib,[3] the phosphodiesterase inhibitor sildenafil,[4] the anorectic anti-obesity rimonabant,[5] and the inhibitor of the blood coagulation Factor Xa razaxaban (Figure 1).[6] In previous

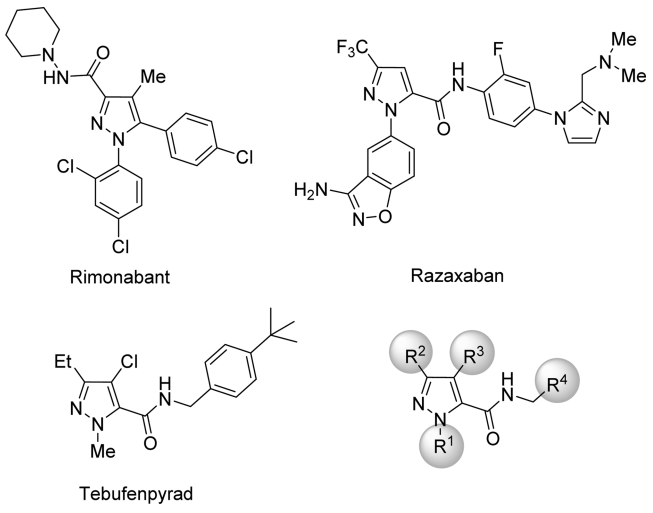


Figure 1. Pyrazoles structurally related to the commercial acaricide tebufenpyrad.

papers we reported the synthesis of a series of fluorinated pyrazoles structurally related to the commercial acaricide tebufenpyrad (Figure 1), some of them displaying important acaricidal activities.[7] Tebufenpyrad and razaxaban are pyrazole 5-carboxamide derivatives, whereas the carboxamide group is at C3 in rimonabant. Moreover, 3-trifluoromethyl-1-methylpyrazole-5-carboxamides are known as non-nucleoside inhibitors of the measles virus RNA-dependent RNA polymerase complex,[8] and razaxaban bears a trifluoromethyl moiety at the C3 position of the pyrazole ring. With these precedents in mind, we decided to explore the potential druglike properties of our tebufenpyrad analogues.

Through the Eli Lilly Open Innovation Drug Discovery Program (OIDD), we submitted these analogues to be evaluated for novelty, druglike characteristics and to access proprietary, disease-relevant phenotypic assays (https://openinnovation.lilly.com/dd/). Biological data from the OIDD anti-angiogenesis effort, suggested that our analogues could be active in the cord formation assay via mitochondrial inhibition mechanisms. Mitochondrial dysfunction is a common mechanism of drug-induced toxicity. Early identification of new chemical entities that perturb mitochondrial function is of significant importance to avoid attrition in later stages of drug development. One of the most informative ways of assessing mitochondrial dysfunction is by measuring mitochondrial oxygen consumption. In the pursuit of novel anti-angiogenic molecules with a desired mechanism of action, we designed new compounds, based on an *in silico* model, in the attempt to eliminate the mitochondrial activity of these series.

The structural study of these compounds allowed us to identify four suggested domains to be modified (Figure 1): (i) *N*-substituent pyrazole center core ($\mathbf{R^1}$); (ii) substituent at C3 ($\mathbf{R^2}$); (iii) substituent at C4 ($\mathbf{R^3}$), and (iv) amide backbone ($\mathbf{R^4}$).

In this sense, we designed a number of fluorinated and fluorine-free pyrazole derivatives, which were synthesized and profiled in the OIDD Phenotypic modules available at the time of the collaboration (Figure 2).[9−12]

Special Issue: Fluorine Chemistry 14

Received: April 7, 2014

dx.doi.org/10.1021/op500114v | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

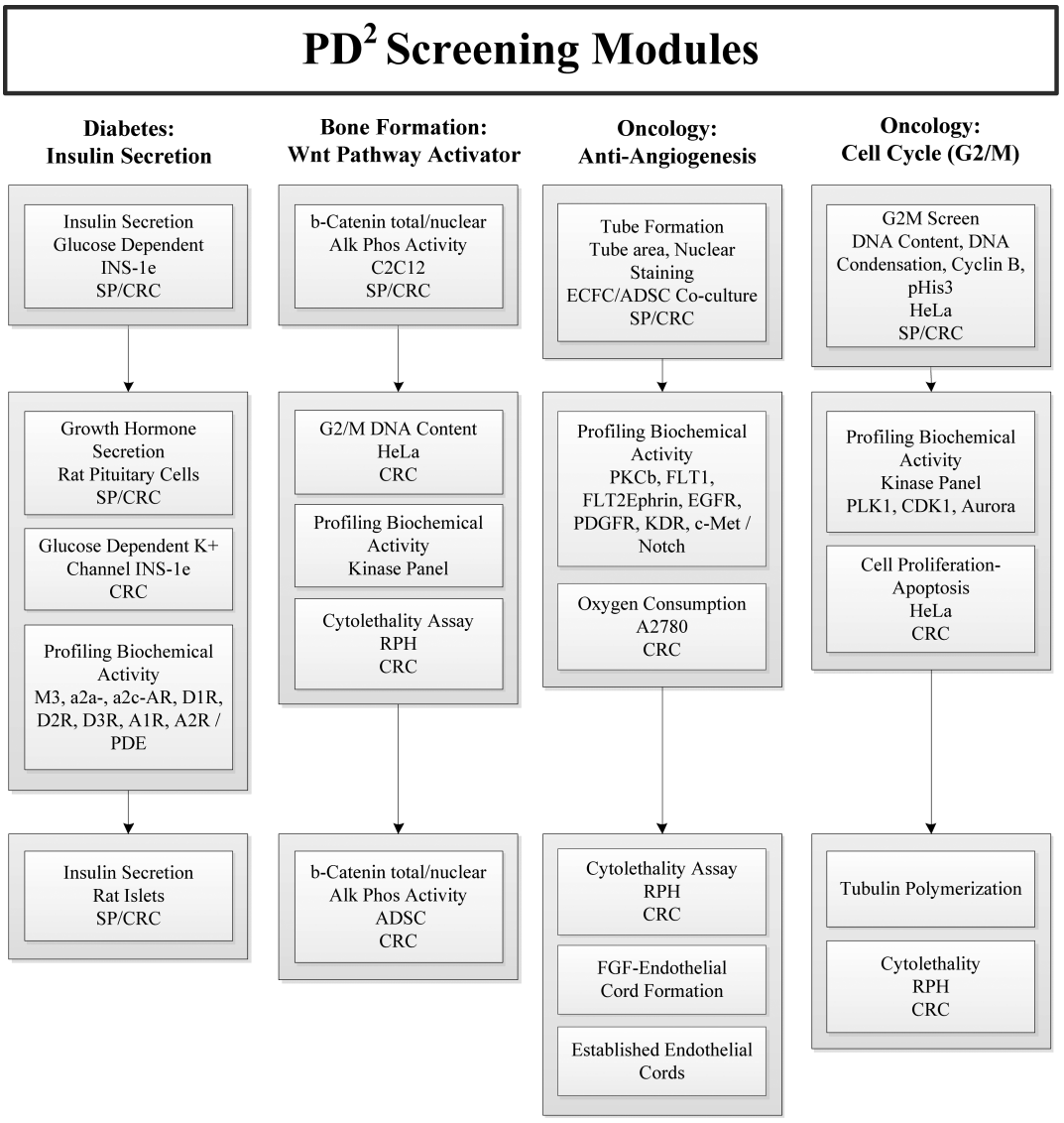


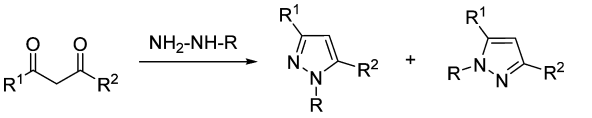
Figure 2. Phenotypic module flow scheme.

RESULTS AND DISCUSSION

1. Synthesis of 1,3,5-Substituted Pyrazole Precursors. The pyrazole ring was obtained by condensation of commercially or easily synthesized 1,3-diketones with the corresponding monosubstituted hydrazines in the reaction conditions previously described in the literature.[1,7,13,14] The reaction afforded mixtures of regioisomers in all cases, which were properly separated by column chromatography (Table 1). The ethoxycarbonyl group was used as a precursor of a variety of fluorinated substituents at C3 in the pyrazole; however, because of the carboxamide function at C5, two precursors were employed, namely 2-furyl for the 3-fluorinated derivatives and ethoxycarbonyl for the fluorine-free compounds.

