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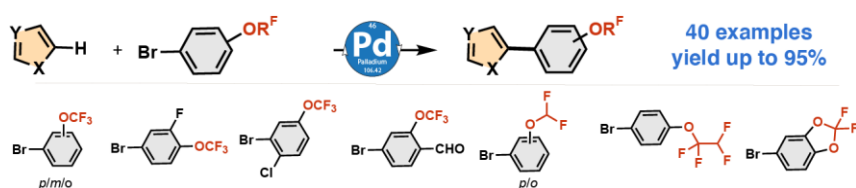
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# Pd-catalyzed direct arylations of heteroarenes with polyfluoroalkoxy-substituted bromobenzenes

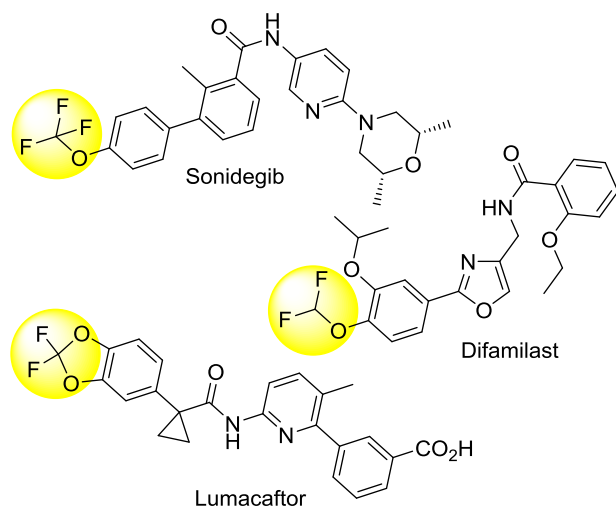
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The reactivity of di-, tri- and tetra-fluoroalkoxy-substituted bromobenzenes in the direct arylation of 5-membered ring heteroarenes using palladium catalysis was explored. High yields in arylated heteroarenes were obtained using only 1 mol% of Pd(OAc)<sub>2</sub> catalyst with KOAc as inexpensive base. Similar yields were obtained with *o/m/p* trifluoromethoxy-, *o/p* difluoromethoxy-, and tetrafluoroethoxy-substituents on the aryl bromide. A bromo-substituted difluorobenzo[*d*][1,3]dioxole was successfully coupled. The major side-products of the reaction are HBr/KOAc. Therefore, this synthetic scheme is very attractive for the access to such polyfluoroalkoxy-containing arylated heteroaromatics in terms of cost, simplicity and low environmental impact, compared to reactions involving arylation of heteroarenes with bromophenols followed by polyfluoroalkylation. Introduction

Many important drugs contain a (polyfluoroalkoxy)benzene unit (Fig. 1). For example, Sonidegib is an anticancer agent for treating basal-cell carcinoma, Lumacaftor is employed to treat Mucoviscidose. Difamilast is a topical, selective, nonsteroidal PDE4 inhibitor developed for the treatment of atopic dermatitis.<sup>[1]</sup> Therefore, the development of simple procedures allowing to have access to polyfluoroalkoxy-substituted benzene derivatives using inexpensive reagents in a few steps is of great interest to researchers working in the field of pharmaceutical chemistry.

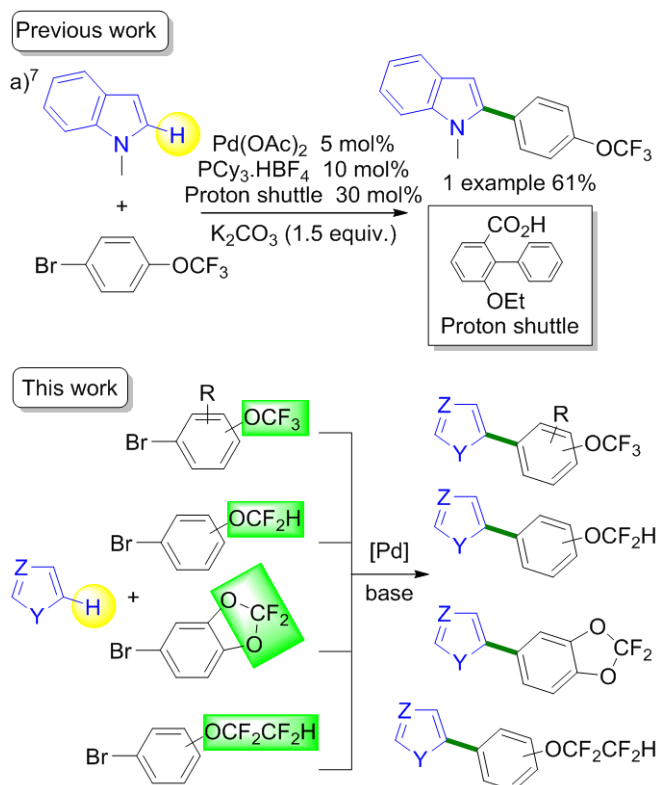


**Figure 1.** Selected examples of drugs containing a di- or a tri-fluoroalkoxybenzene unit

In 1985, Ohta and co-workers reported the arylation of heteroarenes *via* the functionalization of C-H bonds using aryl halides as aryl sources and Pd-catalysts.<sup>[2]</sup> Since these seminal results, the so-called “direct arylation” has been demonstrated to be an extremely effective method for the synthesis of arylated heteroarenes.<sup>[3,4]</sup> For such arylations, a wide variety of aryl halides have been employed. However, so far only a few examples using halophenols have been described and in most cases, expensive bases such as silver salts were used or low yields were obtained.<sup>[5]</sup> In addition, iodo- and bromo-phenols are in several cases not easy to handle because they generally have very unpleasant odors. Moreover, the transformation of phenols into di- or tri-methoxybromobenzenes is a tedious reaction as it employs expensive difluoromethyl sources such as trimethyl(bromodifluoromethyl)silane,<sup>[6a]</sup> difluorobromoacetic acid,<sup>[6b]</sup> diethyl bromodifluoromethylphosphonate,<sup>[6c]</sup> or trifluoromethyl sources such as 2'-(trifluoromethoxy)[1,1'-biphenyl]-2-diazonium,<sup>[6d]</sup> or trimethylsilyltrifluoromethane,<sup>[6e]</sup> and often affords the desired products in moderate yields.

Therefore, the direct use of (polyfluoroalkoxy)bromobenzene derivatives for the synthesis of heteroarenes bearing (polyfluoroalkoxy)benzene units has potential for pharmaceutical chemistry. To the best of our knowledge, the Pd-catalyzed direct arylations of heteroarenes by (difluoromethoxy)bromobenzenes, 2- and 3-(trifluoromethoxy)bromobenzenes or (polyfluoroethoxy)benzenes has not been reported yet; whereas only one example using 1-bromo-4-(trifluoromethoxy)benzene has been described (Scheme 1, top).<sup>[7]</sup> This coupling reaction was performed using 5 mol% Pd(OAc)<sub>2</sub> and 10 mol% PCy<sub>3</sub> as catalyst system in the presence of a 2-arylbenzoic acid (30 mol%) as proton shuttle. In most cases, for such reactions, the more reactive 1-iodo-4-(trifluoromethoxy)benzene was used, or a high loading of an expensive ligand had to be employed.<sup>[8,9]</sup>

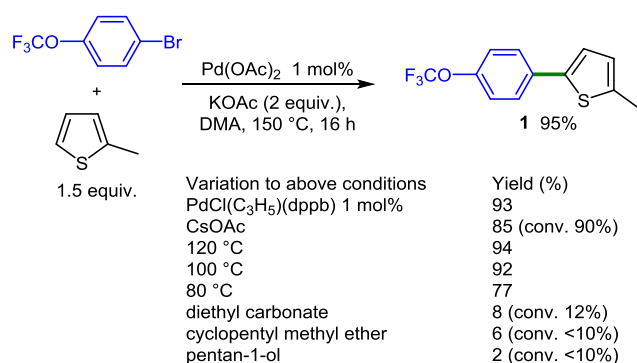
Herein, we report on the reactivity of *o/m/p* polyfluoromethoxy-substituted bromobenzenes and also a difluorobenzo[*d*][1,3]dioxoles and a (tetrafluoroethoxy)benzene in Pd-catalyzed direct arylation of heteroaromatics (Scheme 1, bottom).



