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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02258 • Publication Date (Web): 29 Oct 2019

Regioselective Synthesis of Functionalized 3- or 5-Fluoroalkyl Isoxazoles and Pyrazoles from Fluoroalkyl Ynones and Binucleophiles

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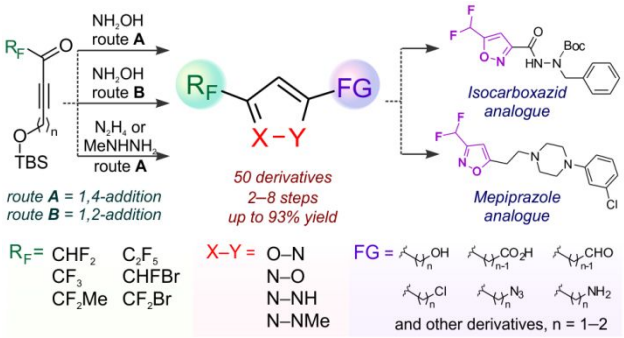
KEYWORDS: Isoxazole; pyrazole; organofluorine compounds; cyclization; ynone



ABSTRACT. A facile synthetic route towards either 3- or 5-fluoroalkyl-substituted isoxazoles or pyrazoles containing an additional functionalization site was developed and applied on a multigram scale. The elaborated approach extends the scope of fluoroalkyl substituents for introduction into the heterocyclic moiety, and uses convenient transformations of the side chain for incorporation of fluoroalkyl substituted azoles into the structures of biologically active molecules. The utility of the obtained building blocks for isosteric replacement of alkyl-substituted isoxazole and pyrazole was shown by the synthesis of fluorinated Isocarboxazid and Mepiprazole analogues.

INTRODUCTION

Importance of isoxazoles and pyrazoles for discovery of new therapeutics and agricultural ingredients was highlighted in a number of reviews.[1–6] Because of advantageous capability of fluorinated substituents to modulate drug-related properties,[7–13] their incorporation to azoles provide promising opportunity for drug discovery. For example, substitution of *tert*-butyl group at isoxazole ring of $BRAF^{V600E}$ inhibitor **1** to its fluorinated analogue in **3** prevented the metabolic oxidation of **1** to significantly less active derivative **2** (Figure 1, **A**)[14] and led to the discovery of clinical candidate Agerafenib. In addition to that, the fluoroalkylated pyrazole moiety is present in structures of marketed anti-inflammatory drug Celecoxib,[15] veterinary drugs Deracoxib[16] and Mavacoxib[17] (also from coxib series, Figure 1, **B**), as well as in structures of marketed agrochemicals Bixafen, Sedaxane, Isopyrazam, and Fluxapyroxad.[5]

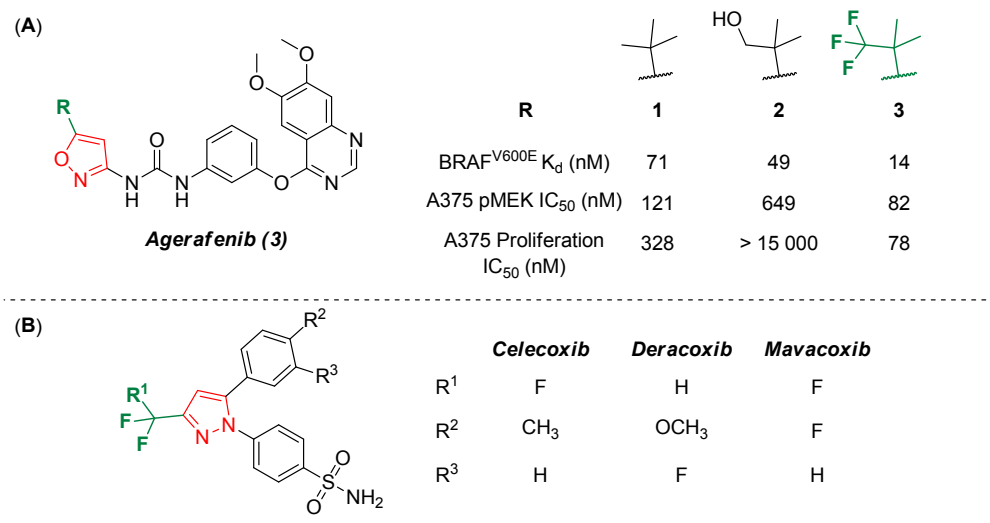
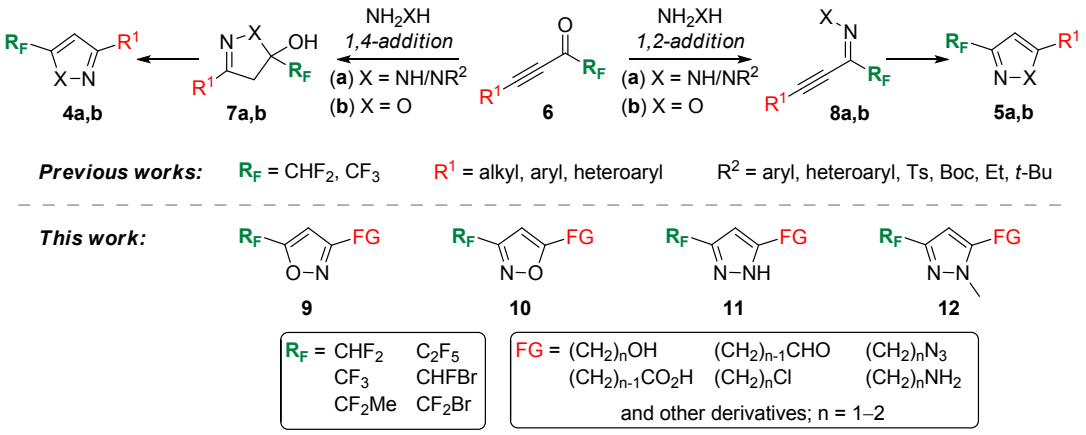


Figure 1. (**A**) Influence of fluoroalkyl substituent on the potency of Agerafenib and its analogues. (**B**) Examples of marketed drugs containing fluoroalkyl-substituted pyrazole moiety.

Among the previously reported approaches to 3- and 5-fluoroalkyl-substituted isoxazoles, the most important are cycloaddition of nitrile oxides with either 1-substituted vinyl bromides or monosubstituted alkynes,[18–22] and reaction of fluoroalkyl-substituted diketones and their synthetic equivalents with NH_2OH.[23–26] However, both these methods were studied for a limited scope of substrates and in several cases were accompanied with regioselectivity issues. In contrast to isoxazoles, the synthetic methods towards fluoroalkyl-substituted pyrazoles are more comprehensively studied.[27]

Recently, synthesis of 5-CF_3- and 3-CF_3-pyrazoles **4a** and **5a** by cyclocondensation of (hetero)aryl- and alkyl-substituted 1,1,1-trifluorobut-3-yn-2-ones **6** with mono- and unsubstituted hydrazines (Scheme 1) was reported in a series of works by Nenajdenko`s and Hseih`s research groups.[28–32] Surprisingly, similar reaction of **6** with NH_2OH leading to the formation of fluoroalkyl-substituted isoxazoles **4b** and **5b** was mentioned just in two patents[33,34] and was studied only in a single article by Linderman and Kirillos in 1989.[35] In their work, the synthesis of only 3- and 5-octyl-substituted isoxazoles bearing either CF_3 or CHF_2 group was achieved. Yet, the suggested cyclization conditions (either NaOMe in MeOH for preparation of **7b** or AcOH with cat. HCl for **8b**) would be hardly adaptable for the preparation of functionalized derivatives. Additionally, increased stability of fluoroalkyl-substituted hemiketal moiety in hydroxypyrazolines **7a** and hydroxyisoxazolines **7b** was previously



Scheme 1. Synthesis of 3- and 5-fluoroalkyl substituted pyrazoles and isoxazoles from ynones **6**, and compounds **9**–**12** attempted in this work.

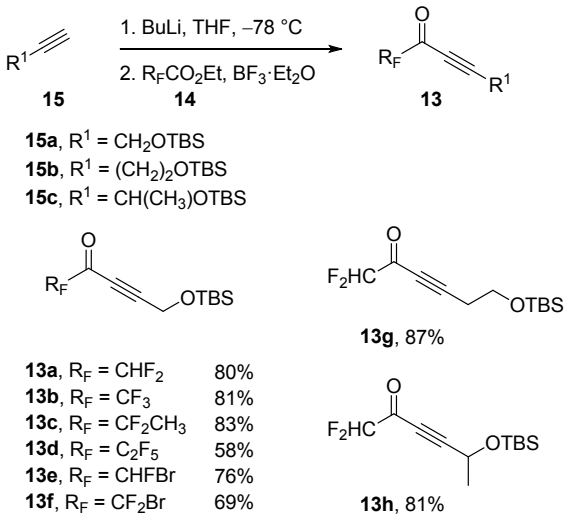
reported to complicate the dehydration step;[36–38] therefore, revision of the dehydration conditions was necessary.

In this report, we have elaborated an efficient approach towards the synthesis of azoles **9**–**12** (Scheme 1) and applied it on a multigram scale. The reaction sequence was designed to meet three main objectives. First, we aimed at the method that could extend the diversity of fluoroalkyl substituents and use commercially available materials as fluorine-containing precursors. Second, the reaction sequence should result in azoles containing various functional groups, which may allow the incorporation of the final building blocks to the structures of more complex biologically active molecules by

commonly used chemical transformations. The third goal was the preparation of all target products from common starting reagents as single regioisomers. In addition to that, the utility of the obtained compounds for isosteric replacement of 5-methylisoxazole and 5-methyl-1*H*-pyrazole moieties was demonstrated by synthesis of fluorinated Isocarboxazid[39] and Mepiprazole[40] analogues.

RESULTS AND DISCUSSION

Synthesis of starting ynones. Our work commenced with synthesis of a series of ynones **13** (Scheme 2). In order to provide diversity of the fluoroalkyl substituents, the reaction of commercially available fluorinated acetic acid esters **14** with deprotonated terminal alkynes **15** was carried out. A selection of alkynes **15** containing TBS-protected alcohol moiety was envisaged to ensure the stability of the side chain group towards heterocyclization reaction conditions and its further mild removal. Thus, the resulting azole with a free OH group can be further transformed to other functionalized derivatives by commonly used reactions.