2. Synthesis of 3-Fluoralkyl *N*-Methylpyrazole Derivatives. *2.1. Tebufenpyrad Analogues.* Tapping on our research group experience in the synthesis of fluorinated analogues of tebufenpyrad,[7] we scaled up the synthesis of the key intermediate aldehyde **8** to be able to make final compounds with a variety of fluorinated substitutions (Scheme 1).

Table 1. Synthesis of 1,3,5-substituted pyrazole precursors



1 2 3

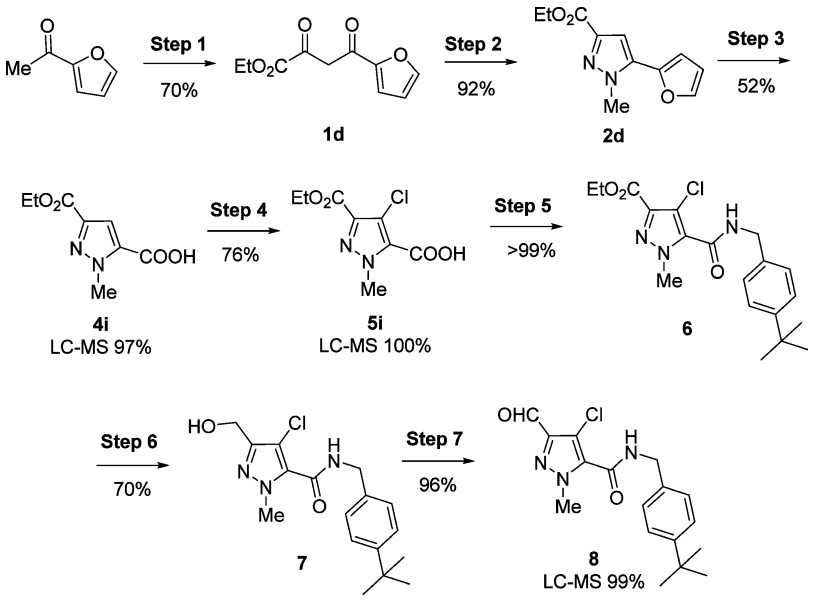
reagent	R	R^1	R^2	product	2:3[a]
1a	CH_3	CF_3	2-furyl	**2a,3a**	97:3 (98)
1b	CH_3	CF_2CH_3	2-furyl	**2b,3b**	98:2 (99)
1c	CH_3	CF_2CF_3	2-furyl	**2c,3c**	99:1 (98)
1d	CH_3	CO_2Et	2-furyl	**2d,3d**	93:7 (98)
1e	CH_3	CH_2CH_3	CO_2Et	**2e,3e**	70:30 (65)
1f	CH_3	cyclopropyl	CO_2Et	**2f,3f**	95:5 (87)
1g	CH_3	3-pyridyl	CO_2Et	**2g,3g**	70:30 (83)
1h	3-Pyridyl	CH_2CH_3	CO_2Et	**2h,3h**	92:8 (49)

[a]In parentheses, overall yield.

The synthesis started with a Knoevenagel condensation from commercially available 1-(2-furyl) ethanone (130 g) and diethyl oxalate to give diketone **1d** with 70% yield and 99% purity after

dx.doi.org/10.1021/op500114v | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

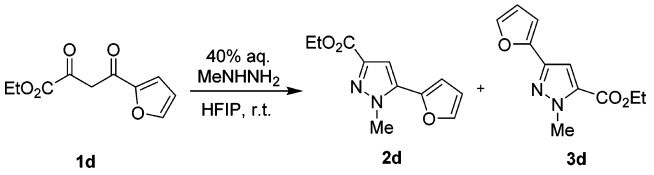
Scheme 1. Synthesis of the key aldehyde intermediate 8[a]



[a]Reaction conditions: **Step 1**: $(CO_2Et)_2$, *t*-BuOK, THF, DME, 3h; **Step 2**: CH_3NHNH_2, TFE, 1 h; **Step 3**: $NaIO_4/RuCl_3{\cdot}3H_2O$/EtOAc/$H_2O$, 2 h; **Step 4**: NaOCl, HOAc, addition 10−12 °C; **Step 5**: a) $(COCl)_2$, DMF, AcCN, b) Et_3N, DMAP, 4-*tert*-butylbenzylamine; **Step 6**: $LiBH_4$, THF, 65 °C, 2 h; **Step 7**: $(ClCO)_2$, DMSO, CH_2Cl_2, 1 h, −60 to 0 °C.

triturating the crude mixture with petroleum ether and ethyl acetate (3:1). The formation of the pyrazole took place with very high regioselectivity (96:4) and yield (92%), producing 167 g of the desired regioisomer. As the scale increased, there was no change in the regiochemical outcome of the reaction or the yield, as shown in Table 2.

Table 2. Effect of the scale in the regiochemistry of pyrazole formation



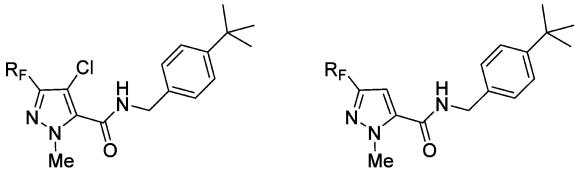
entry	**1d** (g)	ratio (IPC)[a] **2d**/**3d**	yield (%)
1	0.5	95/5	−[b]
2	36.6	94/6	90[c]
3	195.0	96/4	90[c]

[a]IPC: In Process Control (LC−MS). [b]Not isolated. [c]Isolated yield.

The catalytic oxidation of the furan moiety was carried out in cold temperatures by addition of small portions of sodium periodate to control the exothermic reaction.[15] Trituration of the crude mixture with petroleum ether and ethyl acetate (3:1) gave 78 g of pyrazole acid **4i** in 52% yield.

Chlorination of the pyrazole using a mixture of sodium hypochlorite and acetic acid furnished pure compound **5i** with 76% yield after titration with MTBE. The excess of hazardous chlorinating agent was reduced with an aqueous solution of sodium pyrosulfite prior to workup. The amide was made by activating the acid with thionyl chloride.[16] The acid chloride was not isolated, and it was treated with 1.1 equiv of 4-*tert*-butylphenylmethanamine to give the corresponding amide with quantitative yield, which was pure enough to use in the next step. Finally, the reduction to the aldehyde was carried out in two steps. First, the ethyl ester was reduced to alcohol using lithium borohydride and then was oxidized to the aldehyde through a Swern oxidation with a 68% yield for both steps. A total of 26 g of aldehyde intermediate **8** were produced in seven steps with 18% overall yield (Scheme 1).

With this intermediate in hand, with or without chlorine atom, we carried out the preparation of compounds **9** and **10** (Figure 3), already described previously, using the methodology studied in our group.[7] For the synthesis of **10b** and **10c** see Supporting Information (SI).



R_F = CF_3 (**a**), CH_2CH_2F (**b**), CH_2CHF_2 (**c**), CH_2CF_3 (**d**), $CHFCH_3$ (**e**), $CHFCF_3$ (**f**), CF_2CH_3 (**g**), CF_2CF_3 (**h**)

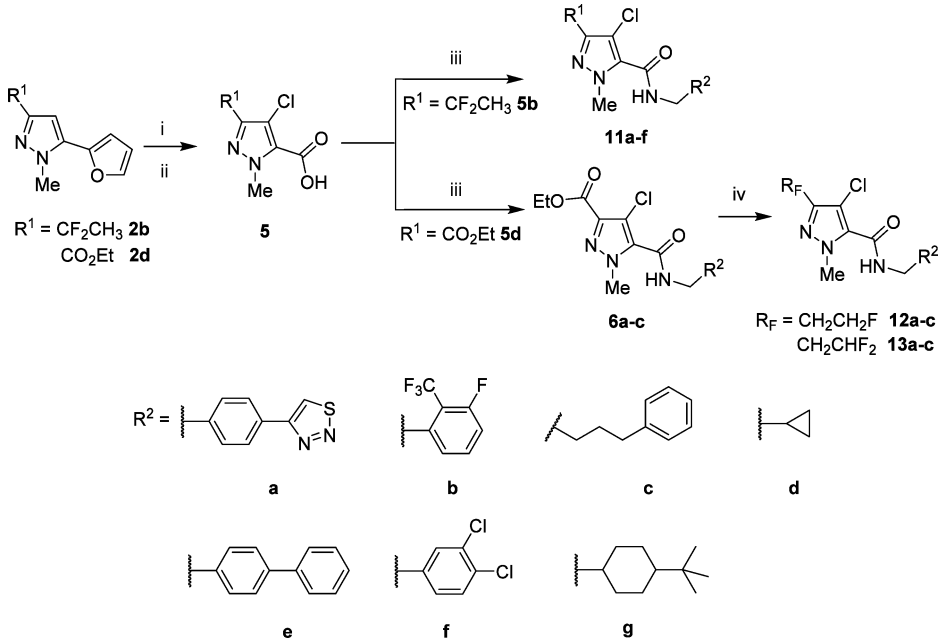
R_F = $CHFCH_3$ (**a**) $CH(OH)CHF_2$ (**b**) $CHFCHF_2$ (**c**)

Figure 3. Fluorinated compounds prepared from the intermediate scaling aldehyde.