**Scheme 1.** Pd-catalyzed direct arylations of heteroarenes by di-, tri- and tetra-(fluoro)alkoxy-substituted bromobenzenes

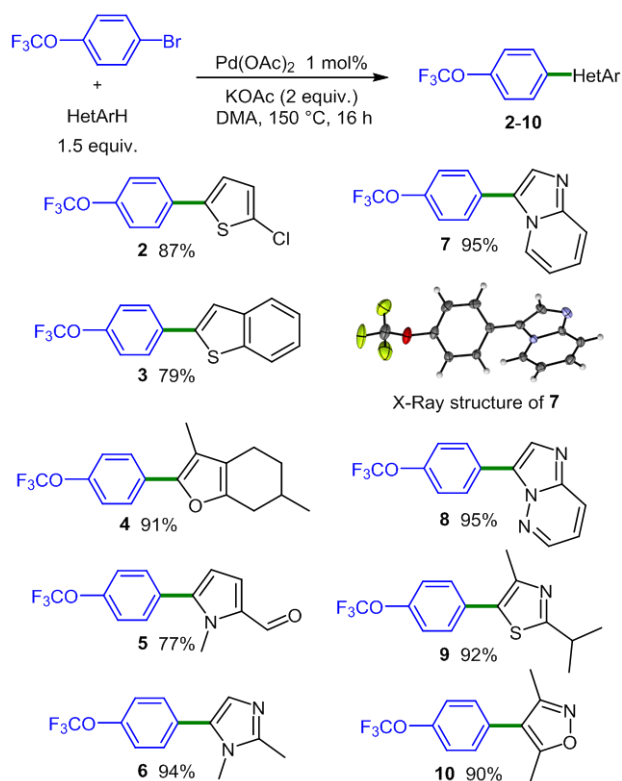
## Results and Discussion

Using reaction conditions similar to those employed with other aryl bromides,<sup>[10]</sup> we first examined the reactivity of 2-methylthiophene<sup>[11]</sup> (1.5 equiv.) with 1-bromo-4-(trifluoromethoxy)benzene (1 equiv.) (Scheme 2). In the presence of 1 mol% PdCl(C<sub>3</sub>H<sub>5</sub>)(dppb) catalyst with KOAc as the base in DMA at 150 °C, the expected C5-arylated thiophene **1** was regioselectively obtained in 93% yield and a complete conversion of the aryl bromide was observed. The use of phosphine-free catalyst Pd(OAc)<sub>2</sub> (1 mol%) also afforded **1** in a very high yield of 95%. The use of lower reaction temperatures (120 or 100 °C) gave the product **1** in similar yields (94% and 92%), and at 80 °C, **1** was obtained in only 77% yield due to a partial conversion of the aryl bromide. Conversely, very low yields in **1** were obtained using diethyl carbonate, cyclopentyl methyl ether or pentan-1-ol as the solvents due to poor conversions of the aryl bromide.



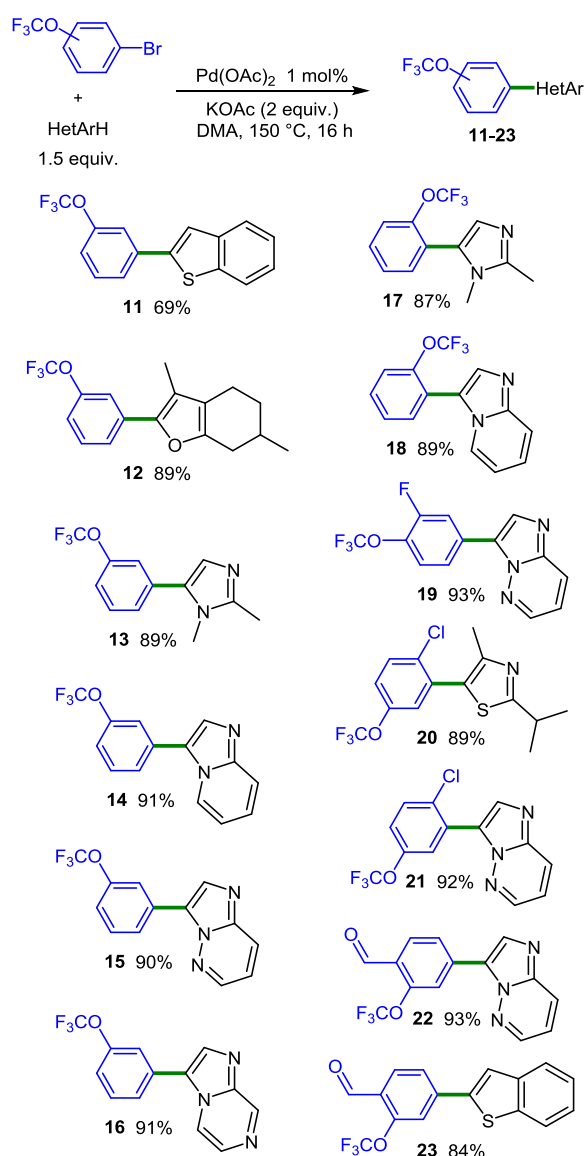
**Scheme 2.** Direct arylation of 2-methylthiophene using 1-bromo-4-(trifluoromethoxy)benzene.

Then, a set of heteroarenes<sup>[12]</sup> was reacted with 1-bromo-4-(trifluoromethoxy)benzene using 1 mol% Pd(OAc)<sub>2</sub> with KOAc in DMA (Scheme 3.) With 2-chlorothiophene and benzothiophene, the desired products **2** and **3** were obtained in 87% and 79% yield, respectively. 2-Formylpyrrole and 1,2-dimethylimidazole afforded the C5-arylated heteroarenes **5** and **6** in 77% and 94% yield, respectively. The arylation of imidazo[1,2-*a*]pyridine and imidazo[1,2-*b*]pyridazine, which are important units in pharmaceutical chemistry, with 1-bromo-4-(trifluoromethoxy)benzene was also successful giving rise to products **7** and **8** in almost quantitative yields. The structure of **7** was confirmed by X-ray analysis.<sup>[13]</sup> Finally, a thiazole derivative was arylated at C5-position and an isoxazole at C4-position affording the products **9** and **10** in 92% and 90% yield, respectively.



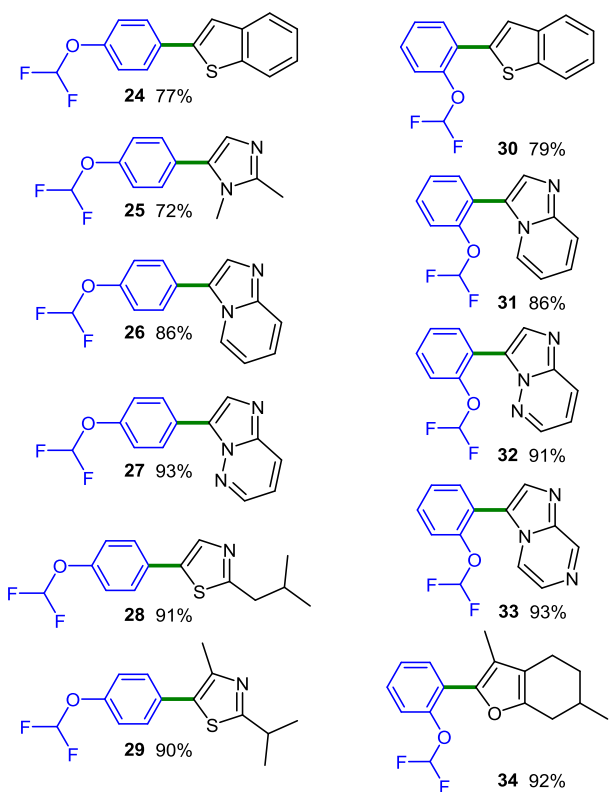
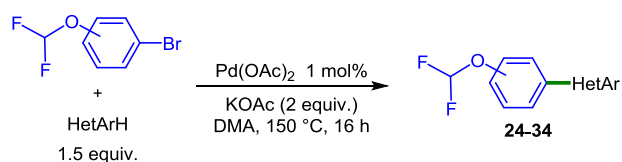
**Scheme 3.** Direct arylations of a set of heteroarenes with 1-bromo-4-(trifluoromethoxy)benzene.