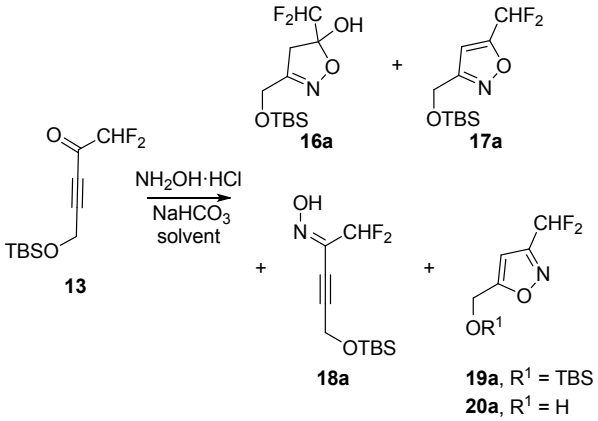
Scheme 2. Preparation of ynones **13.**

To prepare ynones **13**, reaction of esters **14** and lithium acetylenides (obtained *in situ* from **15** and *n*-BuLi) was envisaged. It was found that at these conditions, complex mixtures were formed. Nonetheless, these side reactions could be suppressed when $BF_3{\cdot}OEt_2$ was introduced into the reaction mixture[32,41] immediately after the addition of esters **14**, and the target compounds **13a–h** were obtained in 58–87% yield. Importantly, when $BF_3{\cdot}OEt_2$ was introduced to the reaction mixture more than one hour after the addition of **14**, a significant yield decrease was observed for the products **13.**

Synthesis of 5-fluoroalkyl isoxazoles. Next, the 1,4-addition of NH_2OH to ynone **13a** was studied in a series of solvents on 0.5 g scale (Table 1). When ynone **13a** was

mixed with 1.2 eq of $NH_2OH{\cdot}HCl$, no conversion of the starting material was observed in any solvent system mentioned in Table 1. Therefore, addition of 1.2 eq of $NaHCO_3$ was essential for the reaction to proceed. Although alcohol and alcohol – H_2O solvent systems are commonly used for the synthesis of non-fluorinated hydroxyisoxazolines,[42] in the case of the ynone **13a**, formation of a mixture containing **16a–20a** was indicated by ^1H NMR and ^{19}F NMR at both rt and 0 °C. Although switching to polar aprotic solvents such as DMF and CH_3CN increased the yield of

Table 1. Optimization of reaction conditions for **16a** synthesis.



entry	solvent	T-re	**16a** yield, % [a,b]
1	MeOH–H_2O (1 : 1)	rt	23

2	MeOH–H_2O (1 : 1)	0 °C	51
3	DMF	0 °C	74
4	CH_3CN	0 °C	77
5	CH_2Cl_2	0 °C	91
6	CH_2Cl_2–H_2O (10 : 1)	0 °C	97
7	**THF**	**0 °C**	**99**

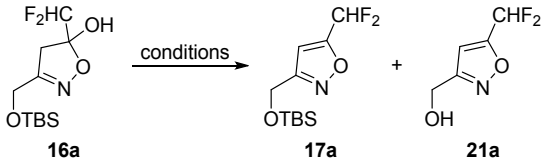
[a] Reaction yields were measured by ^1H NMR and ^{19}F NMR;

[b] The reactions were carried out on 0.5 g scale.

16a up to 74%, formation of the aforementioned byproducts was not eliminated completely. Instead, using nonpolar CH_2Cl_2 gave **16a** as a single product with 91% yield. In order to facilitate the heterogeneous reaction of $NaHCO_3$ with $NH_2OH{\cdot}HCl$ in CH_2Cl_2, the two-phase CH_2Cl_2–H_2O (10:1) system was used under vigorous stirring; this increased the product yield to 97%. Finally, the best result was achieved when a solution of ynone **16a** in THF was treated with a solution of pre-synthesized NH_2OH (from $NH_2OH{\cdot}HCl$ and $NaHCO_3$) in a minimal amount of H_2O (99% on 0.5 g scale and 84% on 200 g scale). Formation of hydroxyisoxazolines **16** instead of isoxazoles **17** in the reaction of ynones **13** with NH_2OH can be explained by modest aromaticity of

isoxazoles[43] along with electron-withdrawing effect of the fluoroalkyl substituents which stabilize hemiketals.[38]

Table 2. Optimization of reaction conditions for **17a** synthesis.



entry	conditions	**16a** conversion,[a,b] %	**17a** yield,[a] %	**21a** yield,[a] %
1	$(CF_3CO)_2O$ (1.2 equiv), py (2.5 equiv), CH_2Cl_2, –10 °C	80	33	14
2	$SOCl_2$ (1.2 equiv), NEt_3 (3 equiv), CH_2Cl_2, –10 °C	100	15	12
3	TsCl (1.1 equiv), py (2 equiv), CH_2Cl_2, 0 °C	38	0	0
4	Ac_2O (1.2 equiv), CH_2Cl_2, rt	30	21	0
5	H_2SO_4 (cat), MeOH, rt	100	0	0
6	Cationite KU-2-8 (20 wt. %), PhH, reflux	0	0	0
7	HBr (33 wt. % in AcOH), rt	100	0	61
8	KOH (3 equiv), EtOH, reflux	100	0	0

9	CDI (1.1 equiv), CH_3CN, reflux	100	84	0
10	CDI (1.1 equiv), CH_3CN, rt	100	91	0
11	**CDI (1.1 equiv), CH_2Cl_2, rt**	**100**	**97**[c]	**0**

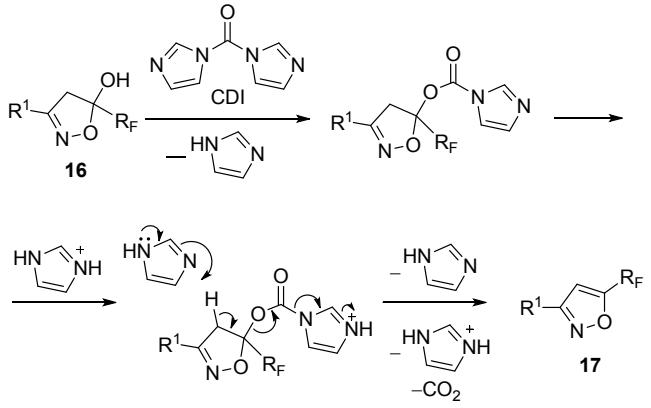
[a] The conversion of **16a** and yields of isoxazoles **17a** and **21a** were measured by ^1H NMR and ^{19}F NMR.

[b] The experiments were carried out on 0.5 g scale.

[c] 94% yield was achieved on 185 g scale.

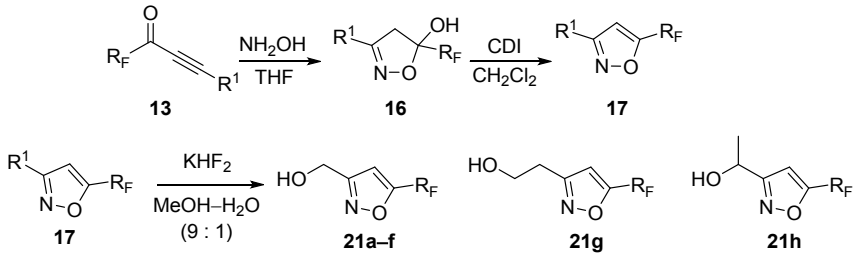
Further dehydration of hydroxyisoxazolines **16** to isoxazoles **17** required careful optimization of the reaction conditions, which were performed with 0.5 g of **16a** as a model substrate (Table 2). The evaluated methods included acylation and sulfonylation of alcohols followed by β-elimination (entries 1–4), as well as dehydration under acidic (entries 5–7) and basic (entry 8) conditions. In more detail, the unsuccessful experiments with both catalytic amounts of H_2SO_4 (entry 5) and 3 equiv of KOH (entry 8) resulted in the formation of mixtures of unidentified byproducts, whereas refluxing with strong cationite KU-2-8 (entry 6) had no effect on the starting reagent **16a**. Reaction of **16a** with TsCl (entry 3) gave only tosylated product and was not followed by further elimination.

Although some of the studied methods allowed the synthesis of compounds **17a** and **21a** either as single products or as a mixture, still all of them were inefficient for the multigram preparation of the target product **17a**. Thus, we have elaborated a new method for dehydration of hydroxyisoxazolines **16** with carbonyldiimidazole (CDI), which provided mild conditions for this transformation (entries 9–11). The best yield (97%) was achieved using 1.1 eq of CDI in CH_2Cl_2 at rt (entry 11). Moreover, the scale-up of this procedure to 185 g of **16a** resulted in 94% yield of the target product **17a**. A proposed mechanism of this reaction is given in Scheme 3.



Scheme 3. Proposed mechanism for the dehydration of hydroxyisoxazolines **16** with CDI.

Table 3. Synthesis of the compounds **16**, **17** and **21**.



entry	R^1	R_F	**16** (yield, %)	**17** (yield, %)	**21** (yield, %)
1	CH_2OTBS	CHF_2	**16a** (84)	**17a** (94)	**21a** (91)[a]
2	CH_2OTBS	CF_3	**16b** (83)	**17b** (91)	**21b** (70)[a]
3	CH_2OTBS	CF_2CH_3	**16c** (77)	**17c**[b]	**21c** (74)[c]
4	CH_2OTBS	C_2F_5	**16d** (75)	**17d** (89)	**21d** (87)[a]
5	CH_2OTBS	CHFBr	**16e** (85)	**17e** (85)	**21e** (81)
6	CH_2OTBS	CF_2Br	**16f** (73)	**17f** (83)	**21f** (-)
7	$(CH_2)_2OTBS$	CHF_2	**16g** (59)	**17g** (75)	**21g** (91)
8	$CH(CH_3)$ OTBS	CHF_2	**16h** (82)	**17h** (83)	**21h** (92)

[a] The three-step reaction sequence was carried out on 179–250 g scale.

[b] The compound was used in the next step without additional purification.

[c] The overall yield for two steps is given.

The optimized protocols for both steps were applied to ynones **13b–h**. As a result, hydroxyisoxazolines **16a–h** were obtained in 59–85% yield on a multigram scale and converted to isoxazoles **17a–h** in 75–94% yield (Table 3). Further removal of the silyl

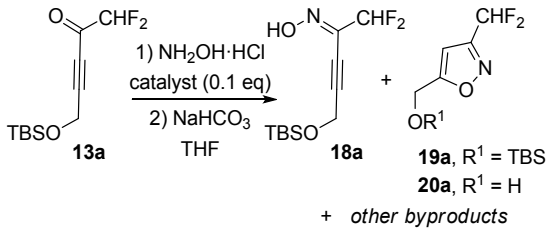
group using KHF_2 led to alcohols **21a–e,g,h** in 70–92% yield. The product **21f** could not be isolated in pure form due to its limited stability. In the case of alkyne **13g**, the reaction with NH_2OH led to a mixture of cyclization product **16g** and corresponding oxime in *ca.* 2:1 ratio, presumably due to less electron-withdrawing effect of the TBS-protected hydroxyethyl group as compared to CH_2OTBS. Thus, compound **16g** was obtained in 59% yield after separation by column chromatography.