2.2. Introducing Variability at the Carboxamide Group. In order to fully explore the effect of substituent R^2 (Scheme 2) in the inhibition of cord formation in endothelial cells and move away from mitochondrial inhibition activity, we used recursive partitioning, a statistical method for multivariable analysis to guide in the design of a variety of pyrazoles by keeping all the substituents fixed except the substituent of the amide backbone, for both series 4-chloro and 4-des-chloro. This model considered HOMO/LUMO orbitals of the target molecules

dx.doi.org/10.1021/op500114v | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 2. Synthesis of the 4-chloro pyrazole amide derivatives 11−13[a]



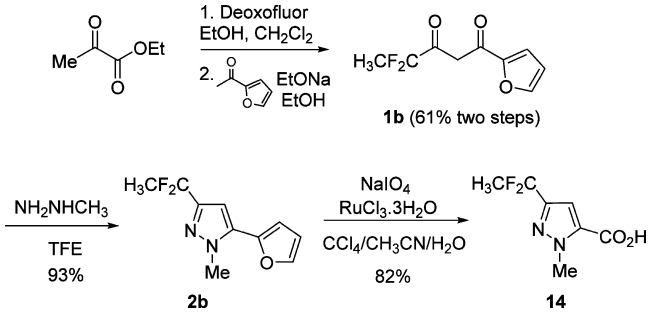
[a]Reaction conditions: (i) $NaIO_4$ (10 equiv), $RuCl_3{\cdot}3H_2O$ (5%), $CH_3CN/CCl_4/H_2O$; rt (ii) NaOCl (13%), AcOH; −12 °C to rt. (iii) a) $(ClCO)_2$, Et_3N, DMAP, CH_2Cl_2, DMF, rt. b) $R_3CH_2NH_2$, rt. (iv) a) $LiBH_4$, THF, reflux. b) MnO_2, CH_3CN, reflux. c) $CH_3OCH_2PPh_3$, NaHMDS, THF, rt. d) HCl 12 N, THF, rt. e) Deoxofluor, EtOH, CH_2Cl_2, rt for $R^1 = CH_2CHF_2$, or f) $NaBH_4$, MeOH, rt, followed by g) Deoxofluor, CH_2Cl_2, rt for $R^1 = CH_2CH_2F$.

as a surrogate to inhibit the mitochondria function,[17] and allowed us to select the substituents on the basis of the predicted lack of mitochondrial disruption.

Thus, a variety of 4-chloro-*N*-methyl derivatives **11−13** (Scheme 2) bearing aliphatic and aromatic residues was selected and prepared using two alternative pathways: one consisted of the formation of the amide bond before elaboration of the fluorinated chain (**12** and **13**, Scheme 2), and the other used a more advanced intermediate with the fluorinated chain fully installed, leaving the formation of the amide for the last step (**11**, Scheme 2).

Following the synthetic sequence shown in Scheme 3, we prepared 12 g of a key advanced intermediate of the fluorinated

Scheme 3. Large-scale synthesis of intermediate 14



pyrazole derivative **14**,[7] which allowed us to access a variety of target compounds by formation of the amide back-bond through rapid parallel synthesis (RPS).

Simple amides **15** were prepared using HATU protocol (Scheme 4), which has been modified to allow rapid synthesis and purification of the products via reverse phase (RP) chromatography without isolating crude materials (Route A). Two variants of this route have been developed using the same stoichiometry of reagents: small excess of HATU (1.25 equiv) and amine (1.25 equiv), and a base/solvent choice (DIEA/NMP), that provided a medium compatible with the purification step. *Method 1* consisted of microwave irradiation at 90 °C for 10 min, with 20 min preirradiation delay, to allow active ester formation. In our hands, this preheating delay resulted in better conversions and cleaner reactions. Upon completion of the heating step, the reaction mixture was diluted with methanol to quench the reactive intermediates and to make the solution less viscous for liquid handling and injections to RP purification system. In *Method 2*, the reaction mixtures were agitated at room temperature for 12 h, and the post-reaction treatment of the samples was the same as described for *Method 1*.

For diamines, mono-Boc protected reagents were utilized, and syntheses of the desired analogues were conducted as a sequence of two steps (Route B): first, amide coupling with Boc protected amine using either *Method 1* or *Method 2* described above, following deprotection by treatment with hydrochloric acid. Two distinct protocols have been used for this route: *Method 3* (two-step), in which the Boc protected intermediate **16** (see, *e.g.* **16b** in Scheme 4) was isolated by RP prior to deprotection; and *Method 4* (*one-pot*), which consisted of the coupling step and *in situ* deprotection. Both protocols (*Method 3* and *Method 4*) utilized RP purification of the final product. Reaction conditions and yields of isolated products for attempted reactions are shown in Table 3.

3. Synthesis of Fluorine-Free *N*-Substituted Pyrazoles with R^3 = 4-*t*-BuC_6H_4. In order to explore the effect of the substituent at the C3 position, we prepared pyrazole precursors **2f** and **2g** (Table 1). As previously described,[7] these compounds can be chlorinated at C4 using *N*-chlorosuccinimide (NCS) under two different conditions: (1) by microwave

dx.doi.org/10.1021/op500114v | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 4. RPS of amide derivatives 15

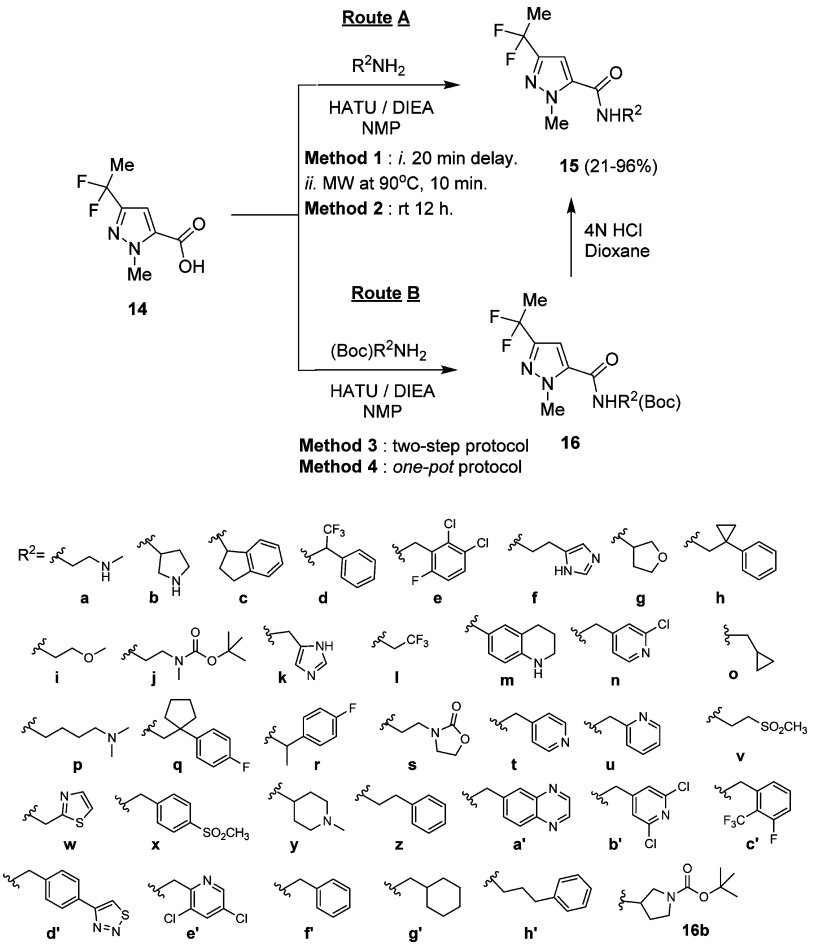


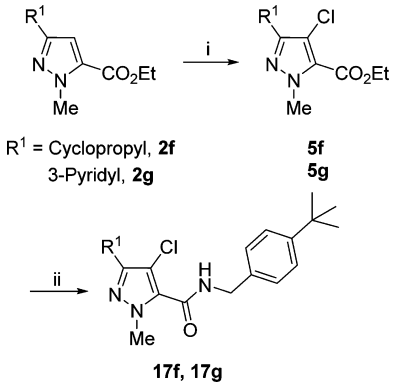
Table 3. Reaction conditions and yields of isolated products 15