Then, the behavior of 3-bromo and 2-bromo substituted (trifluoromethoxy)benzenes was investigated (Scheme 4). The reaction of 1-bromo-3-(trifluoromethoxy)benzene with benzothiophene, menthofuran and 1,2-dimethylimidazole gave the expected products **11-13** in 69-89% yields. Imidazo[1,2-*a*]pyridine, imidazo[1,2-*b*]pyridazine and imidazo[1,2-*a*]pyrazine also reacted nicely with this aryl bromide affording the products **14-16** in 90-91% yields. A minor influence of the steric hindrance on the reaction was observed, and the coupling of 1-bromo-2-(trifluoromethoxy)benzene with 1,2-dimethylimidazole and imidazo[1,2-*a*]pyridine gave the products **17** and **18** in similar yields than for the reaction with the *meta*-bromo substituted (trifluoromethoxy)benzene. The influence of a few additional substituents on the bromo(trifluoromethoxy)benzenes was also studied. 1-Bromo-3-fluoro-4-(trifluoromethoxy)benzene using imidazo[1,2-*b*]pyridazine as coupling partner delivered the product **19** in 93% yield. A chloro-substituent was also tolerated, providing the products **20** and **21** in very high yields without cleavage of the C-Cl bond. 4-Bromo-2-(trifluoromethoxy)benzaldehyde also reacted nicely giving rise to the compounds **22** and **23** in 93% and 84% yield, respectively.



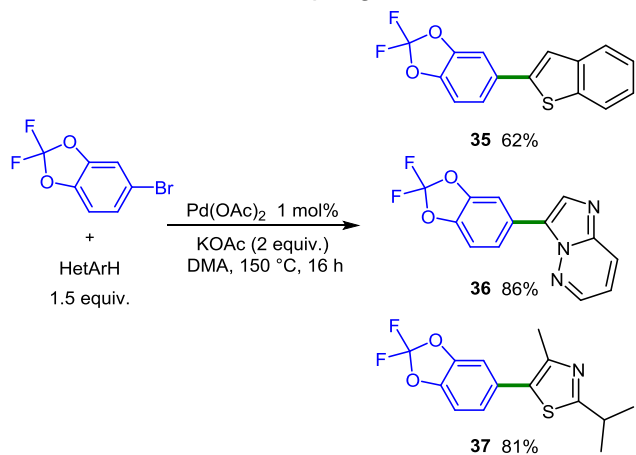
**Scheme 4.** Direct arylations of a set of heteroarenes with 1-bromo-3-(trifluoromethoxy)benzene, 1-bromo-2-(trifluoromethoxy)benzene or functionalized bromo(trifluoromethoxy)benzenes.

The reactivity of bromo-substituted (difluoromethoxy)benzenes in direct arylation of heteroaromatics was also studied (Scheme 5). Again, the use of only 1 mol% Pd(OAc)<sub>2</sub> catalyst promoted very efficiently such reactions. From benzothiophene and 1-bromo-4-(difluoromethoxy)benzene, the C2-arylated benzothiophene **24** was regioselectively obtained in 77% yield. The nitrogen containing heteroaromatics 1,2-dimethylimidazole, imidazo[1,2-*a*]pyridine and imidazo[1,2-*b*]pyridazine afforded the products **25-27** in 72-93% yields. The reactivity of two thiazoles derivatives was also examined. In both cases, the C5-arylated thiazoles **28** and **29** were obtained in very high yields. The more sterically hindered 1-bromo-2-(difluoromethoxy)benzene exhibit a similar reactivity than 1-bromo-4-(difluoromethoxy)benzene. Its coupling with benzothiophene, imidazo[1,2-*a*]pyridine, imidazo[1,2-*b*]pyridazine, imidazo[1,2-*a*]pyrazine and menthofuran gave the products **30-34** in 79-93% yields.



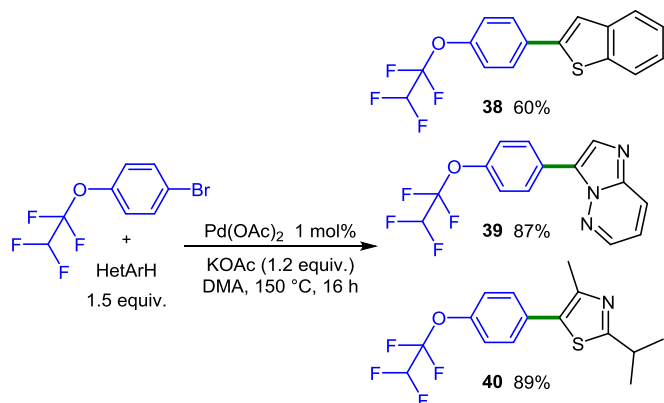
**Scheme 5.** Direct arylations of a set of heteroarenes with 1-bromo-4-(difluoromethoxy)benzene or 1-bromo-2-(difluoromethoxy)benzene.

The introduction of a difluorobenzo[*d*][1,3]dioxole unit on heteroarenes is particularly interesting because of their presence on important pharmaceutical compounds such as Lumacaftor (see fig. 1). The reactivity of 5-bromo-2,2-difluorobenzo[*d*][1,3]dioxole in direct arylation is described in the scheme 6. Again, the reactions proceeded nicely in the presence of 1 mol% Pd(OAc)<sub>2</sub> and KOAc, giving rise to the target products **35-37** in good to high yields. No decomposition of the dioxolane moiety was observed in the course of these couplings.



**Scheme 6.** Direct arylations of a set of heteroarenes with 5-bromo-2,2-difluorobenzo[*d*][1,3]dioxole.

Finally, the reactivity of 1-bromo-4-(1,1,2,2-tetrafluoroethoxy)benzene in direct arylation was evaluated (Scheme 7). Again, in the presence of benzothiophene, imidazo[1,2-*b*]pyridazine and a thiazole derivative, the target products **38-40** were isolated in 60-89% yield. No cleavage of the quite acidic C-H bond of the tetrafluoroethoxy unit was observed, although such deprotonations have already been observed in the presence of a strong base.<sup>[14]</sup>



**Scheme 7.** Direct arylations of a set of heteroarenes with 1-bromo-4-(1,1,2,2-tetrafluoroethoxy)benzene.

## Conclusion

In summary, di- and tri-fluoromethoxy substituents at *o/m/p* positions on bromobenzenes are well tolerated in Pd-catalyzed direct arylations. Phosphine-free Pd(OAc)<sub>2</sub> catalyst with KOAc base was successfully employed to promote the direct arylation of a wide range of heteroaromatics with these fluoro-containing aryl bromides. High yields in the arylated heteroaromatics were obtained in most cases using (benzo)thiophenes, thiazoles, imidazoles, pyrroloquinolines, imidazopyridines, isoxazoles, furans and pyrroles. Difluorobenzo[*d*][1,3]dioxole and 1,1,2,2-tetrafluoroethoxybenzene units were also successfully introduced on heteroaromatics under the same reaction conditions. To our knowledge, these are the first examples of direct arylations of heteroaromatics using (difluoromethoxy)benzenes, difluorobenzo[*d*][1,3]dioxoles, 2- and 3-(trifluoromethoxy)benzenes and tetrafluoroethoxybenzenes. The use of these polyfluoroalkoxy-substituted bromobenzenes in direct arylation is certainly more attractive than the use of bromophenols, as they display a much higher reactivity, as many of them are commercially available, and as there is no need to introduce a polyfluoroalkyl group to obtain the (polyfluoroalkoxy)benzenes. For these reasons, this procedure provides an economically viable and environmentally very attractive access to heteroarenes bearing a (polyfluoroalkoxy)benzene unit.

## Experimental Section

**Typical experiment for coupling reactions:** The reaction of the aryl bromide (1 mmol), heteroaromatic (1.5 mmol) and KOAc (0.196 g, 2 mmol) in the presence of Pd(OAc)<sub>2</sub> (0.0024 g, 1 mol%) in DMA under argon at 150 °C during 16 h, affords the corresponding product after cooling, evaporation of the solvent and filtration on silica gel (pentane/ether).

### 2-Methyl-5-(4-(trifluoromethoxy)phenyl)thiophene (**1**)

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 2-methylthiophene (0.147 g, 1.5 mmol) affords **1** in 95% (0.245 g) yield as a yellow solid: mp 105-107 °C.