Synthesis of 3-fluoroalkyl-substituted isoxazoles. The synthetic route to regioisomeric 3-fluoroalkyl-substituted isoxazoles relied on metal-catalyzed 1,2-addition of NH_2OH to ynones **13**, followed by cyclization of the intermediate oxime. Previous reports discussing analogous cyclization of non-fluorinated ynones through methyl- or benzyl-*O*-substituted and *O*-non-substituted oxime intermediates used Au(III),[44–48] Au(I),[48] Ag(I),[46,48] Cu(II),[48] Cu(I),[49,50] Pd(II),[51] and Fe(III)[52] catalysts. Therefore, salts of these transition metals (except for Au) were screened first for the reaction of **13a** with NH_2OH in THF (Table 4, entries 1–9). Generally, for these (entries 1–9) and other (entries 10–19) catalysts the reaction resulted in formation of oxime **18a**, TBS-deprotected derivative **20a** and other byproducts along with the target isoxazole **19a**. In the case of

$Pd(OAc)_2$, ynone **13a** was fully converted to a mixture of unidentified products. Conversely, the use of Ag(I) salts (entries 2–5) resulted in up to 67% yield of the target product **19a**. However, the high 33% proportion of the starting material along with byproducts was unsatisfactory. The better results were obtained in Cu(I) and Cu(II) catalyst series (entries 6–9). In particular, the cumulative yield of **19a** and **20a** obtained under CuI catalysis was 82%.

Although other transition metal catalysts also appeared to be moderately effective for oxime **18a** cyclization (up to 80% yield, entries 10–16), they did not surpass the results observed for Cu-based catalysts. Hence, the selection of the solvent and catalyst ratio was additionally studied using CuI. When the reaction was carried out in dioxane or dimethoxyethane, the yields of the products **19a** and **20a** were slightly lower as compared to the experiment carried out in THF, whereas the ratio of byproducts was increased. Optimization of the amount of CuI showed that usage of more than 0.10 equiv did not influence the reaction yield, while the usage of less than

Table 4. Catalyst screening for the preparation of **19a**.



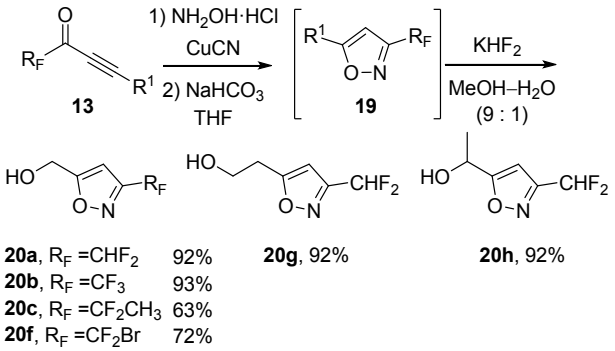
entry	catalyst	**19a** yield,[a] %	**20a** yield,[a] %
1	$Pd(OAc)_2$	0	0
2	$AgBF_4$	20	9
3	$AgNO_3$	23	11
4	AgOAc	25	8
5	$AgOSO_2CF_3$	67	0
6	CuCl	40	28
7	$CuBr_2$	68	4
8	$CuSO_4·5H_2O$	74	6
9	**CuI**	**75**	**7**
10	$Pd(PPh_3)_4$	30	0
11	$NiCl_2·6H_2O$	48	0
12	$Rh_2Cl_2(COD)_2$	56	0
13	$Co_2(CO)_8$	73	0
14	$CeCl_3$	75	0
15	$Zn(CN)_2$	76	0

16	$FeSO_4$	80	0
17	Cu_2O	87	0
18	$Cu(OAc)_2 \cdot H_2O$	89	0
19	**CuCN**	**90**	**0**

[a]Yield was determined from ^1H NMR and ^{19}F NMR spectra. The experiments were carried out on 0.5 g scale.

0.10 equiv slowed the reaction and facilitated formation of undesirable byproducts. Further survey of other Cu-based catalysts allowed achieving even higher yields using Cu_2O, $Cu(OAc)_2 \cdot H_2O$, and CuCN. These catalysts led to the product **19a** in 87–90% yield (entries 17–19) in a mixture with *ca.* 10% of oxime **18a**.

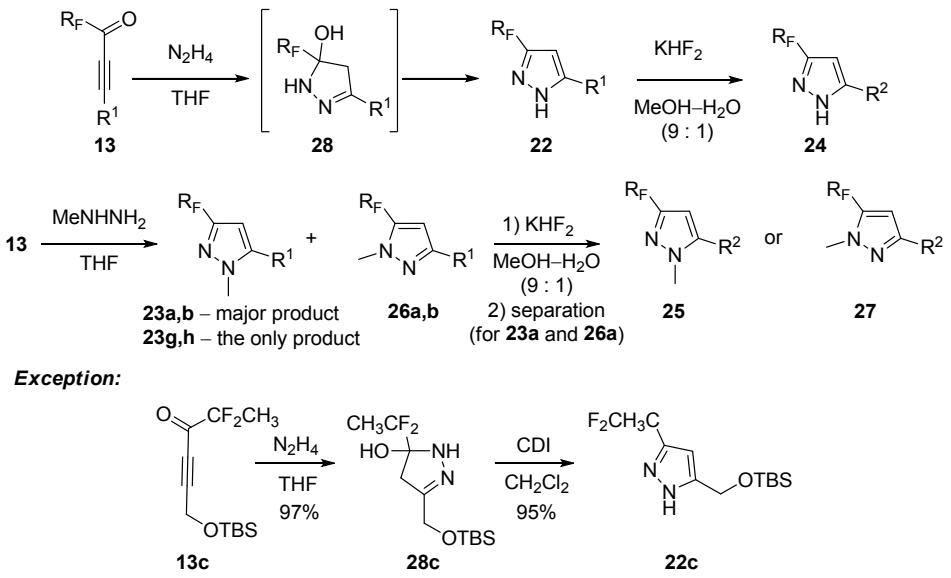
After ynones **13** were subjected to the reaction with NH_2OH under Cu(I)-catalysis, the crude products **19** were further deprotected with KHF_2 to give alcohols **20** (63–93% yield for 2 steps, Scheme 4), which were purified by distillation *in vacuo*. In all cases, CuCN was used as the catalyst at the first step, since it allowed retention of the highest isolated yields for the products **20** upon a scale-up. It should be noted that product **20f** appeared to be unstable, and gradually decomposed after storing at 0 °C for more than one week.



Scheme 4. Synthesis of alcohols **20**.

Synthesis of 3-fluoroalkyl-substituted pyrazoles. In addition to the synthesis of isoxazoles, the potential of 1-fluoroalkyl substituted ynones **13** was further demonstrated by the preparation of pyrazoles containing functionalized side chain. In particular, cyclization of ynones **13** with either N_2H_4 or $MeNHNH_2$ led to the compounds **22** and **23**, respectively, in 72–95% yield (Table 5). Further deprotection of these derivatives with KHF_2 gave alcohols **24** and **25** in up to 97% yield. It was also found that reaction of $MeNHNH_2$ with ynones **13** at 0 °C gave compounds **23g**

Table 5. Synthesis of pyrazoles **22–28**.



entry	R_F	R^1	**22**, **23** or **26** (yield, %)	R^2	**24**, **25** or **27** (yield, %)
1	CHF_2	CH_2OTBS	**22a** (95)[a]	CH_2OH	**24a** (97)
2	CHF_2	CH_2OTBS	**23a** (–)	CH_2OH	**25a** (89)[a,b,c]
3	CHF_2	CH_2OTBS	**26a** (–)	CH_2OH	**27a** (6) [a,b,c]
4	CF_3	CH_2OTBS	**23b** (86)[a,d]	CH_2OH	**25b** (94)
5	CF_3	CH_2OTBS	**26b** (10) [a,d]	CH_2OH	N/A
6	CF_2CH_3	CH_2OTBS	**22c** (92)[b]	CH_2OH	**24c** (95)
7	CF_2CH_3	CH_2OTBS	**23c** (92)	CH_2OH	N/A
8	C_2F_5	CH_2OTBS	**23d** (79)	CH_2OH	N/A
9	CF_2Br	CH_2OTBS	**23e** (72)	CH_2OH	N/A
10	CHF_2	$(CH_2)_2OTBS$	**22g** (–)	$(CH_2)_2OH$	**24g** (82)[b]
11	CHF_2	$(CH_2)_2OTBS$	**23g** (–)	$(CH_2)_2OH$	**25g** (77)[b]

12	CHF_2	$CH(CH_3)OTBS$	**22h** (93)	$CH(CH_3)OH$	**24h** (95)
13	CHF_2	$CH(CH_3)OTBS$	**23h** (88)	$CH(CH_3)OH$	**25h** (97)

[a] The reaction was carried out on 85–120 g scale.

[b] The yield for two steps is given.