cmpd	route	method	yield (%)	cmpd	route	method	yield (%)
15a	B	4	33	**15s**	A	2	66
15b[a]	B	3	77	**15t**	A	2	65
15c[a]	A	2	21[b]	**15u**	A	2	53
15d[a]	A	2	80	**15v**	A	2	31[b]
15e	A	2	83	**15w**	A	2	55
15f	A	2	41	**15x**	A	2	62
15g[a]	A	2	80	**15y**	A	1	96
15h	A	1	80	**15z**	A	1	84
15i	A	1	79	**15a′**	A	2	29[c]
15j	A	1	79	**15b′**	A	2	70
15k	A	2	25[b]	**15c′**	A	2	82
15l	A	2	59	**15d′**	A	2	75
15m	A	2	33	**15e′**	A	2	80
15n	A	2	53	**15f′**	A	2	63
15o	A	1	47	**15g′**	A	1	81
15p	A	1	68	**15h′**	A	1	82
15q	A	2	81	**16b**[a,d]	B	–	81
15r[a]	A	2	73				

[a]Compounds isolated as racemic mixtures. [b]Low yield due to byproducts formation. [c]Low yield due to solubility problems during RP purification. [d]Boc-intermediate was isolated and characterized following route B.

irradiation at 100 °C in $CHCl_3$ (85% yield) or (2) by thermo heating at 15 °C in AcOH (73% yield). The choice of the method will depend on the nature of the starting material (Scheme 5). The hydrolysis of the ethoxycarbonyl group was then carried out at room temperature with a solution of LiOH in THF:H_2O (2:1) with almost quantitative yields (96–98%). The activation of the acid could be done either with oxalyl

Scheme 5. Synthesis of fluorine-free *N*-methyl pyrazoles[a]



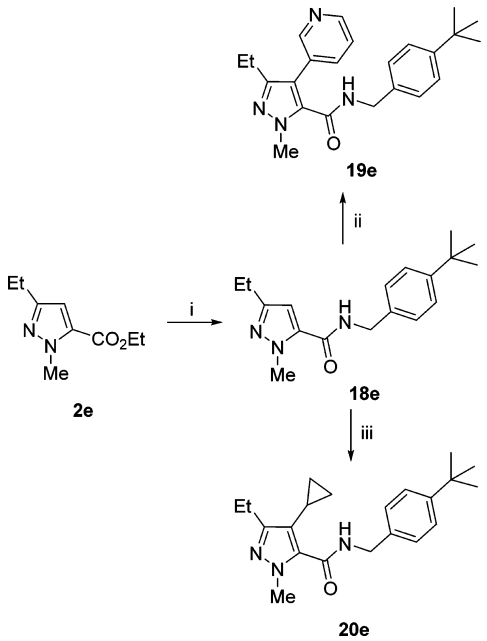
[a]Reaction conditions: (i) R^1 = cyclopropyl: NCS, $CHCl_3$, MW, 100 °C (85%); R^1 = 3-pyridyl: NCS, HOAc, MW, 150 °C (73%). (ii) a) LiOH, THF:H_2O, rt (96–98%); b) R^1 = cyclopropyl: $(COCl)_2$, CH_2Cl_2, rt; R^1 = 3-pyridyl: $SOCl_2$, 80 °C; c) 4-*t*Bu$C_6H_4CH_2NH_2$ (75–80%, two steps).

dx.doi.org/10.1021/op500114v | Org. Process Res. Dev. XXXX, XXX, XXX–XXX

chloride at room temperature or with thionyl chloride at 80 °C. Finally, the addition of 4-*tert*-butylbenzylamine afforded the final products **17** with good yields (Scheme 5).

An analogous treatment of precursor **2h** led to the expected pyrazole derivative with comparable yield (see SI). In addition, two C4 chlorine-free tebufenpyrad analogues were prepared from the pyrazole precursor **2e** (Table 1 and Scheme 6). To achieve this, we followed the two-step sequence of reactions mentioned above, in which intermediate **2e** was first converted into its carboxamide derivative **18e** with excellent yield (96%) followed by the functionalization of the C4 position. Although low yielding (32%), C−H activation of the C4 position in the presence of catalytic amounts of $PdCl(C_3H_5)(dppb)$ allowed us to make and isolate the 4-(3-pyridyl) pyrazole **19e**. As a higher-yielding alternative, treatment of **18e** with *N*-bromosuccinimide, followed by Suzuki coupling with cyclopropyl boronic acid afforded the 4-(3-cyclopropyl) pyrazole derivative **20e** in 88% yield (Scheme 6).

Scheme 6. Synthesis of C-4 chlorine-free *N*-methyl pyrazoles[a]



[a]Reaction conditions: (i) a) $(COCl)_2$, CH_2Cl_2, DMF, rt. b) 4-*t*-$BuC_6H_4CH_2NH_2$ (96%, two steps). (ii) 3-Bromopyridine, $PdCl(C_3H_5)$(dppb), KOAc, DMAC, 150 °C (32%). (iii) a) NBS, HOAc, MW, 150 °C. b) Cyclopropylboronic acid, $Pd(OAc)_2$, PPh_3, Na_2CO_3, toluene:H_2O, MW, 140 °C (88%).

Finally, biological data were obtained for all the compounds in the EDFC/ADSC coculture cord or tube formation assay.[18] Data indicated that small structural modifications of the molecules lead to significant changes in biological activity (Table 4). The substituent on the amide backbone appears to play a key role in the biological activity of the compounds; however, it does not allow for the separation of the two *in vitro* activities, i.e. cord formation inhibition and compound effect on mitochondrial oxygen consumption.

Notably, the most potent compounds in the cord formation inhibition assay (**9b**, **9c**, and **20e**) also exhibit parallel potency in the oxygen consumption assay (Figure 4). The lack of selectivity seen may indicate a probable mechanism of inhibition of blood vessel growth in endothelial cells through mitochondrial impairment. Therefore, even though some of the compounds in the series are very potent anti-angiogenic agents (**9b**, **9c**, and **20e**), we would anticipate drug-induced toxicity in future *in vivo* studies due to mitochondrial dysfunction.

Table 4. Biological activity data of representative compounds[a]

		IC_{50} (μM)	
entry	cmpd	cord formation inhibition	oxygen consumption
1	**9b**	0.10	0.31
2	**9c**	0.10	0.37
3	**9d**	2.36	0.61
4	**9e**	0.48	0.40
5	**9f**	1.10	1.72
6	**9g**	2.37	0.94
7	**10**[b]	3.01	0.16
8	**10b**	0.20	0.50
9	**10c**	0.21	0.66
10	**12**[b]	0.12	–[b]
11	**13**[b]	0.07	–[b]
12	**15c′**	1.98	6.91
13	**15d′**	2.94	6.97
14	**20e**	0.13	0.36

[a]Biological data for additional compounds available in SI. [b]No biological data available.

CONCLUSIONS

In summary, we have prepared a series of biologically active fluorinated analogues of the commercial acaricide tebufenpyrad through large-scale synthesis of the key intermediate aldehyde **8**. With the objective of exploring the structure−activity relationship as anti-angiogenic agents, we have changed the structure of the substituents at the pyrazole ring: *N*-substituent pyrazole center core, substituent at C3, substituent at C4 and amide backbone by rapid parallel synthesis using the key intermediate acid **14**. These structural changes have allowed the synthesis of a large library of fluorinated and fluorine-free pyrazole derivatives.