$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.55 (d,  $J = 8.5$  Hz, 2H), 7.20 (d,  $J = 8.5$  Hz, 2H), 7.08 (d,  $J = 3.5$  Hz, 1H), 6.75-6.72 (m, 1H), 2.51 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.2 (q,  $J = 1.8$  Hz), 140.5, 140.4, 133.7, 126.8, 126.5, 123.7, 121.5 (q,  $J = 1.0$  Hz), 120.5 (q,  $J = 257.0$  Hz), 15.6.

LRMS calcd for  $\text{M}^+$   $\text{C}_{12}\text{H}_9\text{F}_3\text{OS}$  258, found 258.

### **2-Chloro-5-(4-(trifluoromethoxy)phenyl)thiophene (2)**

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 2-chlorothiophene (0.178 g, 1.5 mmol) affords **2** in 87% (0.243 g) yield as a yellow solid: mp 63-65 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.52 (d,  $J = 8.5$  Hz, 2H), 7.22 (d,  $J = 8.5$  Hz, 2H), 7.04 (d,  $J = 3.7$  Hz, 1H), 6.89 (d,  $J = 3.7$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.8 (q,  $J = 1.8$  Hz), 141.4, 132.6, 130.0, 127.4, 127.0, 123.0, 121.7 (q,  $J = 1.0$  Hz), 120.6 (q,  $J = 257.5$  Hz).

LRMS calcd for  $\text{M}^+$   $\text{C}_{11}\text{H}_6\text{ClF}_3\text{OS}$  278, found 278.

### **2-(4-(Trifluoromethoxy)phenyl)benzo[*b*]thiophene (3)**

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **3** in 79% (0.232 g) yield as a white solid: mp 185-187 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.84 (d,  $J = 8.2$  Hz, 1H), 7.79 (d,  $J = 8.2$  Hz, 1H), 7.73 (d,  $J = 8.5$  Hz, 2H), 7.52 (s, 1H), 7.38 (t,  $J = 7.8$  Hz, 1H), 7.34 (t,  $J = 7.8$  Hz, 1H), 7.30 (d,  $J = 8.5$  Hz, 2H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.2 (q,  $J = 1.8$  Hz), 142.6, 140.7, 139.7, 133.2, 128.0, 124.8, 124.7, 123.9, 122.4, 121.6 (q,  $J = 1.0$  Hz), 120.7 (q,  $J = 257.5$  Hz), 120.3.

LRMS calcd for  $\text{M}^+$   $\text{C}_{15}\text{H}_9\text{F}_3\text{OS}$  294, found 294.

### **3,6-Dimethyl-2-(4-(trifluoromethoxy)phenyl)-4,5,6,7-tetrahydrobenzofuran (4)**

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and menthofuran (0.225 g, 1.5 mmol) affords **4** in 91% (0.282 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.62 (d,  $J = 8.5$  Hz, 2H), 7.23 (d,  $J = 8.5$  Hz, 2H), 2.74 (dd,  $J = 16.3, 6.3$  Hz, 1H), 2.50-2.37 (m, 2H), 2.30-2.21 (m, 1H), 2.16 (s, 3H), 2.00-1.83 (m, 2H), 1.48-1.35 (m, 1H), 1.12 (d,  $J = 6.7$  Hz, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.1, 147.3 (q,  $J = 1.8$  Hz), 145.7, 131.4, 126.1, 121.2, 120.1 (q,  $J = 1.0$  Hz), 120.7 (q,  $J = 257.5$  Hz), 116.9, 31.5, 31.4, 29.8, 21.6, 20.2, 9.9.

LRMS calcd for  $\text{M}^+$   $\text{C}_{17}\text{H}_{17}\text{F}_3\text{O}_2$  310, found 310.

### **1-Methyl-5-(4-(trifluoromethoxy)phenyl)-pyrrole-2-carbaldehyde (5)**

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 2-formylpyrrole (0.142 g, 1.5 mmol) affords **5** in 77% (0.207 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.59 (s, 1H), 7.45 (d,  $J = 8.5$  Hz, 2H), 7.31 (d,  $J = 8.5$  Hz, 2H), 6.97 (d,  $J = 4.0$  Hz, 1H), 6.30 (d,  $J = 4.0$  Hz, 1H), 3.92 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  179.9, 149.5 (q,  $J = 1.8$  Hz), 142.7, 133.4, 130.8, 129.9, 124.5, 121.2 (q,  $J = 1.0$  Hz), 120.2 (q,  $J = 257.7$  Hz), 111.1, 34.4.

LRMS calcd for  $\text{M}^+$   $\text{C}_{13}\text{H}_{10}\text{F}_3\text{NO}_2$  269, found 269.

### 1,2-Dimethyl-5-(4-(trifluoromethoxy)phenyl)imidazole (6)

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 1,2-dimethylimidazole (0.144 g, 1.5 mmol) affords **6** in 94% (0.241 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38 (d,  $J = 8.5$  Hz, 2H), 7.28 (d,  $J = 8.5$  Hz, 2H), 6.96 (s, 1H), 3.52 (s, 3H), 2.45 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.7 (q,  $J = 1.8$  Hz), 146.5, 132.3, 130.0, 129.4, 126.4, 121.3 (q,  $J = 1.0$  Hz), 120.6 (q,  $J = 257.5$  Hz), 31.4, 13.7.

LRMS calcd for  $\text{M}^+$   $\text{C}_{12}\text{H}_{11}\text{F}_3\text{N}_2\text{O}$  256, found 256.

### 3-(4-(Trifluoromethoxy)phenyl)imidazo[1,2-a]pyridine (7)<sup>[9d]</sup>

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and imidazo[1,2-a]pyridine (0.177 g, 1.5 mmol) affords **7** in 95% (0.264 g) yield as a white solid: mp 101-103 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.27 (d,  $J = 7.0$  Hz, 1H), 7.69 (s, 1H), 7.67 (d,  $J = 7.0$  Hz, 1H), 7.57 (d,  $J = 8.5$  Hz, 2H), 7.36 (d,  $J = 8.5$  Hz, 2H), 7.21 (dd,  $J = 6.9, 7.8$  Hz, 1H), 6.82 (t,  $J = 6.9$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.9 (q,  $J = 1.8$  Hz), 146.4, 132.9, 129.5, 128.1, 124.6, 124.4, 123.1, 121.8 (q,  $J = 1.0$  Hz), 120.3 (q,  $J = 257.5$  Hz), 118.4, 112.9.

LRMS calcd for  $\text{M}^+$   $\text{C}_{14}\text{H}_9\text{F}_3\text{N}_2\text{O}$  278, found 278.

### 3-(4-(Trifluoromethoxy)phenyl)imidazo[1,2-b]pyridazine (8)

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and imidazo[1,2-b]pyridazine (0.179 g, 1.5 mmol) affords **8** in 95% (0.265 g) yield as a yellow solid: mp 93-95 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.42 (d,  $J = 4.2$  Hz, 1H), 8.09 (d,  $J = 8.5$  Hz, 2H), 8.04 (s, 1H), 8.03 (dd,  $J = 9.1, 0.9$  Hz, 1H), 7.33 (d,  $J = 8.5$  Hz, 2H), 7.07 (dd,  $J = 9.1, 4.4$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.7 (q,  $J = 1.8$  Hz), 143.1, 140.4, 133.1, 128.3, 127.4, 126.3, 121.3 (q,  $J = 0.8$  Hz), 120.4 (q,  $J = 257.5$  Hz), 116.6.

LRMS calcd for  $\text{M}^+$   $\text{C}_{13}\text{H}_8\text{F}_3\text{N}_3\text{O}$  279, found 279.

### 2-Isopropyl-4-methyl-5-(4-(trifluoromethoxy)phenyl)thiazole (9)

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **9** in 92% (0.277 g) yield as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.42 (d,  $J = 8.5$  Hz, 2H), 7.25 (d,  $J = 8.5$  Hz, 2H), 3.27 (sept.,  $J = 7.6$  Hz, 1H), 2.44 (s, 3H), 1.40 (d,  $J = 7.6$  Hz, 6H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  175.9, 148.6 (q,  $J = 1.8$  Hz), 147.5, 131.5, 130.6, 129.0, 121.2 (q,  $J = 1.0$  Hz), 120.5 (q,  $J = 257.4$  Hz), 33.5, 23.3, 16.2.