[c] Isolated after separation of **25a** and **27a** by vacuum distillation

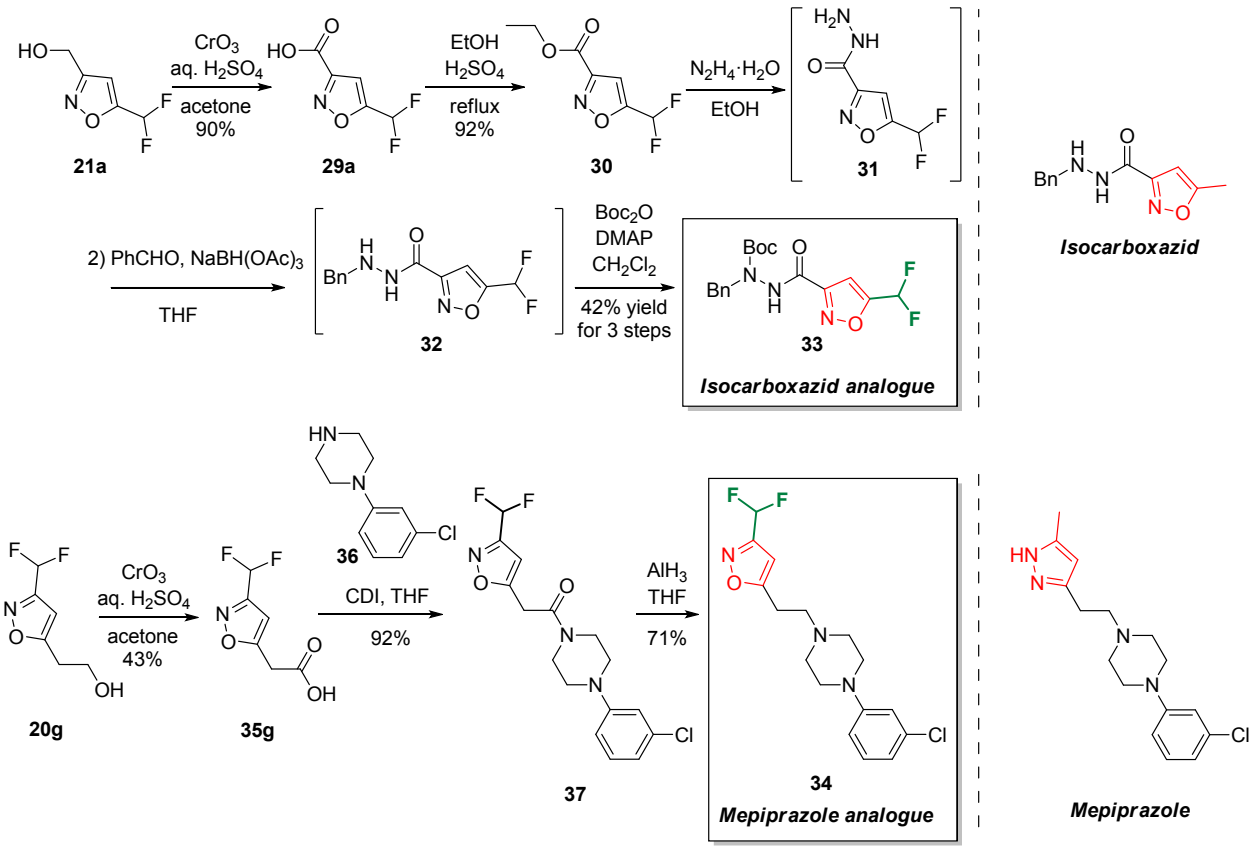
[d] Isolated after separation of **23b** and **26b** by column chromatography

and **23h** from **13g** and **13h**, respectively, as single products, whereas substrates **13a,b** led to the target pyrazoles **23a,b** and **26a,b** as *ca*. 9:1 regioisomeric mixtures. In the case of the compounds **25a** and **27a** (89% and 6% yield, respectively), the individual isomers were separated by distillation of the products obtained after deprotection of the crude mixture of **23a** and **26a**. Conversely, for **23b** and **26b**, the separation was achieved by column chromatography immediately after the cyclization step, and led to individual products **23b** and **26b** in 86% and 10% yields, respectively.

For all ynones **13** (except **13c**), direct preparation of aromatic products **22** was achieved without isolation of intermediate 5-hydroxypyrazolines **28**. Although derivatives **28** were usually present in the reaction mixture along with main products **22** prior to

work-up, the concentration of the reaction mixture *in vacuo* and filtration through silica plug led to the rapid dehydration of **28** to give **22**. Yet, the reaction of **13c** with N_2H_4 resulted in 5-hydroxypyrazoline **28c** as a single product (97% yield). Thus, intermediate **28c** was further dehydrated using CDI in CH_2Cl_2 to give **22c** in 95% yield.

Synthesis of drug analogues. One of the primary goals of this work was to develop an efficient synthetic route towards fluoroalkyl-substituted isoxazoles and pyrazoles, which can be easily used for isosteric replacement of heterocyclic moieties in biologically active compounds. In previous reviews, promising building blocks for drug discovery were referred to as the compounds containing a structural moiety which can be considered as attractive for medicinal chemistry, and one or several functional groups with predictable and controllable chemical reactivity.[53,54] From this point of view, a number of functionalized derivatives bearing carboxylic acid, amine, aldehyde, ketone, halide, azide functional groups were synthesized from alcohols **20**, **21**, **24** and **25** (see Supporting Information for more details). Application of the obtained building blocks was demonstrated by the preparation of antidepressant Isocarboxazid[39] and anxyolitic Mepiprazole[40] analogues (Scheme 5). In order to access the CHF_2-substituted Isocar-



Scheme 5. Synthesis of Isocarboxazid analogue **33** and Mepiprazole analogue **34**.

boxazid analogue, carboxylic acid **29a** was obtained from **21a** and converted to its ethyl ester **30** (92% yield). The treatment of **30** with aq N_2H_4 led to the formation of unstable hydrazide **31**, which was immediately converted to **32** by reductive amination of benzaldehyde. However, purification of the intermediate **32** appeared to be problematic; therefore, crude **32** was subjected to the reaction with Boc_2O to give Boc-protected

Isocarboxazid analogue **33**, which was obtained as a pure product after column chromatography (42% yield for three steps).

Preparation of Mepiprazole analogue **34** was achieved from **20g** by a three-step reaction sequence. After Jones oxidation of alcohol **20g**, carboxylic acid **35g** was subjected to amide coupling with amine **36** (92% yield). Further reduction of amide moiety in **37** with $LiAlH_4$ gave the target 3-(difluoromethyl)isoxazole-containing analogue of Mepiprazole **34** (71% yield).

CONCLUSIONS

Reaction of fluoroalkyl-substituted ynones with NH_2OH, N_2H_4 and $MeNHNH_2$ was used for efficient preparation of 3- or 5-fluoroalkyl isoxazoles and pyrazoles on up to 200 g scale. The studied methods allowed to obtain the target products as single regioisomers by either 1,2- or 1,4-addition route. Thorough and careful optimization of the reaction conditions was performed for each of the key steps of the synthetic sequences. This allowed preparation of 5-fluoroalkyl isoxazoles with up to 79% overall yield for cyclization and dehydration steps, 3-fluoroalkyl isoxazoles – with up to 93%

overall yield for cyclization and side chain desilylation steps, and 3-fluoroalkyl pyrazoles – with up to 95% at the cyclization step. Importantly, using a series of previously unknown fluorinated ynones allowed to increase the scope of fluoroalkyl substituents for incorporation to heterocyclic motifs, as well as provided possibility for extensive functionalization of the side chain. The utility of obtained building blocks for isosteric replacement of alkyl substituted isoxazole and pyrazole moieties was shown by the synthesis of fluorinated Isocarboxazid and Mepiprazole analogues. Therefore, the discussed protocols and fluorinated derivatives might provide new opportunities for lead optimization programs.

EXPERIMENTAL SECTION

General Methods. The solvents were purified according to the standard procedures.[55] All starting materials were purchased from commercial sources. Melting points were measured on automated melting point system. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded at 500 MHz or 400 MHz, 470 or 376 MHz, and 126 MHz or

101 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI), electrospray ionization (ESI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). The X-ray diffraction data sets were collected with a CCD diffractometer for compound **29a**, **35g**, **24h**. CCDC- 1945644 (**29a**), - 1945645 (**35g**), - 1945642 (**24h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the preparation of the compounds 13. To a pre-cooled (–78 ºC) solution of alkyne **15** (1.00 mol) in THF (1 L) under argon, 2.5 M solution of *n*-BuLi (1.00 mol, 400 mL) in hexanes was added dropwise. The resulting mixture was warmed to –15 ºC, stirred for additional 15 min at the same temperature and then cooled to –40 ºC. The corresponding ethyl ester **14** (1.00 mol) was added dropwise, followed by $BF_3{\cdot}Et_2O$ (1.05 mol, 129.6 mL) in one portion. The resulting mixture was allowed to warm to rt and

stirred overnight. After the reaction was complete, the mixture was quenched by addition of cold saturated solution of NH_4Cl (500 mL) at 0 ºC under argon flow. The organic layer was separated and concentrated under reduced pressure, whereas the aqueous layer was extracted with EtOAc (4×350 mL). The residue obtained after evaporation of THF and EtOAc solution was combined, washed with brine (2×150 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the final product was achieved by distillation *in vacuo*.

5-((*tert*-Butyldimethylsilyl)oxy)-1,1-difluoropent-3-yn-2-one (13a). Yield 309 g (80%), from 265 g of *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (**15a**) and 193 g of CHF_2CO_2Et. Colorless liquid, bp = 80–81 °C/7.7 mbar. ^1H NMR (400 MHz, $CDCl_3$): δ 5.77 (t, J = 54.0 Hz, 1H), 4.55 (s, 2H), 0.92 (s, 9H), 0.16 – 0.12 (m, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 175.1 (t, J = 30.0 Hz), 108.8 (t, J = 253.0 Hz), 99.1, 79.9, 51.7, 25.8, 18.3, –5.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ –126.5 (d, J = 54.0 Hz) ppm. GC−MS (*m/z*): 248 (M^+), 197 ($M^+ – CHF_2$). Anal. Calcd. for $C_{11}H_{18}F_2O_2Si$: C, 53.20; H, 7.31. Found: C, 52.81; H, 7.12.

5-((*tert*-Butyldimethylsilyl)oxy)-1,1,1-trifluoropent-3-yn-2-one (13b).[56] Yield 180 g (81%), from 142 g of of *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (**15a**) and 119 g of CF_3CO_2Et. Colorless liquid, bp = 61–62 °C/7.7 mbar. ^1H NMR (400 MHz, $CDCl_3$): δ 4.57 (s, 2H), 0.92 (s, 9H), 0.14 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 167.0 (q, J = 42.4 Hz), 114.8 (q, J = 288.1 Hz), 100.5, 78.9, 51.7, 25.7, 18.3, –5.3 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –78.8 ppm. GC−MS (*m/z*): 209 ($M^+ - C(CH_3)_3$), 197 ($M^+ - CF_3$). Anal. Calcd. for $C_{11}H_{17}F_3O_2Si$: C, 49.61; H, 6.43. Found: C, 49.41; H, 6.47.

6-((*tert*-Butyldimethylsilyl)oxy)-2,2-difluorohex-4-yn-3-one (13c). Yield 61.4 g (83%), from 48.0 g of *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (**15a**) and 40.0 g of $CF_2(CH_3)CO_2Et$. Colorless liquid, bp = 53–54 °C/1 mbar. ^1H NMR (400 MHz, $CDCl_3$): δ 4.54 (s, 2H), 1.76 (t, J = 18.6 Hz, 3H), 0.92 (s, 9H), 0.14 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 176.7 (t, J = 36.0 Hz), 116.5 (t, J = 249.0 Hz), 98.0, 80.0, 51.7, 25.7, 19.7 (t, J = 25.2 Hz), 18.3, –5.2 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –100.1 ppm. GC−MS (*m/z*): 205 ($M^+ - C(CH_3)_3$), 197 ($M^+ - CF_2CH_3$). Anal. Calcd. for $C_{12}H_{20}F_2O_2Si$: C, 54.93; H, 7.68. Found: C, 55.02; H, 7.49.