The SAR analysis illustrated that small structural modifications lead to significant changes in biological activity; specifically the substituent on the amide backbone appears to play a key role. Even though we made very potent compounds, we could not separate the desired anti-angiogenic activity from the undesired mitochondrial inhibition activity. Further applications of the new compounds and biological studies are underway in our laboratory.

EXPERIMENTAL SECTION

All reactions were carried out under nitrogen. The solvents were purified prior to use. The reactions were monitored with the aid of TLC on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light. Flash column chromatography was performed on silica gel 60 (particle size 0.040−0.063 mm) with the solvents indicated in each case. Melting points were measured with a Büchi B-540 apparatus. ^1H and ^{13}C NMR spectra were recorded with 300 MHz Bruker AC300 and 400 MHz Bruker Avance spectrometers. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Coupling constants (J) are given in hertz (Hz). The letters m, s, d, t, and q represent

dx.doi.org/10.1021/op500114v | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

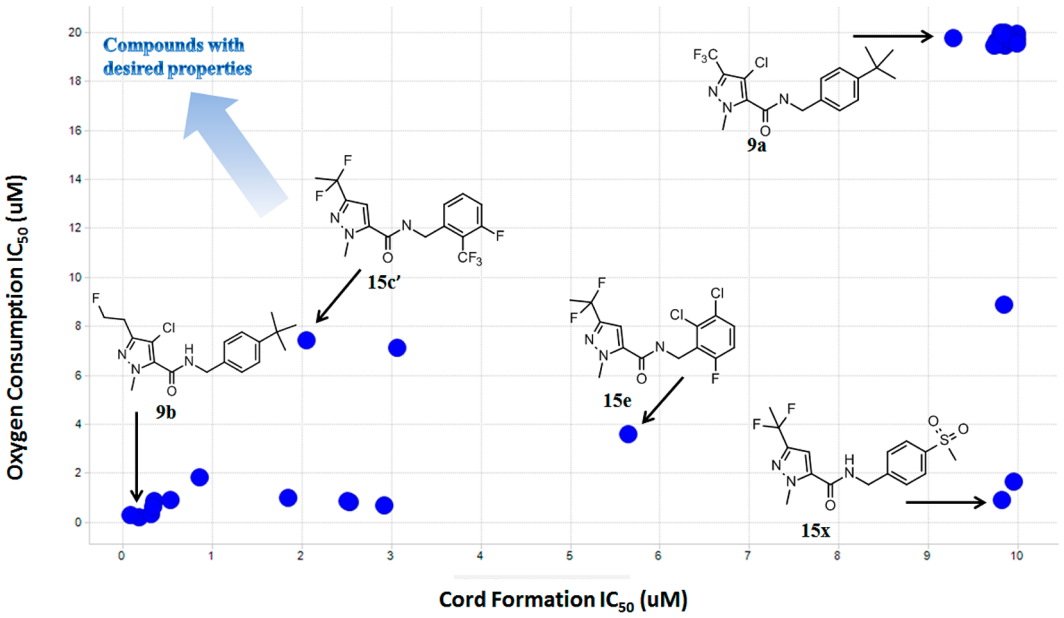


Figure 4. Dual inhibitors. Vessel formation and mitochondrial function inhibitors.

multiplet, singlet, doublet, triplet, and quartet, respectively. The letters br indicate that the signal is broad.

Microwave reactions were carried out in a 0.5−2 mL vial with a Biotage Initiator TM 2.0 microwave synthesizer. The solutions were stirred before the irradiation was started, and the absorbance of the solvent was set as "normal". The reaction time was initiated as soon the system reached the input temperature, although it took approximately 2 min to reach it.

High-resolution mass spectra were recorded with a VGmAutospec (VG Analytical, Micromass Instruments) by the Universitat de València Mass Spectrometry Service.

Ethyl 3-cyclopropyl-1-methyl-1*H*-pyrazole-5-carboxylate (2f). Flash chromatography (*n*-hexane/EtOAc, 5:1) afforded **2f** as a colourless oil (EtOH: 259 mg; 57%, TFE: 3.5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.66−0.72 (m, 2H; C*H*H+C*H*H), 0.88−0.93 (m, 2H; CH*H*+CH*H*), 1.35 (t, J = 7.2 Hz, 3H; CH_3), 1.88−1.94 (m, 1H; C*H*), 4.08 (s, 3H; CH_3), 4.30 (q, J = 7.2 Hz, 2H; CH_2), 6.46 (s, 1H; C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.8, 8.7, 14.2, 39.1, 60.8, 107.0, 132.8, 153.4, 159.8 ppm. HRMS: calc for $C_{10}H_{14}N_2O_2$ (M + 1): 195.1128; found 195.1126.

Ethyl 5-Cyclopropyl-1-methyl-1*H*-pyrazole-3-carboxylate (3f). Flash chromatography (*n*-hexane/EtOAc, 5:1) afforded **3f** as a colourless oil (EtOH: 80 mg; 18%, TFE: 160 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.64−0.69 (m, 2H; C*H*H+C*H*H), 0.96−1.02 (m, 2H; CH*H*+CH*H*), 1.35 (t, J = 7.0 Hz, 3H; CH_3), 1.65−1.74 (m, 1H; C*H*), 3.95 (s, 3H; CH_3), 4.35 (q, J = 7.0 Hz, 2H; CH_2), 6.36 (s, 1H; C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 5.9, 6.8, 14.3, 36.9, 60.6, 105.5, 141.9, 146.6, 162.5 ppm. HRMS: calc for $C_{10}H_{14}N_2O_2$ (M + 1): 195.1128; found 195.1125.

Ethyl 1-Methyl-3-(3-pyridinyl)-1*H*-pyrazole-5-carboxylate (2g). Flash chromatography (*n*-hexane/EtOAc, 2:1) afforded **2g** as a pale-yellow solid (24 mg; 25%); mp 73−75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, J = 7.5 Hz, 3H; CH_3), 4.22 (s, 3H; CH_3), 4.36 (q, J = 7.5 Hz, 2H; CH_2), 7.15 (s, 1H; C*H*), 7.29−7.34 (m, 1H; C*H*), 8.06−8.09 (m, 1H; C*H*), 8.54 (dd, ^1J = 4.8 Hz, ^2J = 1.5 Hz, 1H; C*H*), 9.00 (d, J = 1.5 Hz, 1H; C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.2, 39.7, 61.2, 107.9, 123.5, 128.4, 132.6, 134.0, 146.7, 146.9, 148.9, 159.6 ppm. HRMS: calc for $C_{12}H_{13}N_3O_2$ (M^+): 231.1008; found 231.1000.

Ethyl 1-Methyl-5-(3-pyridinyl)-1*H*-pyrazole-3-carboxylate (3g). Flash chromatography (*n*-hexane/EtOAc, 2:1) afforded **3g** as a pale-yellow oil (55 mg; 58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, J = 7.0 Hz, 3H; CH_3), 3.95 (s, 3H; CH_3), 4.40 (q, J = 7.0 Hz, 2H; CH_2), 6.89 (s, 1H; C*H*), 7.38−7.43 (m, 1H; C*H*), 7.71−7.75 (m, 1H; C*H*), 8.66−8.69 (m, 2H; C*H*+C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.3, 38.3, 61.0, 109.4, 123.5, 125.7, 135.9, 141.5, 142.9, 149.2, 150.0, 161.9 ppm. HRMS: calc for $C_{12}H_{13}N_3O_2$ (M^+): 231.1008; found 231.1009.

Ethyl 3-Ethyl-1-(3-pyridinyl)-1*H*-pyrazole-5-carboxylate (2h). Flash chromatography (*n*-hexane/EtOAc, 3:1) afforded **2h** as a pale-yellow solid (31 mg; 30% two steps); mp 48−50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J = 6.9 Hz, 3H; CH_3), 1.30 (t, J = 7.5 Hz, 3H; CH_3), 2.73 (q, J = 7.5 Hz, 2H; CH_2), 4.24 (q, J = 7.2 Hz, 2H; CH_2), 6.89 (s, 1H; C*H*), 7.36−7.41 (m, 1H; C*H*), 7.76−7.80 (m, 1H; C*H*), 8.63, (dd, ^1J = 4.8 Hz, ^2J = 1.5 Hz, 1H; C*H*), 8.68 (d, J = 2.4 Hz, 1H, C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.5, 13.9, 21.3, 61.2, 111.5, 122.9, 133.2, 134.1, 137.0, 147.0, 149.1, 155.8, 159.0 ppm. HRMS: calc for $C_{13}H_{15}N_3O_2$ (M + 1): 246.1237; found 246.1233.