LRMS calcd for  $\text{M}^+$   $\text{C}_{14}\text{H}_{14}\text{F}_3\text{NOS}$  301, found 301.

### **3,5-Dimethyl-4-(4-(trifluoromethoxy)phenyl)isoxazole (10)**

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 2,4-dimethylisoxazole (0.145 g, 1.5 mmol) affords **10** in 90% (0.231 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.28 (s, 4H), 2.41 (s, 3H), 2.27 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  165.6, 158.6, 148.7 (q,  $J = 1.8$  Hz), 130.6, 129.4, 121.5 (q,  $J = 1.0$  Hz), 120.4 (q,  $J = 257.4$  Hz), 115.7, 11.7, 10.9.

LRMS calcd for  $\text{M}^+$   $\text{C}_{12}\text{H}_{10}\text{F}_3\text{NO}_2$  257, found 257.

### **2-(3-Trifluoromethoxy)phenyl)benzo[*b*]thiophene (11)**

1-Bromo-3-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **11** in 69% (0.203 g) yield as a white solid: mp 113-115 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.84 (d,  $J = 8.2$  Hz, 1H), 7.80 (d,  $J = 8.2$  Hz, 1H), 7.63 (d,  $J = 8.3$  Hz, 1H), 7.58 (s, 1H), 7.56 (bs, 1H), 7.45 (t,  $J = 8.1$  Hz, 1H), 7.40-7.32 (m, 2H), 7.20 (d,  $J = 8.3$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.9 (q,  $J = 1.8$  Hz), 142.5, 140.6, 139.8, 136.5, 130.5, 125.0, 124.9, 124.0, 122.5, 120.7, 120.6 (q,  $J = 257.5$  Hz), 120.5 (q,  $J = 0.8$  Hz), 119.6, 119.1 (q,  $J = 0.8$  Hz).

LRMS calcd for  $\text{M}^+$   $\text{C}_{15}\text{H}_9\text{F}_3\text{OS}$  294, found 294.

### **3,6-Dimethyl-2-(3-(trifluoromethoxy)phenyl)-4,5,6,7-tetrahydrobenzofuran (12)**

1-Bromo-3-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and menthofuran (0.225 g, 1.5 mmol) affords **12** in 89% (0.276 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.53 (d,  $J = 8.0$  Hz, 1H), 7.47 (s, 1H), 7.38 (t,  $J = 7.7$  Hz, 1H), 7.05 (d,  $J = 8.2$  Hz, 1H), 2.74 (dd,  $J = 16.3, 6.3$  Hz, 1H), 2.50-2.33 (m, 2H), 2.30-2.21 (m, 1H), 2.18 (s, 3H), 2.01-1.83 (m, 2H), 1.48-1.35 (m, 1H), 1.12 (d,  $J = 6.7$  Hz, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.4, 149.7 (q,  $J = 1.8$  Hz), 145.4, 134.5, 129.9, 123.0, 120.7 (q,  $J = 257.5$  Hz), 120.3, 118.1, 117.7, 117.3, 31.5, 31.3, 29.8, 21.6, 20.1, 10.0.

LRMS calcd for  $\text{M}^+$   $\text{C}_{17}\text{H}_{17}\text{F}_3\text{O}_2$  310, found 310.

### **1,2-Dimethyl-5-(3-(trifluoromethoxy)phenyl)imidazole (13)**

1-Bromo-3-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 1,2-dimethylimidazole (0.144 g, 1.5 mmol) affords **13** in 89% (0.228 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38 (t,  $J = 7.7$  Hz, 1H), 7.23 (d,  $J = 8.2$  Hz, 1H), 7.17-7.10 (m, 2H), 6.93 (s, 1H), 3.48 (s, 3H), 2.38 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.4 (q,  $J = 1.8$  Hz), 146.7, 132.5, 132.0, 130.1, 126.7, 126.6, 120.7, 120.6 (q,  $J = 257.4$  Hz), 119.8, 31.3, 13.6.

LRMS calcd for  $\text{M}^+$   $\text{C}_{12}\text{H}_{11}\text{F}_3\text{N}_2\text{O}$  256, found 256.

### **3-(3-(Trifluoromethoxy)phenyl)imidazo[1,2-a]pyridine (14)**

1-Bromo-3-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and imidazo[1,2-a]pyridine (0.177 g, 1.5 mmol) affords **14** in 91% (0.253 g) yield as a white solid: mp 63-65 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.29 (d,  $J = 7.0$  Hz, 1H), 7.70 (s, 1H), 7.65 (d,  $J = 7.0$  Hz, 1H), 7.55-7.43 (m, 2H), 7.39 (s, 1H), 7.26-7.21 (m, 1H), 7.20 (dd,  $J = 6.9, 7.8$  Hz, 1H), 6.82 (t,  $J = 6.9$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.9 (q,  $J = 1.8$  Hz), 146.5, 133.2, 131.4, 130.8, 126.1, 124.7, 124.3, 123.1, 120.5 (q,  $J = 257.5$  Hz), 120.4 (q,  $J = 1.0$  Hz), 120.2 (q,  $J = 1.0$  Hz), 118.5, 113.1.

LRMS calcd for  $\text{M}^+$   $\text{C}_{14}\text{H}_9\text{F}_3\text{N}_2\text{O}$  278, found 278.

### **3-(3-(Trifluoromethoxy)phenyl)imidazo[1,2-b]pyridazine (15)**

1-Bromo-3-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and imidazo[1,2-b]pyridazine (0.179 g, 1.5 mmol) affords **15** in 90% (0.251 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.44 (d,  $J = 4.2$  Hz, 1H), 8.11-7.97 (m, 4H), 7.50 (t,  $J = 8.1$  Hz, 1H), 7.22 (d,  $J = 8.1$  Hz, 1H), 7.09 (dd,  $J = 9.1, 4.4$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.5 (q,  $J = 1.8$  Hz), 143.0, 140.5, 133.3, 130.5, 130.0, 127.0, 126.1, 124.8, 120.6 (q,  $J = 257.5$  Hz), 120.0 (q,  $J = 0.8$  Hz), 119.1 (q,  $J = 0.8$  Hz), 116.7.

LRMS calcd for  $\text{M}^+$   $\text{C}_{13}\text{H}_8\text{F}_3\text{N}_3\text{O}$  279, found 279.

### **3-(3-(Trifluoromethoxy)phenyl)imidazo[1,2-a]pyrazine (16)**

1-Bromo-3-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and imidazo[1,2-a]pyrazine (0.179 g, 1.5 mmol) affords **16** in 91% (0.254 g) yield as a yellow solid: mp 84-86 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.12 (d,  $J = 1.3$  Hz, 1H), 8.19 (dd,  $J = 4.7, 1.4$  Hz, 1H), 7.90 (d,  $J = 4.7$  Hz, 1H), 7.87 (s, 1H), 7.57 (t,  $J = 8.0$  Hz, 1H), 7.49 (d,  $J = 7.8$  Hz, 1H), 7.40 (s, 1H), 7.30 (dd,  $J = 8.2, 2.0$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.0, 144.8, 141.6, 135.0, 131.1, 130.4, 129.9, 126.2, 125.4, 121.3, 120.5 (q,  $J = 258.1$  Hz), 120.4, 116.1.

LRMS calcd for  $\text{M}^+$   $\text{C}_{13}\text{H}_8\text{F}_3\text{N}_3\text{O}$  279, found 279.

### **1,2-Dimethyl-5-(2-(trifluoromethoxy)phenyl)imidazole (17)**

1-Bromo-2-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 1,2-dimethylimidazole (0.144 g, 1.5 mmol) affords **17** in 87% (0.223 g) yield as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.46-7.39 (m, 1H), 7.37-7.33 (m, 3H), 6.93 (s, 1H), 3.37 (s, 3H), 2.44 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  147.9 (q,  $J = 1.5$  Hz), 146.2, 132.8, 130.0, 128.1, 127.5, 127.0, 124.3, 120.9 (q,  $J = 1.5$  Hz), 120.7 (q,  $J = 257.4$  Hz), 31.2, 13.8.