6-((*tert*-Butyldimethylsilyl)oxy)-1,1,1,2,2-pentafluorohex-4-yn-3-one (13d). Yield 108 g (58%), from 100 g of *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (**15a**) and 113 g of $C_2F_5CO_2Et$. Colorless liquid, bp = 57–59 °C/7.7 mbar. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 (s, 2H), 0.92 (s, 9H), 0.14 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 169.2 (t, J = 31.2 Hz), 117.8 (qt, J = 286.9, 34.4 Hz), 106.5 (tq, J = 266.0, 38.8 Hz), 101.3, 79.5, 51.7, 25.7, 18.3, –5.3 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –82.2 (s, 3F), –122.5 (s, 2F) ppm. GC−MS (*m/z*): 316 (M^+), 259 ($M^+ - C(CH_3)_3$), 197 ($M^+ - C_2F_5$). Anal. Calcd. for $C_{12}H_{17}F_5O_2Si$: C, 45.56; H, 5.42. Found: C, 45.20; H, 5.33.

1-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-1-fluoropent-3-yn-2-one (13e). Yield 138 g (76%), from 100 g of *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (**15a**) and 109 g of $CHFBrCO_2Et$. Light yellow liquid, bp = 46–48 °C/1 mbar. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (d, J = 51.2 Hz, 1H), 4.55 (s, 2H), 0.92 (s, 9H), 0.15 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 174.6 (d, J = 27.4 Hz), 98.2 (d, J = 1.8 Hz), 86.9 (d, J = 268.3 Hz), 78.9, 51.6, 26.0 – 25.6 (m), 18.3, –5.2 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –151.6 ppm. GC−MS (*m/z*): 251/253 ($M^+ - C(CH_3)_3$), 197 (M^+ – CHFBr). Anal. Calcd. for $C_{11}H_{18}BrFO_2Si$: C, 42.72; H, 5.87; Br, 25.84. Found: C, 42.53; H, 5.73; Br, 26.14.

1-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-1,1-difluoropent-3-yn-2-one (13f). Yield 97.0 g (69%), from 73.0 g of *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (**15a**) and 87.2 g of CF_2BrCO_2Et. Light yellow liquid, bp = 49–50 °C/1 mbar. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 (s, 2H), 0.92 (s, 9H), 0.15 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.0 (t, J = 32.6 Hz), 112.6 (t, J = 316.7 Hz), 100.4, 77.7, 51.8, 25.7, 18.3, –5.2 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –64.3 ppm. GC−MS (*m/z*): 269/271 ($M^+ - C(CH_3)_3$), 197 ($M^+ - CF_2Br$). Anal. Calcd. for $C_{11}H_{17}BrF_2O_2Si$: C, 40.37; H, 5.24; Br, 24.42. Found: C, 40.21; H, 4.88; Br, 24.23.

6-((*tert*-Butyldimethylsilyl)oxy)-1,1-difluorohex-3-yn-2-one (13g). Yield 105 g (87%), from 85 g of (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (**15b**) and 57.3 g of CHF_2CO_2Et. Colorless liquid, bp = 49–51 °C/1 mbar. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (t, J = 54.2 Hz, 1H), 3.83 (t, J = 6.6 Hz, 2H), 2.69 (t, J = 6.6 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 175.4 (t, J = 29.6 Hz), 108.8 (t, J = 252.7 Hz), 100.8, 77.6, 60.4, 25.9, 23.9, 18.3, –5.4 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –126.4 ppm. GC−MS (*m/z*): 247 ($M^+ - CH_3$), 211 ($M^+ - CHF_2$), 205 ($M^+ - C(CH_3)_3$). Anal. Calcd. for $C_{12}H_{20}F_2O_2Si$: C, 54.93; H, 7.68. Found: C, 55.27; H, 7.32.

5-((*tert*-Butyldimethylsilyl)oxy)-1,1-difluorohex-3-yn-2-one (13h). Yield 214 g (81%), from 185 g of (but-3-yn-2-yloxy)(*tert*-butyl)dimethylsilane (**15c**) and 125 g of CHF_2CO_2Et. Colorless liquid, bp = 73–74 °C/23 mbar. ^1H NMR (400 MHz, $CDCl_3$): δ 5.76 (t, J = 54.1 Hz, 1H), 4.72 (q, J = 6.7 Hz, 1H), 1.51 (d, J = 6.7 Hz, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 175.3 (t, J = 29.8 Hz), 108.8 (t, J = 252.8 Hz), 102.4, 78.3, 59.0, 25.7, 24.3, 18.2, –4.7, –5.0 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –126.5 ppm. GC−MS (*m/z*): 247 ($M^+ - CH_3$), 211 ($M^+ - CHF_2$). Anal. Calcd. for $C_{12}H_{20}F_2O_2Si$: C, 54.93; H, 7.68. Found: C, 55.31; H, 7.74.

General procedure for the preparation of the compounds 16. Aqueous solution of NH_2OH was prepared by stirring $NH_2OH{\cdot}HCl$ (83.4 g, 1.20 mol) and $NaHCO_3$ (101 g, 1.20 mol) in H_2O (300 mL) for 30 min. This solution was added dropwise to a pre-cooled to 0 °C solution of the corresponding ynone **13** (1.00 mol) in THF (2.5 L), and the mixture was stirred overnight. After the reaction was complete (monitored by ^1H NMR analysis), the resulting solution was concentrated *in vacuo* and the residue was dissolved in EtOAc (1.5 L). The organic phase was washed with brine (2×500 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(difluoromethyl)-4,5-dihydroisoxazol-5-ol (16a). Yield 0.56 g (99 %) from 0.50 g of **13a**, or 191 g (84 %) from 200 g of **13a**. White solid, mp = 67–69 °C, bp = 104 °C/1 mbar. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 (t, J = 55.1 Hz, 1H), 4.46 (s, 2H), 3.48 (br s, 1H), 3.33 (d, J = 18.4 Hz, 1H), 3.08 (d, J = 18.4 Hz, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.7, 112.2 (t, J = 247.9 Hz), 104.2 (t, J = 25.8 Hz), 58.3, 42.0, 25.8, 18.4, –5.32, –5.34 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ –130.3 (dd, J = 289.2, 55.1 Hz, 1F), –132.6 (dd, J = 289.2, 55.1 Hz, 1F) ppm. Anal. Calcd. for $C_{11}H_{21}F_2NO_3Si$: C, 46.96; H, 7.52; N, 4.98. Found: C, 47.21; H, 7.12; N, 5.03.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (16b). Yield 234 g (83 %) from 251 g of **13b**. White solid, mp = 62–64 °C, bp = 87–90 °C/1 mbar. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.45 (s, 1H), 4.42 (s, 2H), 3.42 (d, J = 18.6 Hz, 1H), 3.12 (d, J = 18.6 Hz, 1H), 0.87 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 158.9, 122.4 (q, J = 284.4 Hz), 102.9 (q, J = 32.8 Hz), 57.7, 42.4, 25.6, 17.8, –5.52, –5.53 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –82.7

ppm. Anal. Calcd. for $C_{11}H_{20}F_3NO_3Si$: C, 44.13; H, 6.73; N, 4.68. Found: C, 43.74; H, 6.33; N, 4.55.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(1,1-difluoroethyl)-4,5-dihydroisoxazol-5-ol (16c). Yield 10.4 g (77 %) from 12.0 g of **13c**. White solid, mp = 84–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.45 (s, 2H), 3.54 (br s, 1H), 3.39 (d, J = 18.5 Hz, 1H), 3.05 (d, J = 18.5 Hz, 1H), 1.75 (t, J = 18.7 Hz, 3H), 0.90 (s, 9H), 0.11 – 0.09 (m, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 158.5, 121.3 (t, J = 244.4 Hz), 105.6 (t, J = 30.9 Hz), 58.1, 41.3, 25.6, 18.1 (t, J = 25.2 Hz), 17.9, –5.48, –5.50 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –102.7 (d, J = 245.8 Hz, 1F), –104.5 (d, J = 245.8 Hz, 1F) ppm. Anal. Calcd. for $C_{12}H_{23}F_2NO_3Si$: C, 48.79; H, 7.85; N, 4.74. Found: C, 48.61; H, 7.51; N, 4.97.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(perfluoroethyl)-4,5-dihydroisoxazol-5-ol (16d). Yield 148 g (75 %) from 179 g of **13d**. White solid, mp = 77–79 °C, bp = 81–84 °C/1 mbar. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.61 (s, 1H), 4.43 (s, 2H), 3.47 (d, J = 18.7 Hz, 1H), 3.12 (d, J = 18.7 Hz, 1H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.8, 118.7 (qt, J = 286.9, 35.0 Hz), 111.3 (tq, J = 262.1, 36.7 Hz), 103.9 (dd, J = 27.5, 25.2 Hz), 58.1, 44.1, 25.8, 18.3, –5.37, –5.39 ppm. ^{19}F{^{1}H}

NMR (376 MHz, DMSO-d_6): δ –79.9 (s, 3F), –123.2 (d, J = 273.3 Hz, 1F), –127.6 (d, J = 273.3 Hz, 1F) ppm. Anal. Calcd. for $C_{12}H_{20}F_5NO_3Si$: C, 41.25; H, 5.77; N, 4.01. Found: C, 41.47; H, 5.41; N, 3.71.

5-(Bromofluoromethyl)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5-dihydroisoxazol-5-ol (16e). Yield 42.4 g (85 %) from 45.0 g of **13e**. Brown solid, mp = 65–66 °C. The compound was obtained as *ca.* 1:1 diastereomeric mixture. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.76 (br s, 1H), 7.71 (br s, 1H), 6.83 (d, J = 47.8 Hz, 1H), 6.75 (d, J = 48.4 Hz, 1H), 4.38 (s, 2×2H), 3.33 (d, J = 18.5 Hz, 1H), 3.29 (d, J = 18.2 Hz, 1H), 2.95 (dd, J = 18.4, 3.0 Hz, 1H), 2.93 (dd, J = 18.4, 2.2 Hz, 1H), 0.87 (s, 2×9H), 0.08 – 0.06 (m, 2×6H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 158.6 and 158.4, 107.2 (d, J = 23.1 Hz) and 106.0 (d, J = 21.8 Hz), 94.6 (d, J = 256.9 Hz) and 93.6 (d, J = 256.5 Hz), 58.1, 42.9 and 41.7, 25.6 (d, J = 3.6 Hz), 17.9, –5.5 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –146.1 and –147.8 ppm. Anal. Calcd. for $C_{11}H_{21}BrFNO_3Si$: C, 38.60; H, 6.18; N, 4.09; Br, 23.34. Found: C, 38.46; H, 6.45; N, 4.17; Br, 23.32.