Ethyl 5-Ethyl-1-(3-pyridinyl)-1*H*-pyrazole-3-carboxylate (3h). Flash chromatography (*n*-hexane/EtOAc, 2:1) afforded **3h** as a pale-yellow solid (67 mg; 45%); mp 45−47 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, J = 7.5 Hz, 3H; CH_3), 1.35 (t, J = 6.9 Hz, 3H; CH_3), 2.62 (q, J = 7.5 Hz, 2H; CH_2), 4.36 (q, J = 6.9 Hz, 2H; CH_2), 6.75 (s, 1H; C*H*), 7.38−7.42 (m, 1H; C*H*), 7.76−7.81 (m, 1H; C*H*), 8.63, (dd, ^1J = 4.8 Hz, ^2J = 1.2 Hz, 1H; C*H*), 8.69 (d, J = 1.8 Hz, 1H, C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.7, 14.2, 19.5, 60.9, 107.7, 123.6, 133.0, 134.1, 135.8, 144.8, 146.3, 147.2, 149.6, 162.2 ppm. HRMS: calc for $C_{13}H_{15}N_3O_2$ (M + 1): 246.1237; found 246.1232.

***N*-[4-(1,2,3-Thiadiazol-4-yl)benzyl]-4-chloro-3-(1,1-difluoroethyl)-1-methyl-1*H*-pyrazole-5-carboxamide**

dx.doi.org/10.1021/op500114v | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

(11a). Flash chromatography (*n*-hexane/EtOAc, 2:1) afforded **11a** as a white solid (40 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.03 (t, J_{HF} = 17.7 Hz, 3H; CH_3), 4.19 (s, 3H, CH_3), 4.71 (d, J = 5.6 Hz, 2H; CH_2), 7.15 (t, J = 5.6 Hz, 1H; NH), 7.49 (d, J = 8.4 Hz, 2H; 2CH), 8.05 (d, J = 8.4 Hz, 2CH), 8.65 (s, 1H; SCH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.3 (t, $^2J_{CF}$ = 26.6 Hz), 41.4, 43.3, 107.2, 118.6 (t, $^1J_{CF}$ = 234.3 Hz), 127.9, 128.3, 130.1, 130.3, 132.7, 138.5, 143.3, 157.9, 162.3 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −87.4 (q, J = 17.7 Hz, 2F; CF_2) ppm. HRMS: calc for $C_{16}H_{14}ClF_2N_5OS$ (M + 1): 420.0468; found 420.0470.

4-Chloro-3-(1,1-difluoroethyl)-*N*-(3-fluoro-2-trifluoromethylbenzyl)-1-methyl-1*H*-pyrazole-5-carboxamide (11b). Flash chromatography (*n*-hexane/EtOAc, 5:1) afforded **11b** as a white solid (106 mg, 85%); mp: 100−102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02 (t, J = 18.6 Hz, 3H; CH_3), 4.16 (s, 3H; CH_3), 4.80−4.82 (m, 2H; CH_2), 7.13−7.19 (m, 1H; CH), 7.26 (br, 1H; NH), 7.40 (d, J= 7.8 Hz, 1H; CH), 7.53 (m, 1H; CH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.3 (t, $^2J_{CF}$ = 26.6 Hz), 41.0 (q, $^5J_{CF}$ = 3.4 Hz), 107.4, 116.9 (d, $^2J_{CF}$ = 22.8), 118.6 (t, $^1J_{CF}$ = 234.5 Hz), 111.6−125.4 (CF_3), 126.5 (d, $^1J_{CF}$ = 3.4 Hz), 132.3, 133.6 (d, $^4J_{CF}$ = 9.8 Hz), 137.7, 143.4 (t, $^2J_{CF}$ = 32.7), 157.9, 160.5 (d, $^1J_{CF}$ = 258.1) ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −111.8 (qdd, $^1J_{FF}$ = 26.1 Hz, $^2J_{FH}$ = 11.0 Hz, $^3J_{HF}$ = 5.1 Hz, 1F; CF), −87.5 (q, J_{FH} = 18.6 Hz, 2F; CF_2), −55.0 (d, J_{FF} = 26.1 Hz, 3F; CF_3) ppm. HRMS: calc for $C_{15}H_{12}ClF_6N_3O$ (M + 1): 400.0646; found 400.0650.

***N*-[4-(1,2,3-Thiadiazol-4-yl)benzyl]-4-chloro-3-(2-fluoroethyl)-1-methyl-1*H*-pyrazole-5-carboxamide (12a).** Flash chromatography (*n*-hexane/EtOAc, 2:1) afforded **12a** as a white solid (80.3 mg, 70% two steps); mp: 165−167 °C. ^{1}H NMR (300 MHz, CD_3COCD_3): δ 2.99 (dt, $^1J_{HF}$ = 22.5 Hz, ^2J = 6.6 HZ, 2H; CH_2), 4.02 (s, 3H; CH_3), 4.69 (dt, $^1J_{HF}$ = 47.1 Hz, ^2J = 6.6 Hz, 2H; CH_2F), 4.73 (d, J = 6.3 Hz, 2H; CH_2), 7.60 (d, J = 8.4 Hz, 2H; 2CH), 8.07 (br, 1H; NH), 8.15 (d, J = 8.4 Hz, 2H; 2CH), 9.35 (s, 1H; SCH) ppm; ^{13}C NMR (75.5 MHz, CD_3COCD_3): δ 26.8 (d, $^2J_{CF}$ = 13.3 Hz), 39.2, 42.6, 81.5 (d, $^1J_{CF}$ = 100.6 Hz), 107.9, 127.4, 128.3, 130.1, 131.4, 133.1, 140.2, 143.5 (d, $^3J_{CF}$ = 4.4 Hz), 158.4, 162.3 ppm; ^{19}F NMR (282.4 MHz, CD_3COCD_3): δ −218.3 (tt, $^1J_{FH}$ = 47.1 Hz, $^2J_{FH}$ = 22.4 Hz, 1F; CH_2F) ppm. HRMS: calc for $C_{16}H_{15}ClFN_5OS$ (M + 1): 380.0743; found 380.0732.

***N*-[4-(1,2,3-Thiadiazol-4-yl)benzyl]-4-chloro-3-(2,2-difluoroethyl)-1-methyl-1*H*-pyrazole-5-carboxamide (13a).** Flash chromatography (*n*-hexane/EtOAc, 1:1) afforded **13a** as a white solid (82.9 mg, 73% two steps); mp: 178−180 °C. ^{1}H NMR (300 MHz, CD_3COCD_3): δ 3.20 (td, $^1J_{HF}$ = 16.8 Hz, ^2J = 4.5 Hz, 2H; CH_2), 4.04 (s, 3H; CH_3), 4.73 (d, J = 6.0 Hz, 2H; CH_2), 6.21 (tt, $^1J_{HF}$ = 56.4 Hz, ^2J = 4.7 Hz, 1H; CHF_2), 7.60 (d, J = 8.7 Hz, 2H; 2CH), 8.15 (d, J = 8.7 Hz, 2H; 2CH), 8.15 (br, 1H; NH), 9.35 (s, 1H; SCH) ppm; ^{13}C NMR (75.5 MHz, CD_3COCD_3): δ 30.0 (t, $^2J_{CF}$ = 14.1 Hz), 39.3, 42.6, 108.7, 115.6 (t, $^1J_{CF}$ = 143.8 Hz), 127.4, 128.3, 130.1, 131.4, 139.9, 140.2, 158.3, 163.2 ppm; ^{19}F NMR (282.4 MHz, CD_3COCD_3): δ −116.5 (dt, $^1J_{FH}$ = 56.2 Hz, $^2J_{FH}$ = 16.7 Hz, 2F; CHF_2) ppm. HRMS: calc for $C_{16}H_{14}ClF_2N_5OS$ (M + 1): 398.0648; found 398.0639.