LRMS calcd for  $\text{M}^+$   $\text{C}_{12}\text{H}_{11}\text{F}_3\text{N}_2\text{O}$  256, found 256.

### **3-(2-(Trifluoromethoxy)phenyl)imidazo[1,2-a]pyridine (18)**

1-Bromo-2-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and imidazo[1,2-a]pyridine (0.177 g, 1.5 mmol) affords **18** in 89% (0.247 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.88 (d,  $J = 7.0$  Hz, 1H), 7.68 (s, 1H), 7.64 (d,  $J = 7.0$  Hz, 1H), 7.53-7.34 (m, 4H), 7.18 (dd,  $J = 6.9, 7.8$  Hz, 1H), 6.76 (t,  $J = 6.9$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  147.1 (q,  $J = 1.5$  Hz), 146.2, 134.1, 132.0, 130.2, 127.4, 124.6, 124.1, 122.6, 121.3 (q,  $J = 1.5$  Hz), 120.4, 120.3 (q,  $J = 258.5$  Hz), 118.0, 112.4.

LRMS calcd for  $\text{M}^+$   $\text{C}_{14}\text{H}_9\text{F}_3\text{N}_2\text{O}$  278, found 278.

### **3-(3-Fluoro-4-(trifluoromethoxy)phenyl)imidazo[1,2-b]pyridazine (19)**

1-Bromo-3-fluoro-4-(trifluoromethoxy)benzene (0.259 g, 1 mmol) and imidazo[1,2-b]pyridazine (0.179 g, 1.5 mmol) affords **19** in 93% (0.276 g) yield as a yellow solid: mp 99-101 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.42 (d,  $J = 4.2$  Hz, 1H), 8.12-8.05 (m, 2H), 8.03 (d,  $J = 9.1$  Hz, 1H), 7.83 (d,  $J = 8.5$  Hz, 1H), 7.40 (t,  $J = 8.5$  Hz, 1H), 7.12 (dd,  $J = 9.1, 4.4$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  154.6 (d,  $J = 251.8$  Hz), 143.2, 140.7, 136.7 (dq,  $J = 12.6, 2.0$  Hz), 133.6, 129.2 (d,  $J = 8.0$  Hz), 126.4, 126.3, 124.0 (d,  $J = 0.6$  Hz), 122.7 (d,  $J = 3.7$  Hz), 120.6 (qd,  $J = 259.0, 0.7$  Hz), 117.0, 115.3 (d,  $J = 21.2$  Hz).

LRMS calcd for  $\text{M}^+$   $\text{C}_{13}\text{H}_7\text{F}_4\text{N}_3\text{O}$  297, found 297.

### **5-(2-Chloro-5-(trifluoromethoxy)phenyl)-2-isopropyl-4-methylthiazole (20)**

1-Bromo-2-chloro-5-(trifluoromethoxy)benzene (0.275 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **20** in 89% (0.299 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.48 (d,  $J = 8.8$  Hz, 1H), 7.23 (s, 1H), 7.17 (d,  $J = 8.8$  Hz, 1H), 3.28 (sept.,  $J = 7.6$  Hz, 1H), 2.27 (s, 3H), 1.41 (d,  $J = 7.6$  Hz, 6H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  177.4, 150.1, 147.4 (q,  $J = 2.0$  Hz), 133.2, 133.0, 131.2, 125.2 (q,  $J = 1.0$  Hz), 122.1 (q,  $J = 1.0$  Hz), 118.7, 120.4 (q,  $J = 258.2$  Hz), 33.5, 23.2, 16.0.

LRMS calcd for  $\text{M}^+$   $\text{C}_{14}\text{H}_{13}\text{ClF}_3\text{NOS}$  335, found 335.

### **3-(2-Chloro-5-(trifluoromethoxy)phenyl)imidazo[1,2-b]pyridazine (21)**

1-Bromo-2-chloro-5-(trifluoromethoxy)benzene (0.275 g, 1 mmol) and imidazo[1,2-b]pyridazine (0.179 g, 1.5 mmol) affords **21** in 92% (0.289 g) yield as a yellow solid: mp 85-87 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.36 (d,  $J = 4.2$  Hz, 1H), 8.08 (s, 1H), 8.04 (dd,  $J = 9.1, 1.6$  Hz, 1H), 7.65 (d,  $J = 2.7$  Hz, 1H), 7.56 (d,  $J = 8.8$  Hz, 1H), 7.21 (dd,  $J = 3.0, 1.2$  Hz, 1H), 7.11 (dd,  $J = 9.2, 4.5$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  147.5 (q,  $J = 2.0$  Hz), 143.2, 139.8, 135.3, 132.2, 131.4, 129.0, 126.2, 125.0, 124.2 (q,  $J = 0.9$  Hz), 122.2 (q,  $J = 0.9$  Hz), 120.4 (d,  $J = 259.0$  Hz), 117.3.

LRMS calcd for  $\text{M}^+$   $\text{C}_{13}\text{H}_7\text{ClF}_3\text{N}_3\text{O}$  313, found 313.

#### 4-(Imidazo[1,2-*b*]pyridazin-3-yl)-2-(trifluoromethoxy)benzaldehyde (22)

4-Bromo-2-(trifluoromethoxy)benzaldehyde (0.269 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **22** in 92% (0.286 g) yield as a yellow solid: mp 123-125 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  10.32 (s, 1H), 8.47 (dd,  $J = 4.4, 1.6$  Hz, 1H), 8.32-8.27 (m, 1H), 8.20 (s, 1H), 8.09 (dm,  $J = 9.1$  Hz, 1H), 8.04 (dd,  $J = 9.1, 1.7$  Hz, 1H), 7.99 (d,  $J = 8.2$  Hz, 1H), 7.16 (dd,  $J = 9.2, 4.5$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  186.8, 151.2 (q,  $J = 2.0$  Hz), 143.4, 141.5, 136.0, 134.9, 129.2, 127.0, 126.4, 125.9, 124.5, 120.5 (q,  $J = 259.2$  Hz), 118.4 (q,  $J = 1.3$  Hz), 117.6.

LRMS calcd for  $\text{M}^+$   $\text{C}_{14}\text{H}_8\text{F}_3\text{N}_3\text{O}_2$  307, found 307.

#### 4-(Benzo[*b*]thiophen-2-yl)-2-(trifluoromethoxy)benzaldehyde (23)

4-Bromo-2-(trifluoromethoxy)benzaldehyde (0.269 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **23** in 84% (0.270 g) yield as a yellow solid: mp 94-96 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  10.37 (s, 1H), 8.02 (d,  $J = 8.1$  Hz, 1H), 7.89-7.82 (m, 2H), 7.76 (d,  $J = 8.4$  Hz, 1H), 7.72 (s, 1H), 7.67-7.65 (m, 1H), 7.43-7.37 (m, 2H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  186.9, 151.4, 141.9, 141.0, 140.3, 129.8, 127.6, 125.8, 125.3, 125.2, 124.5, 122.8, 122.6, 120.5 (q,  $J = 259.2$  Hz).

LRMS calcd for  $\text{M}^+$   $\text{C}_{16}\text{H}_9\text{F}_3\text{O}_2\text{S}$  322, found 322.

#### 2-(4-(Difluoromethoxy)phenyl)benzo[*b*]thiophene (24)

1-Bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **24** in 77% (0.213 g) yield as a pink solid: mp 197-199 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.83 (d,  $J = 8.2$  Hz, 1H), 7.78 (d,  $J = 8.2$  Hz, 1H), 7.71 (d,  $J = 8.5$  Hz, 2H), 7.50 (s, 1H), 7.37 (t,  $J = 7.8$  Hz, 1H), 7.33 (t,  $J = 7.8$  Hz, 1H), 7.19 (d,  $J = 8.5$  Hz, 2H), 6.55 (t,  $J = 73.7$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  151.2 (t,  $J = 3.0$  Hz), 143.0, 140.8, 139.6, 131.9, 128.0, 124.8, 124.6, 123.8, 122.4, 120.2 (t,  $J = 0.8$  Hz), 119.8, 115.9 (t,  $J = 260.6$  Hz).

LRMS calcd for  $\text{M}^+$   $\text{C}_{15}\text{H}_{10}\text{F}_2\text{OS}$  276, found 276.