5-(Bromodifluoromethyl)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5-dihydroisoxazol-5-ol (16f). Yield 2.41 g (73 %) from 3.00 g of **13f**. Brown solid, mp = 75–77 °C. ^{1}H NMR

(400 MHz, $CDCl_3$): δ 4.45 (s, 2H), 3.58 (br s, 1H), 3.47 (d, *J* = 18.5 Hz, 1H), 3.22 (d, *J* = 18.5 Hz, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 159.8, 120.8 (t, *J* = 312.4 Hz), 106.4 (t, *J* = 27.4 Hz), 58.3, 43.0, 25.8, 18.3, –5.32, –5.33 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –62.2 (d, *J* = 166.1 Hz, 1F), –63.4 (d, *J* = 166.1 Hz, 1F) ppm. Anal. Calcd. for $C_{11}H_{20}BrF_2NO_3Si$: C, 36.67; H, 5.60; N, 3.89; Br, 22.18. Found: C, 36.61; H, 5.79; N, 4.14; Br, 22.30.

3-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-5-(difluoromethyl)-4,5-dihydroisoxazol-5-ol (16g). The product was obtained after column chromatography (gradient hexanes–*t*-BuOMe as eluent) of the mixture of **16g** and **18g**. Yield 53.2 g (59 %) from 80.0 g of **13g**. White solid, mp = 71–73 °C (dec). ^1H NMR (500 MHz, $CDCl_3$): δ 5.81 (t, *J* = 55.3 Hz, 1H), 5.23 – 5.11 (m, 1H), 3.90 – 3.77 (m, 2H), 3.34 (d, *J* = 18.5 Hz, 1H), 2.99 (d, *J* = 18.5 Hz, 1H), 2.67 – 2.54 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 159.1, 112.2 (t, *J* = 247.4 Hz), 104.0 (t, *J* = 26.1 Hz), 60.4, 44.1, 30.9, 25.9, 18.2, –5.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ –129.8 (dd, *J* = 287.9, 55.3 Hz, 1F), –131.8 (dd, *J* = 287.9, 54.9 Hz, 1F) ppm. Anal. Calcd. for $C_{12}H_{23}F_2NO_3Si$: C, 48.79; H, 7.85; N, 4.74. Found: C, 48.65; H, 7.61; N, 4.70.

6-((*tert*-Butyldimethylsilyl)oxy)-1,1-difluorohex-3-yn-2-one oxime (18g). An analytical sample was obtained after column chromatography (gradient hexanes–*t*-BuOMe as eluent) of the mixture of **16g** and **18g**. Colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.97 (s, 1H), 6.72 (t, J = 54.1 Hz, 1H), 3.82 (t, J = 6.8 Hz, 2H), 2.64 (t, J = 6.8 Hz, 2H), 0.90 (s, 9H), 0.10 (s, 6H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 140.9 (t, J = 26.3 Hz), 104.6 (t, J = 241.3 Hz), 95.3, 71.2, 61.4, 25.9, 23.8, 18.5, –5.3 ppm. ^{19}F{^{1}H} NMR (376 MHz, , $CDCl_3$): δ –125.1 ppm. Anal. Calcd. for $C_{12}H_{21}F_2NO_2Si$: C, 51.96; H, 7.63; N, 5.05. Found: C, 51.99; H, 7.60; N, 4.89.

3-(1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-5-(difluoromethyl)-4,5-dihydroisoxazol-5-ol (16h). Yield 6.69 g (82 %) from 10.0 g of **13h**. White solid, mp = 60–62 °C, bp = 84–86 °C/1 mbar. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 (t, J = 52.7 Hz, 1H), 6.97 (s, 1H), 5.08 (q, J = 6.5 Hz, 1H), 1.43 (d, J = 6.5 Hz, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.02 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 167.7, 162.7 (t, J = 28.5 Hz), 107.5 (t, J = 236.2 Hz), 103.0 (t, J = 3.6 Hz), 63.1, 25.5, 23.7, 17.7, –5.1, –5.3 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –118.5 ppm. Anal. Calcd. for $C_{12}H_{23}F_2NO_3Si$: C, 48.79; H, 7.85; N, 4.74. Found: C, 48.68; H, 7.77; N, 4.86.

General procedure for the preparation of the compounds 17. The corresponding 5-hydroxyisoxazoline **16** (0.10 mol) was dissolved in CH_2Cl_2 (250 mL) and CDI (17.8 g, 0.11 mol) was added. The resulting mixture was stirred overnight. After the reaction was complete (monitored by ^1H NMR analysis), the organic layer was washed with sat. $NaHSO_4$ (2×80 mL) and brine (2×80 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(difluoromethyl)isoxazole (17a). Yield 163 g (94 %) from 185 g of **16a**. Colorless liquid, bp = 49–51 °C/1 mbar. ^1H NMR (400 MHz, DMSO-d_6): δ 7.33 (t, J = 52.7 Hz, 1H), 6.93 (s, 1H), 4.78 (s, 2H), 0.87 (s, 9H), 0.09 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 163.8, 162.7 (t, J = 28.3 Hz), 107.5 (t, J = 236.1 Hz), 104.4 (t, J = 3.7 Hz), 56.5, 25.6, 17.9, –5.5 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ –118.4 (d, J = 52.3 Hz) ppm. Anal. Calcd. for $C_{11}H_{19}F_2NO_2Si$: C, 50.17; H, 7.27; N, 5.32. Found: C, 50.54; H, 7.42; N, 5.65.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(trifluoromethyl)isoxazole (17b). Yield 197 g (91 %) from 230 g of **16b**. Colorless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (s, 1H), 4.80 (s, 2H), 0.92 (s, 9H), 0.12 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 164.6,

158.8 (q, J = 42.6 Hz), 118.1 (q, J = 270.1 Hz), 104.7, 57.1, 25.8, 18.4, –5.4 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –64.8 ppm. Anal. Calcd. for $C_{11}H_{18}F_3NO_2Si$: C, 46.96; H, 6.45; N, 4.98. Found: C, 47.09; H, 6.30; N, 4.62.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(perfluoroethyl)isoxazole (17d). Yield 122 g (89 %) from 145 g of **16d**. Colorless liquid, bp = 43–44 °C/1 mbar. ^1H NMR (400 MHz, $CDCl_3$): δ 6.79 (s, 1H), 4.82 (s, 2H), 0.92 (s, 9H), 0.11 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 164.5, 157.9 (t, J = 31.6 Hz), 118.0 (qt, J = 286.1, 36.2 Hz), 108.2 (tq, J = 254.4, 41.1 Hz), 106.2, 56.8, 25.5, 18.1, –5.8 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –85.0 (s, 3F), –115.8 (s, 2F) ppm. Anal. Calcd. for $C_{12}H_{18}F_5NO_2Si$: C, 43.50; H, 5.48; N, 4.23. Found: C, 43.24; H, 5.36; N, 4.42.

5-(Bromofluoromethyl)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)isoxazole (17e). Yield 33.4 g (85 %) from 41.5 g of **16e**. Yellowish liquid, bp = 92–94 °C/1 mbar. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 48.6 Hz, 1H), 6.59 (s, 1H), 4.77 (s, 2H), 0.92 (s, 9H), 0.11 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 166.2 (d, J = 27.9 Hz), 164.4 (d, J = 1.2 Hz), 102.6 (d, J = 1.5 Hz), 80.3 (d, J = 250.2 Hz), 57.2, 25.8, 18.3, –5.3 ppm. $^{19}F\{^1H\}$

NMR (376 MHz, $CDCl_3$): δ –141.5 ppm. Anal. Calcd. for $C_{11}H_{19}BrFNO_2Si$: C, 40.74; H, 5.91; N, 4.32; Br, 24.64. Found: C, 40.97; H, 5.64; N, 4.18; Br, 24.68.

5-(Bromodifluoromethyl)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)isoxazole (17f). Yield 1.18 g (83 %) from 1.50 g of **16f**. Yellowish liquid, bp = 66–68 °C/1 mbar. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65 (s, 1H), 4.79 (s, 2H), 0.92 (s, 9H), 0.11 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 164.5, 163.7 (t, J = 33.5 Hz), 109.3 (t, J = 299.8 Hz), 102.7, 57.2, 25.9, 18.3, –5.3 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –48.3 ppm. Anal. Calcd. for $C_{11}H_{18}BrF_2NO_2Si$: C, 38.60; H, 5.30; N, 4.09; Br, 23.35. Found: C, 38.94; H, 5.12; N, 3.77; Br, 23.61.

3-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-5-(difluoromethyl)isoxazole (17g). Yield 35.2 g (75 %) from 50.0 g of **16g**. Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68 (t, J = 53.8 Hz, 1H), 6.50 (s, 1H), 3.86 (d, J = 5.8 Hz, 2H), 2.89 (d, J = 5.8 Hz, 2H), 0.84 (s, 9H), 0.00 (s, 6H) ppm. $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$): δ 163.0 (t, J = 30.7 Hz), 162.2, 107.4 (t, J = 238.8 Hz), 104.6 (t, J = 2.2 Hz), 61.4, 29.6, 25.9, 18.3, –5.4 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –118.2 ppm. Anal. Calcd. for $C_{12}H_{21}F_2NO_2Si$: C, 51.96; H, 7.63; N, 5.05. Found: C, 51.74; H, 7.39; N, 4.81.

3-(1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-5-(difluoromethyl)isoxazole (17h). Yield 2.26 g (83 %) from 2.90 g of **16h**. Colorless liquid, bp = 81–84 °C/1 mbar. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 (t, J = 52.7 Hz, 1H), 6.97 (s, 1H), 5.08 (q, J = 6.5 Hz, 1H), 1.43 (d, J = 6.5 Hz, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.02 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 167.7, 162.7 (t, J = 28.4 Hz), 107.5 (t, J = 236.2 Hz), 103.0 (t, J = 3.3 Hz), 63.1, 25.5, 23.7, 17.7, –5.1, –5.3 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –118.5 ppm. Anal. Calcd. for $C_{12}H_{21}F_2NO_2Si$: C, 51.96; H, 7.63; N, 5.05. Found: C, 51.83; H, 7.73; N, 5.02.

General procedure for the preparation of the compounds 21. KHF_2 (3.91 g, 0.05 mol) was added to a solution of isoxazole **17** (0.10 mol) in MeOH–H_2O (9 : 1) mixture (250 mL), and the reaction mixture was stirred overnight. After the reaction was complete (monitored by ^{1}H NMR analysis), MeOH was evaporated under reduced pressure. The residue was dissolved in EtOAc (250 mL) and washed with brine (2×70 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained product was purified by distillation *in vacuo*.