Synthesis and Purification of Carboxamides 15. *Route A.* A 5-mL vial was charged with 5-(1,1-difluoroethyl)-2-methyl-pyrazole-3-carboxylic acid (76.1 mg, 0.400 mmol), HATU (190.1 mg, 1.25 equiv) and a solution of corresponding amine (1.25 equiv) and DIEA (140 μL, 2 equiv) in NMP (2.5 mL). The resulting solution was heated in a Biotage Initiator microwave synthesizer at 90 °C for 10 min (20 min incubation delay, fixed heating time, absorption setting: very high, **Method A**), or agitated at rt for 12 (**Method B**). The resulting solution was then diluted with MeOH to 3 mL, stirred at rt for 30 min, and used directly for high-pH reverse phase purification to afford the corresponding 5-(1,1-difluoroethyl)-2-methyl-pyrazole-3-carboxamide.

Route B. A 5-mL microwave vial (Biotage) was charged with 5-(1,1-difluoroethyl)-2-methyl-pyrazole-3-carboxylic acid (76.1 mg, 0.400 mmol), HATU (190.1 mg, 1.25 equiv) and a solution of corresponding carboxylate (1.25 equiv) for **Method C**, or carbamate (1.25 equiv) for **Method D**, and DIEA (140 μL, 2 equiv) in NMP (2.5 mL). The resulting solution was heated in a Biotage Initiator microwave synthesizer at 90 °C for 10 min (20 min incubation delay, fixed heating time, absorption setting: very high). For **Method D**, 4 N HCl/dioxane (5 equiv) was then added to the vial, and the vial was heated in a Biotage Initiator microwave synthesizer at 120 °C for 10 min (fixed heating time, absorption setting: very high).

High-pH Prep on LC/MS Prep Instrument for Purification of Carboxamides 15. Mobile phase: Solvent A - 10 mM ammonium bicarbonate pH 10/5% MeOH; Sovent - acetonitrile. Phenomenex Gemini-NX 5 μm C18 110 Å, axial 75 cm × 30 cm column with 15 mm × 30 mm guard column. Mobile phase at 50 °C via in-line heater. Reaction mixtures after dilution with MeOH (final volume: 3 mL/inj) were used directly for injections. Focused gradients used depended on compound of interest elution time. Peak collection detection via UV/MS combination thresholding.

*3-(1,1-Difluoroethyl)-1-methyl-N-[2-(methylamino)ethyl]-1H-pyrazole-5-carboxamide (**15a**).* Purification with high-pH RP afforded **15a** as a colourless oil (32.5 mg, 33%). ^{1}H NMR (400 MHz, DMSO) δ 8.48 (br, 1H; NH), 7.08 (s, 1H; CH), 4.02 (s, 3H; CH_3), 3.28 (t, J = 6.5 Hz, 2H; CH_2), 2.60 (t, J = 6.5 Hz, 2H; CH_2), 2.28 (s, 3H; CH_3), 1.97 (t, J_{HF} = 18.8 Hz, 3H; CH_3) ppm; ^{13}C NMR (125.8 MHz, DMSO) δ 23.5 (t, $^2J_{CF}$ = 27.0 Hz), 35.8, 38.6, 50.4, 104.3, 119.2 (t, $^1J_{CF}$ = 231.7 Hz), 136.7, 146.0 (t, $^2J_{CF}$ = 33.4 Hz), 158.7 ppm; ^{19}F NMR (376.2 MHz, DMSO) δ −82.3 (q, J_{FH} = 19.1 Hz; 2F; CF_2). HRMS: calc for $C_{10}H_{16}F_2N_4O$ (M^+): 246.1306; found 246.1292.

*3-(1,1-Difluoroethyl)-1-methyl-N-(3-pyrrolidinyl)-1H-pyrazole-5-carboxamide (**15b**).* Purification with high-pH RP afforded **15b** as a colourless oil (66.6 mg, 77%). ^{1}H NMR (400 MHz, DMSO) δ 8.46 (d, J = 7.0 Hz, 1H; NH), 7.12 (s, 1H; CH), 4.25 (m, 1H; CH), 4.06 (s, 3H; CH_3), 2.96−2.84 (m, 2H; CH_2), 2.73 (m, 1H; CH), 2.64 (dd, ^1J = 11.4 Hz, ^2J = 4.4 Hz, 2H; CH_2), 1.92 (t, J_{HF} = 18.9 Hz, 3H; CH_3), 1.97 (m, 1H; CH), 1.63 (m, 1H; CH) ppm; ^{13}C NMR (125.8 MHz, DMSO) δ 23.5 (t, $^2J_{CF}$ = 27.0 Hz), 32.5, 45.3, 50.3, 52.6, 104.5, 119.2 (t, $^1J_{CF}$ = 231.7 Hz), 136.6, 146.0 (t, $^2J_{CF}$ = 33.8 Hz), 158.3 ppm; ^{19}F NMR (376.2 MHz, DMSO) δ −82.3 (q, J_{FH} = 19.1 Hz; 2F; CF_2). HRMS: calc for for $C_{11}H_{17}F_2N_4O$ (M + H)$^+$: 259.1365; found 259.1388.

*N-(4-tert-Butylbenzyl)-4-chloro-3-cyclopropyl-1-methyl-1H-pyrazole-5-carboxamide (**17f**).* Flash chromatography (*n*-hexane/EtOAc, 6:1) afforded **17f** as a colourless oil (63.5 mg, 82% two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87−0.94 (m, 4H; 4CH), 1.32 (s, 9H; $3CH_3$), 1.80−1.95 (m, 1H; CH); 4.09 (s, 3H; CH_3), 4.61 (d, J = 5.7 Hz, 2H; CH2), 7.03 (br, 1H; NH), 7.29 (d, J = 8.4 Hz, 2CH), 7.39 (d, J = 8.4 Hz, 2H; 2CH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 6.5, 6.9, 31.7, 34.5, 40.6, 43.1, 108.3, 125.7, 127.3, 130.9, 134.4, 149.1, 150.6, 158.4

dx.doi.org/10.1021/op500114v | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

ppm. HRMS: calc for $C_{19}H_{24}ClN_3O$ (M + 1): 346.1681; found 346.1681.

*N-(4-tert-Butylbenzyl)-4-chloro-1-methyl-3-(3-pyridinyl)-1H-pyrazole-5-carboxamide (**17g**).* Flash chromatography (*n*-hexane/EtOAc, 2:1) afforded **17g** as a colourless oil (103.5 mg, 80% two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 9H; 3C*H*3), 4.24 (s, 3H; CH_3), 4.64 (d, J = 5.7 Hz, 2H; CH_2), 7.09 (br, 1H; N*H*), 7.30 (d, J = 8.4 Hz, 2H; 2C*H*), 7.33−7.38 (m, 1H; C*H*), 8.09−8.13 (m, 1H; C*H*), 8.60 (dd, ^1J = 4.8 Hz, ^2J = 1.8 Hz, 1H; C*H*), 9.07 (d, J = 1.5 Hz, 1H; C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 31.2, 34.5, 41.2, 43.3, 107.2, 123.3, 125.8, 127.0, 127.4, 132.7, 134.1, 134.7, 143.4, 148.4, 149.4, 150.8, 158.1 ppm. HRMS: calc for $C_{21}H_{23}ClN_4O$ (M + 1): 383.1633; found 383.1634.

*N-(4-tert-Butylbenzyl)-4-chloro-3-ethyl-1-(3-pyridinyl)-1H-pyrazole-5-carboxamide (**17h**).* Flash chromatography (*n*-hexane/EtOAc, 2:1) afforded **17h** as a white solid (110 mg, 75% two steps); mp: 80−82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, J = 7.5 Hz, 3H; CH_3), 1.21 (s, 9H; 3CH_3), 2.61 (q, J = 7.5 Hz, 2H; CH_2), 4.45 (d, J = 5.7 Hz, 2H; CH_2), 6.81 (t, J = 4.8 Hz, 1H; N*H*), 7.15 (d, J = 8.4 Hz, 2H; 2C*H*), 7.27 (d, J = 8.4 Hz, 2H; 2C*H*), 7.65−7.69 (m, 1H; C*H*), 8.48 (dd, ^1J = 4.8 Hz, ^2J = 1.5 Hz, 1H; C*H*), 8.55 (d, J = 2.4 Hz, 1H; C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.4, 19.4, 31.3, 34.5, 43.4, 110.6, 123.1, 125.7, 127.5, 132.4, 132.9, 134.0, 137.0, 146.0, 148.9, 150.8, 152.5, 157.5 ppm. HRMS: calc for $C_{22}H_{25}ClN_4O$ (M + 1): 397.1790; found 397.1787.

Synthesis of 19e by Cross-Coupling Reaction with 3-Bromopyridine. Starting of compound **2e**, carboxamide **18e** was obtained following the methodology described above.