#### 5-(4-(Difluoromethoxy)phenyl)-1,2-dimethylimidazole (25)

1-Bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and 1,2-dimethylimidazole (0.144 g, 1.5 mmol) affords **25** in 72% (0.171 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.35 (d,  $J = 8.2$  Hz, 2H), 7.18 (d,  $J = 8.2$  Hz, 2H), 6.94 (s, 1H), 6.55 (t,  $J = 73.7$  Hz, 1H), 3.51 (s, 3H), 2.45 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.7 (t,  $J = 3.0$  Hz), 146.3, 132.6, 130.2, 128.1, 126.3, 120.0 (t,  $J = 0.8$  Hz), 115.9 (t,  $J = 260.5$  Hz), 31.4, 13.9.

LRMS calcd for  $\text{M}^+$   $\text{C}_{12}\text{H}_{12}\text{F}_2\text{N}_2\text{O}$  238, found 238.

### 3-(4-(Difluoromethoxy)phenyl)imidazo[1,2-a]pyridine (26)

1-Bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and imidazo[1,2-a]pyridine (0.177 g, 1.5 mmol) affords **26** in 86% (0.224 g) yield as a white solid: mp 87-89 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.22 (d,  $J = 7.0$  Hz, 1H), 7.64 (s, 1H), 7.63 (d,  $J = 7.0$  Hz, 1H), 7.50 (d,  $J = 8.5$  Hz, 2H), 7.25 (d,  $J = 8.5$  Hz, 2H), 7.16 (dd,  $J = 6.9, 7.8$  Hz, 1H), 6.77 (t,  $J = 6.9$  Hz, 1H), 6.57 (t,  $J = 73.6$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.8 (t,  $J = 3.0$  Hz), 146.2, 132.7, 129.6, 126.6, 124.6, 124.4, 123.1, 120.4 (t,  $J = 0.8$  Hz), 118.3, 115.8 (t,  $J = 260.6$  Hz), 112.7.

LRMS calcd for  $\text{M}^+$   $\text{C}_{14}\text{H}_{10}\text{F}_2\text{N}_2\text{O}$  260, found 260.

### 3-(4-(Difluoromethoxy)phenyl)imidazo[1,2-b]pyridazine (27)

1-Bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and imidazo[1,2-b]pyridazine (0.179 g, 1.5 mmol) affords **27** in 93% (0.243 g) yield as a yellow solid: mp 113-115 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.38 (d,  $J = 4.2$  Hz, 1H), 8.08-7.97 (m, 4H), 7.23 (d,  $J = 8.5$  Hz, 2H), 7.05 (dd,  $J = 9.1, 4.4$  Hz, 1H), 6.56 (t,  $J = 73.7$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  150.8 (t,  $J = 2.8$  Hz), 143.0, 140.2, 132.8, 128.4, 127.6, 126.1, 126.0, 119.8, 116.5, 115.9 (t,  $J = 260.5$  Hz).

LRMS calcd for  $\text{M}^+$   $\text{C}_{13}\text{H}_9\text{F}_2\text{N}_3\text{O}$  261, found 261.

### 5-(4-(Difluoromethoxy)phenyl)-2-isobutylthiazole (28)

1-Bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and 2-isobutylthiazole (0.212 g, 1.5 mmol) affords **28** in 91% (0.257 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.78 (s, 1H), 7.51 (d,  $J = 8.5$  Hz, 2H), 7.14 (d,  $J = 8.5$  Hz, 2H), 6.52 (t,  $J = 73.7$  Hz, 1H), 2.88 (d,  $J = 7.6$  Hz, 2H), 2.20-2.15 (m, 1H), 1.02 (d,  $J = 7.6$  Hz, 6H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.0, 150.8 (t,  $J = 2.8$  Hz), 137.9, 137.3, 129.2, 128.1, 120.2 (t,  $J = 0.8$  Hz), 115.8 (t,  $J = 260.5$  Hz), 42.6, 29.9, 22.4.

LRMS calcd for  $\text{M}^+$   $\text{C}_{14}\text{H}_{15}\text{F}_2\text{NOS}$  283, found 283.

### 5-(4-(Difluoromethoxy)phenyl)-2-isopropyl-4-methylthiazole (29)

1-Bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **29** in 90% (0.255 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.40 (d,  $J$  = 8.5 Hz, 2H), 7.16 (d,  $J$  = 8.5 Hz, 2H), 6.54 (t,  $J$  = 73.7 Hz, 1H), 3.28 (sept.,  $J$  = 7.6 Hz, 1H), 2.44 (s, 3H), 1.41 (d,  $J$  = 7.6 Hz, 6H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  175.7, 150.6 (t,  $J$  = 2.9 Hz), 147.2, 130.7, 130.0, 129.3, 119.8 (t,  $J$  = 0.8 Hz), 115.9 (t,  $J$  = 260.5 Hz), 33.5, 23.4, 16.2.

LRMS calcd for  $\text{M}^+$   $\text{C}_{14}\text{H}_{15}\text{F}_2\text{NOS}$  283, found 283.

### **2-(2-(Difluoromethoxy)phenyl)benzo[*b*]thiophene (30)**

1-Bromo-2-(difluoromethoxy)benzene (0.223 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **30** in 79% (0.218 g) yield as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.95-7.84 (m, 2H), 7.81-7.75 (m, 2H), 7.48-7.27 (m, 5H), 6.57 (t,  $J$  = 7.3 Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.1 (t,  $J$  = 2.5 Hz), 140.2, 140.1, 138.3, 130.7, 129.4, 126.7, 126.1, 124.8, 124.6, 124.0, 123.9, 122.1, 120.3, 116.3 (t,  $J$  = 260.4 Hz).

LRMS calcd for  $\text{M}^+$   $\text{C}_{15}\text{H}_{10}\text{F}_2\text{OS}$  276, found 276.

### **3-(2-(Difluoromethoxy)phenyl)imidazo[1,2-*a*]pyridine (31)**

1-Bromo-2-(difluoromethoxy)benzene (0.223 g, 1 mmol) and imidazo[1,2-*a*]pyridine (0.177 g, 1.5 mmol) affords **31** in 86% (0.224 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.88 (d,  $J$  = 6.0 Hz, 1H), 7.66 (s, 1H), 7.62 (d,  $J$  = 9.0 Hz, 1H), 7.48-7.36 (m, 2H), 7.32-7.26 (m, 2H), 7.15 (dd,  $J$  = 8.1, 1.3 Hz, 1H), 6.74 (t,  $J$  = 6.8 Hz, 1H), 6.31 (t,  $J$  = 73.4 Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.7 (t,  $J$  = 2.6 Hz), 146.1, 133.8, 132.0, 130.2, 126.0, 124.5, 124.4, 121.4, 121.0, 119.9, 117.8, 115.5 (t,  $J$  = 261.6 Hz), 112.1.

LRMS calcd for  $\text{M}^+$   $\text{C}_{14}\text{H}_{10}\text{F}_2\text{N}_2\text{O}$  260, found 260.

### **3-(2-(Difluoromethoxy)phenyl)imidazo[1,2-*b*]pyridazine (32)**

1-Bromo-2-(difluoromethoxy)benzene (0.223 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **32** in 91% (0.238 g) yield as a white solid: mp 85-87 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.30 (dd,  $J$  = 4.2, 1.7 Hz, 1H), 8.02 (s, 1H), 7.97 (dd,  $J$  = 9.1, 1.7 Hz, 1H), 7.90 (dd,  $J$  = 7.6, 1.7 Hz, 1H), 7.45-7.22 (m, 3H), 7.02 (dd,  $J$  = 9.1, 4.4 Hz, 1H), 6.50 (t,  $J$  = 73.8 Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.0 (t,  $J$  = 2.5 Hz), 142.8, 139.6, 134.9, 131.0, 129.8, 125.9, 125.4, 124.0, 120.7 (t,  $J$  = 0.9 Hz), 119.4 (t,  $J$  = 0.8 Hz), 116.7, 116.2 (t,  $J$  = 259.5 Hz).

LRMS calcd for  $\text{M}^+$   $\text{C}_{13}\text{H}_9\text{F}_2\text{N}_3\text{O}$  261, found 261.