(5-(Difluoromethyl)isoxazol-3-yl)methanol (21a). Yield 77.3 g (91 %) from 150 g of **17a**. Colorless liquid, bp = 41–43 °C/1 mbar. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (t, J = 53.6 Hz, 1H), 6.60 (s, 1H), 4.70 (s, 2H), 3.96 (br s, 1H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 163.9, 163.7 (t, J = 31.0 Hz), 107.2 (t, J = 239.2 Hz), 103.1, 56.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ –118.6 (d, J = 53.6 Hz) ppm. GC–MS (*m/z*): 149 (M^+), 130 (M^+ – F). Anal. Calcd. for $C_5H_5F_2NO_2$: C, 40.28; H, 3.38; N, 9.39. Found: C, 40.64; H, 3.33; N, 9.14.

(5-(Trifluoromethyl)isoxazol-3-yl)methanol (21b).[57] Yield 79.0 g (70 %) from 190 g of **17b**. Colorless liquid, bp = 64–66 °C/10 mbar. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.36 (s, 1H), 5.69 (t, J = 5.9 Hz, 1H), 4.59 (d, J = 6.0 Hz, 2H) ppm. $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6): δ 165.6, 156.8 (q, J = 41.7 Hz), 118.1 (q, J = 269.6 Hz), 106.2, 54.7 ppm. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6): δ –64.2 ppm. GC–MS (*m/z*): 167 (M^+), 148 (M^+ – F). Anal. Calcd. for $C_5H_4F_3NO_2$: C, 35.94; H, 2.41; N, 8.38. Found: C, 36.24; H, 2.26; N, 8.56.

(5-(1,1-Difluoroethyl)isoxazol-3-yl)methanol (21c). The product was synthesized from 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(1,1-difluoroethyl)-4,5-dihydroisoxazol-5-ol

(**16c**) (9.50 g, 32.2 mmol), which was first converted to 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(1,1-difluoroethyl)isoxazole (**17c**) by the general procedure for the preparation of the compounds **17**. The obtained crude product **17c** was subjected to desilylation by general procedure for the preparation of the compounds **21** without additional purification. Yield 3.88 g (74 %) from 9.50 g of **16c**. Colorless liquid, bp = 59–62 °C/1 mbar. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (s, 1H), 4.79 (s, 2H), 2.44 (s, 1H), 2.01 (t, J = 18.4 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 166.3 (t, J = 36.2 Hz), 163.9, 115.9 (t, J = 237.3 Hz), 101.7, 56.1, 23.0 (t, J = 26.5 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –89.4 ppm. GC–MS (*m/z*): 163 (M^+), 144 (M^+ – F). Anal. Calcd. for $C_6H_7F_2NO_2$: C, 44.18; H, 4.33; N, 8.59. Found: C, 43.79; H, 4.36; N, 8.73.

(5-(Perfluoroethyl)isoxazol-3-yl)methanol (21d). Yield 68.4 g (87 %) from 120 g of **17d**. Colorless liquid, bp = 72–74 °C/32 mbar. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 (s, 1H), 4.84 (s, 2H), 2.32 (s, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 164.3, 158.6 (t, J = 31.8 Hz), 118.1 (qt, J = 285.9, 35.8 Hz), 108.2 (tq, J = 254.8, 41.2 Hz), 106.3, 56.3 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –85.1 (s, 3F), –116.0 (s, 2F) ppm. GC−MS (*m/z*): 217

(M^+), 198 (M^+ –F), 148 (M^+ –CF_3). Anal. Calcd. for $C_6H_4F_5NO_2$: C, 33.20; H, 1.86; N, 6.45. Found: C, 33.46; H, 1.76; N, 6.47.

(5-(Bromofluoromethyl)isoxazol-3-yl)methanol (21e). Yield 15.8 g (81 %) from 30.0 g of **17e**. Colorless liquid, bp = 96–98 °C/1 mbar. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 48.6 Hz, 1H), 6.62 (s, 1H), 4.77 (s, 2H), 2.63 (br s, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.3 (d, *J* = 27.7 Hz), 164.0, 102.5, 80.0 (d, *J* = 250.1 Hz), 56.1 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –141.9 ppm. LC–MS (*m/z*): 210/212 (M + H^+). Anal. Calcd. for $C_5H_5BrFNO_2$: C, 28.60; H, 2.40; N, 6.67; Br, 38.05. Found: C, 28.98; H, 2.17; N, 6.74; Br, 37.83.

2-(5-(Difluoromethyl)isoxazol-3-yl)ethanol (21g). Yield 17.9 g (91 %) from 33.5 g of **17g**. Colorless liquid, bp = 84–86 °C/1 mbar. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (t, *J* = 53.8 Hz, 1H), 6.53 (s, 1H), 4.02 – 3.95 (m, 2H), 3.01 – 2.94 (m, 2H), 2.06 (br s, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 163.5 (t, *J* = 30.8 Hz), 162.0, 107.4 (t, *J* = 239.1 Hz), 104.4 (t, *J* = 1.9 Hz), 60.5, 29.6 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –118.3 ppm. LCMS (*m/z*): 164 (M + H^+). Anal. Calcd. for $C_6H_7F_2NO_2$: C, 44.18; H, 4.33; N, 8.59. Found: C, 44.37; H, 3.97; N, 8.96.

1-(5-(Difluoromethyl)isoxazol-3-yl)ethanol (21h). Yield 1.03 g (92 %) from 1.90 g of **17h**. Colorless liquid, bp = 92–94 °C/10 mbar. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (t, *J* = 53.6 Hz, 1H), 6.63 (s, 1H), 5.09 (q, *J* = 6.6 Hz, 1H), 2.27 (s, 1H), 1.58 (d, *J* = 6.6 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 167.8, 163.6 (t, *J* = 30.7 Hz), 107.2 (t, *J* = 239.0 Hz), 102.0, 62.7, 22.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ –118.6 (d, *J* = 53.6 Hz) ppm. GC–MS (*m/z*): 163 (M^+), 144 (M^+ – F). Anal. Calcd. for $C_6H_7F_2NO_2$: C, 44.18; H, 4.33; N, 8.59. Found: C, 44.32; H, 4.37; N, 8.27.

General procedure for the preparation of the compounds 20. To the corresponding ynone **13** (0.10 mol) and $NH_2OH{\cdot}HCl$ (8.34 g, 0.12 mol) in THF (240 mL), CuCN (0.90 g, 0.01 mol) was added, and the reaction was stirred at rt overnight. When the conversion of the starting substrate **13** was complete (monitored by ^{1}H NMR analysis), $NaHCO_3$ (10.1 g, 0.12 mol) was added to the mixture, and the reaction was stirred overnight. The resulting solution was concentrated under reduced pressure; the residue was dissolved in *t*-BuOMe (250 mL) and filtered through a silica plug. The filtrate was concentrated *in vacuo*, and the obtained crude product was subjected to the next step without additional purification. KHF_2 (3.91 g, 0.05 mol) was added to a solution of crude isoxazole (0.10

mol) in MeOH–H_2O (9 : 1) mixture (250 mL), and the reaction mixture was stirred overnight. After the reaction was complete (monitored by ^{1}H NMR analysis), MeOH was evaporated under reduced pressure. The residue was dissolved in EtOAc (150 mL) and washed with brine (2×70 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained product was purified by distillation *in vacuo*.

(3-(Difluoromethyl)isoxazol-5-yl)methanol (20a). Yield 60.8 g (92 %) from 110 g of **13a**. Colorless liquid, bp = 45–47 °C/1 mbar. For spectral and physical data, see ref.[18]

(3-(Trifluoromethyl)isoxazol-5-yl)methanol (20b).[20] Yield 70.1 g (93 %) from 120 g of **13b**. Colorless liquid, bp = 49–52 °C/1 mbar. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.01 (s, 1H), 5.84 (br s, 1H), 4.67 (s, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 177.0, 154.9 (q, J = 37.6 Hz), 120.1 (q, J = 270.5 Hz), 99.6, 55.0 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –62.7 ppm. GC−MS (*m/z*): 167 (M^+), 148 (M^+ –F). Anal. Calcd. for $C_5H_4F_3NO_2$: C, 35.94; H, 2.41; N, 8.38. Found: C, 36.28; H, 2.33; N, 8.77.

(3-(1,1-Difluoroethyl)isoxazol-5-yl)methanol (20c). Yield 13.7 g (63 %) from 35.0 g of **13c**. Colorless liquid, bp = 42–44 °C/1 mbar. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.69 (s,

1H), 5.74 (d, J = 5.8 Hz, 1H), 4.61 (d, J = 5.8 Hz, 2H), 2.03 (t, J = 19.3 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 175.2, 160.8 (t, J = 33.0 Hz), 118.1 (t, J = 235.0 Hz), 99.2, 54.8, 23.1 (t, J = 25.8 Hz) ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –87.2 ppm. LC−MS (*m/z*): 164 ($M + H^+$). Anal. Calcd. for $C_6H_7F_2NO_2$: C, 44.18; H, 4.33; N, 8.59. Found: C, 43.78; H, 4.58; N, 8.24.

(3-(Bromodifluoromethyl)isoxazol-5-yl)methanol (20f). Yield 0.79 g (72 %) from 1.27 g of **13f**. Colorless liquid, bp = 66–68 °C/1 mbar. ^1H NMR (400 MHz, $CDCl_3$): δ 6.70 (s, 1H), 4.81 (s, 2H), 2.11 (br s, 1H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 164.02, 164.01 (t, J = 31.8 Hz), 109.1 (t, J = 299.9 Hz), 102.6, 56.4 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –48.6 ppm. GC−MS (*m/z*): 227/229 (M^+), 208/210 (M^+ – F). Anal. Calcd. for $C_5H_4BrF_2NO_2$: C, 26.34; H, 1.77; N, 6.14; Br, 35.05. Found: C, 26.19; H, 1.86; N, 6.01; Br, 34.81.

2-(3-(Difluoromethyl)isoxazol-5-yl)ethanol (20g).[18] Yield 8.59 g (92 %) from 15.0 g of **13g**. Colorless liquid, bp = 68–70 °C/1 mbar. ^1H NMR (400 MHz, DMSO-d_6): δ 7.22 (t, J = 53.3 Hz, 1H), 6.63 (s, 1H), 4.91 (t, J = 5.2 Hz, 1H), 3.75 – 3.69 (m, 2H), 2.96 (t, J = 6.3 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 174.1, 158.7 (t, J = 28.7 Hz), 109.8

(t, J = 235.0 Hz), 99.1, 58.5, 30.1 ppm. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6): δ –116.4 ppm. GC–MS (*m/z*): 163 (M^+), 144 (M^+ – F). Anal. Calcd. for $C_6H_7F_2NO_2$: C, 44.18; H, 4.33; N, 8.59. Found: C, 44.58; H, 4.41; N, 8.26.