Preparation of the PdCl(C_3H_5)(dppb) Catalyst. An oven-dried, 25-mL Schlenk tube equipped with a magnetic stirring bar under a nitrogen atmosphere was charged with [Pd(C_3H_5)-Cl]$_2$ (128 mg, 0.36 mmol) and dppb (312 mg, 0.72 mmol). Anhydrous dichloromethane (7 mL) was added, and then the solution was stirred at room temperature for 20 min. The solvent was removed *in vacuum*. The yellow powder was used without purification.

Procedure for Direct Arylation Reactions. 3-Bromopyridine (0.4 mmol), pyrazol derivative **18e** (0.33 mmol), KOAc (0.66 mmol), and PdCl(C_3H_5)(dppb) (0.003 mmol) were dissolved in DMAc (1.3 mL) under nitrogen atmosphere. The reaction mixture was stirred at 150 °C for 16 h. Then, the solvent was evaporated, and the product was purified by silica gel column chromatography.

*N-(4-tert-Butylbenzyl)-3-ethyl-1-methyl-4-(3-pyridinyl)-1H-pyrazole-5-carboxamide (**19e**).* Flash chromatography (*n*-hexane/EtOAc, 1:1) afforded **19e** as a white solid (40 mg, 32% yield, 40% conv.); mp: 138−140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2 (t, J = 7.5 Hz, 3H; CH_3), 1.31 (s, 9H; 3CH_3), 2.53 (q, J = 7.5 Hz, 2H; CH_2), 4.13 (s, 3H; CH_3), 4.35 (d, J = 5.7 Hz, 2H; CH_2), 5.72 (t, J = 5.5 Hz, 1H; N*H*), 6.94 (d, J = 8.4 Hz, 2H; 2C*H*), 7.16−7.20 (m, 1H; C*H*), 7.27 (d, J = 8.3 Hz, 2H; 2C*H*), 7.49−7.53 (m, 1H; C*H*), 8.50−8.52 (m, 2H; 2C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.9, 19.6, 31.2, 34.4, 38.9, 43.3, 116.4, 123.5, 125.6, 127.3, 128.5, 133.9, 134.1, 137.4, 148.7, 150.3, 150.6, 150.9, 159.8 ppm. HRMS: calc for $C_{23}H_{28}N_4O$ (M + 1): 377.2336; found 377.2328.

Synthesis of 20e by Cross-Coupling Reaction with Cyclopropylboronic Acid. In a 5-mL glass microwave vessel were placed pyrazol derivative (**18e**) (59 mg, 0.2 mmol), NBS (42 mg, 0.23 mmol), and HOAc (1.5 mL). The reaction was heated under microwave irradiation at 150 °C for 15 min. After completion of the reaction, as indicated by TLC, the solvent was removed, and the residue was purified by flash chromatography to afford the corresponding 4-bromopyrazole derivative, which was dissolved in aqueous toluene (toluene/H_2O, 15:1) (1.4 mL), and cyclopropylboronic acid (14.5 mg, 0.17 mmol), Pd(OAc)$_2$ (3 mg, 0.013 mmol), PPh_3 (15.7 mg, 0.06 mmol) and potassium carbonate (63 mg, 0.45 mmol) were added. The reaction mixture was heated under microwave irradiation at 140 °C. The resulting solution was filtered, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography.

*N-(4-tert-Butylbenzyl)-4-cyclopropyl-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (**20e**).* Flash chromatography (*n*-hexane/EtOAc, 3:1) afforded **20e** as a white solid (35 mg, 88%); mp: 60−62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.52−0.57 (m, 2H, 2C*H*), 0.80−0.86 (m, 2H; 2C*H*), 1.22 (t, J = 7.5 Hz, 3H; CH_3), 1.31 (s, 9H; 3CH_3), 2.65 (q, J = 7.5 Hz, 2H; CH_2), 4.08 (s, 3H; CH_3), 4.59 (d, J = 5.8 Hz, 2H; CH_2), 6.98 (br, 1H; N*H*), 7.29 (d, J = 8.5 Hz, 2H; 2C*H*), 7.38 (d, J = 8.5 Hz, 2H; 2C*H*) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 5.1, 7.2, 13−7, 20.1, 31.3, 34.5, 39.4, 43.3, 118.5, 125.7, 127.7, 134.4, 134.6, 150.7, 152.6, 160.3 ppm. HRMS: calc for $C_{21}H_{30}N_3O$ (M + 1): 340.2383; found 340.2389.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and complete characterization data including ^{1}H, ^{13}C, and ^{19}F NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-Mail: santos.fustero@uv.es

Author Contributions

§R.R. and A.N. contributed equally to this paper.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Dr. Fátima Iradier, Dr. Iván Collado, and Dr. Marta Piñeiro-Nuñez for the organization and logistics behind the collaboration; Dr. Daniel J. Sall and Dr. Mark T. Uhlik for their valuable help with the generation of the biological data. We also thank Robert D. Boyer and Christopher T. Reutter for the analytical and spectral support. We also would like to acknowledge the OIDD team (Eli Lilly & Company) for their partnership. Support for research carried out at University of Valencia was provided in part by Eli Lilly and Company. We thank the Spanish Ministerio de Ciencia e Innovación (CTQ2010-19774-C02-01) and the Generalitat Valenciana (PROMETEO/2010/061) for their financial support.

■ REFERENCES

(1) (a) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (b) Fustero, S.; Simón-Fuentes, A.; Sanz-Cervera, J. F. *Org. Prep. Proced. Int.* **2009**, *41*, 253.

(2) Marcic, D. *Exp. Appl. Acarol.* **2005**, *36*, 177.

(3) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.;

Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
(4) Boolell, M.; Gepi-Atel, S.; Gingell, J. C.; Allen, M. J. *British J. Urol.* **1996**, *78*, 257.
(5) Rinaldi-Carmona, M.; Barth, F.; Heaulme, M.; Alonso, R.; Shire, D.; Congy, C.; Soubrie, P.; Breliere, J. C.; Le Fur, G. *Life Sci.* **1995**, *56*, 1941.
(6) Qiao, J. X.; Cheng, X.; Smallher, J. M.; Galemmo, R. A.; Drummond, S.; Pinto, J. P.; Cheney, D. L.; He, K.; Wong, P. C.; Luettgen, J. M.; Knabb, R. M.; Wexler, R. R.; Lam, P. Y. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1432.
(7) (a) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Cuñat, A. C.; Villanova, S.; Murguía, M. *J. Org. Chem.* **2008**, *73*, 3523. (b) Fustero, S.; Román, R.; Sanz-Cervera, J. F.; Simón-Fuentes, A.; Bueno, J.; Villanova, S. *J. Org. Chem.* **2008**, *73*, 8545.
(8) Sun, A.; Chandrakumar, N.; Yoon, J. J.; Plemper, R. K.; Snyder, J. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5199.
(9) Ellis, L. M.; Hicklin, D. J. *Nat. Rev. Cancer* **2008**, *8*, 670.
(10) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. *Science* **1999**, *286*, 971.
(11) Eliasson, L. *J. Physiol.* **2008**, *14*, 3313.
(12) Chen, Y.; Alman, B. A. *J. Cell. Biochem.* **2009**, *160*, 353.
(13) Song, H.; Liu, Y.; Xiong, L.; Li, Y.; Yang, N.; Wang, Q. *J. Agric. Food Chem.* **2012**, *60*, 1470.
(14) Chang, K. Y.; Kim, S. H.; Nam, G.; Seo, J. H.; Kim, J. H.; Ha, D.-Ch. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1211.
(15) Ethyl acetate was used in place of carbon tetrachloride, which was used in the small-scale original synthesis. The reaction was cleaner and more environmentally friendly. See Experimental Section.
(16) Oxalyl chloride had been used at small scale, but at large scale it could produce a large amount of gas that could increase the pressure of the reactor.
(17) Pearson, R. G. *Proc. Nat. Acad. Sci. U.S.A.* **1986**, *83*, 8440.
(18) Lee, J. A.; Chu, S.; Willard, F. S.; Cox, K. L.; Galvin, R. J.; Peery, R. B.; Oliver, S. E.; Oler, J.; Meredith, T. D.; Heidler, S. A.; Gough, W. H.; Husain, S.; Palkowitz, A. D.; Moxham, C. M. *J. Biomol. Screen.* **2011**, *16*, 588.