### **3-(2-(Difluoromethoxy)phenyl)imidazo[1,2-*a*]pyrazine (33)**



1-Bromo-2-(difluoromethoxy)benzene (0.223 g, 1 mmol) and imidazo[1,2-*a*]pyrazine (0.179 g, 1.5 mmol) affords **33** in 93% (0.243 g) yield as a white solid: mp 98-100 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.13 (d, *J* = 0.7 Hz, 1H), 7.91-7.84 (m, 3H), 7.55-7.48 (m, 2H), 7.42-7.33 (m, 2H), 6.37 (t, *J* = 73.8 Hz, 1H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 148.8 (t, *J* = 2.5 Hz), 144.2, 141.5, 135.9, 132.0, 131.1, 129.6, 126.3, 122.7, 120.2, 120.0, 117.7, 115.5 (t, *J* = 262.9 Hz).

LRMS calcd for M<sup>+</sup> C<sub>13</sub>H<sub>9</sub>F<sub>2</sub>N<sub>3</sub>O 261, found 261.

### **2-(2-(Difluoromethoxy)phenyl)-3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran (34)**

1-Bromo-2-(difluoromethoxy)benzene (0.223 g, 1 mmol) and menthofuran (0.225 g, 1.5 mmol) affords **34** in 92% (0.268 g) yield as a yellow solid: mp 54-56 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.50 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.36-7.21 (m, 3H), 6.44 (t, *J* = 75.0 Hz, 1H), 2.74 (dd, *J* = 16.3, 6.3 Hz, 1H), 2.50-2.37 (m, 2H), 2.30-2.21 (m, 1H), 2.01 (s, 3H), 2.00-1.97 (m, 1H), 1.93-1.86 (m, 1H), 1.50-1.37 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 150.8, 148.2, 142.9, 130.7, 128.7, 125.8, 124.9, 121.1, 119.3, 118.8, 116.7 (t, *J* = 258.7 Hz), 31.6, 31.4, 29.8, 21.7, 20.3, 9.6.

LRMS calcd for M<sup>+</sup> C<sub>17</sub>H<sub>18</sub>F<sub>2</sub>O<sub>2</sub> 292, found 292.

### **5-(Benzo[*b*]thiophen-2-yl)-2,2-difluorobenzo[*d*][1,3]dioxole (35)**

5-Bromo-2,2-difluorobenzo[*d*][1,3]dioxole (0.237 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **35** in 62% (0.180 g) yield as a white solid: mp 151-153 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.46 (s, 1H), 7.45-7.40 (m, 2H), 7.40-7.30 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 1H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 144.5 (t, *J* = 0.8 Hz), 143.8 (t, *J* = 0.9 Hz), 142.8, 140.6, 139.6, 131.8 (t, *J* = 255.6 Hz), 131.0, 124.9, 124.8, 123.8, 122.4, 122.3, 120.1, 109.9, 107.9.

LRMS calcd for M<sup>+</sup> C<sub>15</sub>H<sub>8</sub>F<sub>2</sub>O<sub>2</sub>S 290, found 290.

### **3-(2,2-Difluorobenzo[*d*][1,3]dioxol-5-yl)imidazo[1,2-*b*]pyridazine (36)**

5-Bromo-2,2-difluorobenzo[*d*][1,3]dioxole (0.237 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **36** in 86% (0.236 g) yield as a yellow solid: mp 113-115 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.40 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.04-7.98 (m, 2H), 7.88 (d, *J* = 1.7 Hz, 1H), 7.71 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 9.1, 4.4 Hz, 1H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 144.1 (t, *J* = 0.8 Hz), 143.3 (t, *J* = 0.9 Hz), 143.1, 140.3, 132.9, 131.8 (t, *J* = 255.6 Hz), 127.4, 126.3, 124.8, 122.9, 116.6, 109.8, 108.3.

LRMS calcd for M<sup>+</sup> C<sub>13</sub>H<sub>7</sub>F<sub>2</sub>N<sub>3</sub>O<sub>2</sub> 275, found 275.

### **5-(2,2-Difluorobenzo[*d*][1,3]dioxol-5-yl)-2-isopropyl-4-methylthiazole (37)**

5-Bromo-2,2-difluorobenzo[d][1,3]dioxole (0.237 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **37** in 81% (0.240 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.15-7.05 (m, 3H), 3.28 (sept.,  $J = 7.6$  Hz, 1H), 2.42 (s, 3H), 1.41 (d,  $J = 7.6$  Hz, 6H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  175.9, 147.6, 144.0, 143.3, 131.8 (t,  $J = 255.6$  Hz), 129.1, 128.7, 124.9, 110.6, 109.6, 33.5, 23.3, 16.1.

LRMS calcd for  $\text{M}^+$   $\text{C}_{14}\text{H}_{13}\text{F}_2\text{NO}_2\text{S}$  297, found 297.

### 2-(4-(1,1,2,2-Tetrafluoroethoxy)phenyl)benzo[b]thiophene (38)

1-Bromo-4-(1,1,2,2-tetrafluoroethoxy)benzene (0.273 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **38** in 60% (0.196 g) yield as a white solid: mp 201-203 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.83 (d,  $J = 7.5$  Hz, 1H), 7.79 (d,  $J = 7.5$  Hz, 1H), 7.73 (d,  $J = 8.8$  Hz, 2H), 7.52 (s, 1H), 7.40-7.29 (m, 2H), 7.27 (d,  $J = 8.8$  Hz, 2H), 5.94 (tt,  $J = 53.1, 2.8$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.8 (t,  $J = 1.7$  Hz), 142.8, 140.7, 139.7, 133.0, 127.9, 124.8, 124.7, 123.8, 122.4, 122.2, 120.2, 116.5 (tt,  $J = 272.1, 28.7$  Hz), 107.8 (tt,  $J = 251.8, 41.3$  Hz).

LRMS calcd for  $\text{M}^+$   $\text{C}_{16}\text{H}_{10}\text{F}_4\text{OS}$  326, found 326.

### 3-(4-(1,1,2,2-Tetrafluoroethoxy)phenyl)imidazo[1,2-*b*]pyridazine (39)

1-Bromo-4-(1,1,2,2-tetrafluoroethoxy)benzene (0.273 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **39** in 87% (0.270 g) yield as a yellow solid: mp 79-81 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.36 (dd,  $J = 4.2, 1.7$  Hz, 1H), 8.05 (d,  $J = 8.8$  Hz, 2H), 8.01 (s, 1H), 7.98 (dd,  $J = 9.1, 1.7$  Hz, 1H), 7.30 (d,  $J = 8.8$  Hz, 2H), 7.03 (dd,  $J = 9.1, 4.4$  Hz, 1H), 5.94 (tt,  $J = 53.1, 2.8$  Hz, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  148.3 (t,  $J = 1.7$  Hz), 143.0, 140.3, 132.9, 128.1, 127.4, 127.1, 126.1, 121.8, 116.5 (tt,  $J = 272.1, 28.7$  Hz), 107.8 (tt,  $J = 251.8, 41.4$  Hz).

LRMS calcd for  $\text{M}^+$   $\text{C}_{14}\text{H}_9\text{F}_4\text{N}_3\text{O}$  311, found 311.

### 2-Isopropyl-4-methyl-5-(4-(1,1,2,2-tetrafluoroethoxy)phenyl)thiazole (40)

1-Bromo-4-(1,1,2,2-tetrafluoroethoxy)benzene (0.273 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **40** in 89% (0.296 g) yield as a yellow oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.41 (d,  $J = 8.5$  Hz, 2H), 7.23 (d,  $J = 8.5$  Hz, 2H), 5.92 (tt,  $J = 53.1, 2.8$  Hz, 1H), 3.27 (sept.,  $J = 7.6$  Hz, 1H), 2.44 (s, 3H), 1.40 (d,  $J = 7.6$  Hz, 6H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  175.7, 148.2 (t,  $J = 1.7$  Hz), 147.4, 131.2, 130.5, 129.1, 121.8, 116.6 (tt,  $J = 272.1, 28.7$  Hz), 107.8 (tt,  $J = 251.8, 41.4$  Hz), 33.5, 23.3, 16.2.

LRMS calcd for  $\text{M}^+$   $\text{C}_{15}\text{H}_{15}\text{F}_4\text{NOS}$  333, found 333.

## Supporting information

Copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of new compounds and  $^1\text{H}$  NMR spectra of known compounds.

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