1-(3-(Difluoromethyl)isoxazol-5-yl)ethanol (20h). Yield 0.72 g (92 %) from 1.25 g of **13h**. Colorless liquid, bp = 51–53 °C/1 mbar. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.07 (t, J = 53.4 Hz, 1H), 6.52 (s, 1H), 5.73 (d, J = 5.4 Hz, 1H), 4.87 (quint, J = 6.2 Hz, 1H), 1.45 (d, J = 6.2 Hz, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6): δ 179.0, 158.7 (t, J = 28.6 Hz), 110.0 (t, J = 235.1 Hz), 98.0, 61.7, 22.3 ppm. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6): δ –116.4 ppm. GC−MS (*m/z*): 163 (M^+), 148 (M^+ – CH_3), 144 (M^+ – F). Anal. Calcd. for $C_6H_7F_2NO_2$: C, 44.18; H, 4.33; N, 8.59. Found: C, 43.96; H, 4.69; N, 8.46.

General procedure for the preparation of the compounds 22a,h and 28c. To a solution of ynone **13** (0.10 mol) in THF (100 mL), a solution of N_2H_4 in H_2O (25 mL, 20% wt) was added dropwise at 0°C, and the mixture was stirred overnight. After the reaction was complete (monitored by ^{1}H NMR analysis), the resulting solution was concentrated under reduced pressure. The residue was dissolved in EtOAc (200 mL), filtered through a silica plug, and concentrated *in vacuo*.

5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(difluoromethyl)-1*H*-pyrazole (22a). Yield 85.3 g (95 %) from 85.0 g of **13a**. Colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.19 (s, 1H), 6.92 (t, J = 54.9 Hz, 1H), 6.39 (s, 1H), 4.70 (s, 2H), 0.87 (s, 9H), 0.06 (s, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 146.2 (t, J = 28.8 Hz), 143.9, 112.0 (t, J = 231.1 Hz), 100.5, 56.1, 25.7, 18.0, –5.5 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ –110.4 (d, J = 54.9 Hz) ppm. Anal. Calcd. for $C_{11}H_{20}F_2N_2OSi$: C, 50.36; H, 7.68; N, 10.68. Found: C, 50.04; H, 7.80; N, 10.72.

5-(1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-(difluoromethyl)-1*H*-pyrazole (22h). Yield 4.88 g (93 %) from 5.00 g of **13h**. Colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.68 (t, J = 55.1 Hz, 1H), 6.26 (s, 1H), 5.04 (q, J = 6.4 Hz, 1H), 1.48 (d, J = 6.4 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 149.6, 147.4, 111.4 (t, J = 233.4 Hz), 98.8, 64.3, 25.8, 25.4, 18.2, –4.8, –5.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ –111.9 (d, J = 55.1 Hz) ppm. Anal. Calcd. for $C_{12}H_{22}F_2N_2OSi$: C, 52.15; H, 8.02; N, 10.14. Found: C, 52.30; H, 8.20; N, 10.12.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(1,1-difluoroethyl)-4,5-dihydro-1*H*-pyrazol-5-ol (28c). Yield 5.44 g (97 %) from 5.00 g of **13c**. Colorless oil. ^{1}H NMR (400 MHz,

$CDCl_3$): δ 5.88 (s, 1H), 4.40 (d, *J* = 13.1 Hz, 1H), 4.34 (d, *J* = 13.1 Hz, 1H), 3.79 (br s, 1H), 3.12 (d, *J* = 18.1 Hz, 1H), 2.79 (d, *J* = 18.1 Hz, 1H), 1.73 (t, *J* = 18.7 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.4, 122.1 (t, *J* = 243.7 Hz), 94.0 (t, *J* = 28.0 Hz), 60.7, 42.0, 25.9, 19.3 (t, *J* = 26.3 Hz), 18.4, –5.3 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –102.8 (d, *J* = 247.0 Hz), –104.3 (d, *J* = 247.0 Hz) ppm. Anal. Calcd. for $C_{12}H_{24}F_2N_2O_2Si$: C, 48.95; H, 8.22; N, 9.52. Found: C, 48.83; H, 8.57; N, 9.28.

5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1,1-difluoroethyl)-1*H*-pyrazole (22c). To a solution of 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(1,1-difluoroethyl)-4,5-dihydro-1*H*-pyrazol-5-ol (**28c**) (5.00 g, 17.0 mmol) in CH_2Cl_2 (50 mL), CDI (3.03 g, 19.0 mmol) was added. The resulting mixture was stirred overnight. The organic layer was washed with cold 10% aq K_2CO_3 (2×15 mL) and brine (2×15 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Yield 4.46 g (95 %). Colorless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 6.28 (s, 1H), 4.79 (s, 2H), 2.01 (t, *J* = 18.4 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.5 (2C), 119.2 (t, *J* = 232.5 Hz), 99.7, 57.5, 25.9, 23.9 (t, *J* = 27.5 Hz), 18.4, –5.3 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –84.9 ppm. LC–

MS (*m/z*): 277 (M + H^+). Anal. Calcd. for $C_{12}H_{22}F_2N_2OSi$: C, 52.15; H, 8.02; N, 10.14. Found: C, 52.23; H, 8.23; N, 10.18.

General procedure for the preparation of the compounds 23 and 26b. NH_2NHMe (7.84 mL, 0.15 mol) was added to a solution of ynone **13** (0.10 mol) in THF (250 mL) at 0°C, and the mixture was stirred overnight. After the reaction was complete (monitored by ^1H NMR analysis), the resulting solution was concentrated under reduced pressure. The residue was dissolved in EtOAc (250 mL), filtered through a silica plug, and concentrated *in vacuo*.

5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole (23b). The reaction led to the formation of *ca*. 9:1 regioisomeric mixture of **23b** and **27b**, which was subjected to chromatographic separation (gradient hexanes–*t*-BuOMe as eluent). Isomer **23b** was isolated as a single product. Yield 114 g (86 %) from 120 g of **13b**. Colorless liquid. ^1H NMR (500 MHz, DMSO-d_6): δ 6.62 (s, 1H), 4.75 (s, 2H), 3.86 (s, 3H), 0.86 (s, 9H), 0.07 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 143.6, 139.0 (q, J = 37.4 Hz), 121.5 (q, J = 267.8 Hz), 103.4, 55.4, 37.1, 25.5, 17.7, –5.7 ppm.

$^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6): δ –61.2 ppm. Anal. Calcd. for $C_{12}H_{21}F_3N_2OSi$: C, 48.96; H, 7.19; N, 9.52. Found: C, 49.13; H, 6.95; N, 9.83.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-methyl-5-(trifluoromethyl)-1*H*-pyrazole (26b). The compound was synthesized by the same procedure described for **23b**. The product was obtained as a single isomer after chromatographic separation (gradient hexanes–*t*-BuOMe as eluent) of *ca*. 9:1 regioisomeric mixture of **23b** and **26b**. Yield 13.3 g (10 %) from 120 g of **13b**. Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38 (s, 1H), 4.68 (s, 2H), 3.92 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H) ppm. $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6): δ 143.6, 138.9 (q, J = 37.4 Hz), 121.5 (q, J = 267.8 Hz), 103.5, 55.4, 37.2, 25.6, 17.8, –5.6 ppm. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6): δ –60.1 ppm. Anal. Calcd. for $C_{12}H_{21}F_3N_2OSi$: C, 48.96; H, 7.19; N, 9.52. Found: C, 48.61; H, 7.42; N, 9.29.

5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1,1-difluoroethyl)-1-methyl-1*H*-pyrazole (23c). Yield 5.09 g (92 %) from 5.00 g of **13c**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (s, 1H), 4.66 (s, 2H), 3.88 (s, 3H), 1.98 (t, J = 18.3 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H) ppm. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 147.8 (t, J = 33.3 Hz), 142.5, 119.2 (t, J = 232.4 Hz), 102.6, 56.2, 37.0, 25.8, 23.9 (t, J = 27.8 Hz), 18.2, –5.4 ppm. $^{19}F\{^{1}H\}$ NMR (376 MHz,

$CDCl_3$): δ –84.7 ppm. LC–MS (*m/z*): 291 ($M + H^+$). Anal. Calcd. for $C_{13}H_{24}F_2N_2OSi$: C, 53.76; H, 8.33; N, 9.65. Found: C, 53.91; H, 8.70; N, 9.99.

5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-methyl-3-(perfluoroethyl)-1*H*-pyrazole (23d). Yield 4.14 g (79 %) from 5.00 g of **13d**. ^1H NMR (400 MHz, $CDCl_3$): δ 6.41 (s, 1H), 4.69 (s, 2H), 3.94 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 143.3, 139.4 (t, J = 28.6 Hz), 119.1 (qt, J = 285.1, 37.9 Hz), 111.0 (tq, J = 250.0, 39.0 Hz), 105.0, 56.1, 37.5, 25.7, 18.2, –5.5 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –85.3 (s, 3F), –113.4 (s, 2F) ppm. LC–MS (*m/z*): 345 ($M + H^+$). Anal. Calcd. for $C_{13}H_{21}F_5N_2OSi$: C, 45.34; H, 6.15; N, 8.13. Found: C, 45.16; H, 5.91; N, 7.82.

3-(Bromodifluoromethyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyl-1*H*-pyrazole (23e). Yield 3.91 g (72 %) from 5.00 g of **13e**. ^1H NMR (400 MHz, $CDCl_3$): δ 6.36 (s, 1H), 4.66 (s, 2H), 3.92 (s, 3H), 0.90 (s, 9H), 0.09 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 147.1 (t, J = 29.0 Hz), 142.9, 114.5 (t, J = 298.4 Hz), 102.8 (t, J = 2.2 Hz), 56.0, 37.4, 25.7, 18.1, –5.5 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –42.1 ppm. LC–MS (*m/z*): 355/357 ($M + H^+$). Anal. Calcd. for $C_{12}H_{21}BrF_2N_2OSi$: C, 40.57; H, 5.96; N, 7.88; Br, 22.49. Found: C, 40.92; H, 5.87; N, 7.61; Br, 22.30.

5-(1-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-(difluoromethyl)-1-methyl-1*H*-pyrazole (23h). Yield 4.87 g (88 %) from 5.00 g of **13h**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.62 (t, *J* = 55.4 Hz, 1H), 6.30 (s, 1H), 4.97 (q, *J* = 6.5 Hz, 1H), 3.92 (s, 3H), 1.49 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), –0.01 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 147.5, 145.2 (t, *J* = 29.2 Hz), 111.5 (t, *J* = 233.4 Hz), 101.2 (t, *J* = 1.7 Hz), 63.7, 37.8, 25.8, 24.1, 18.2, –4.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ –111.80 (d, *J* = 55.4 Hz), –111.83 (d, *J* = 55.4 Hz) ppm. Anal. Calcd. for $C_{13}H_{24}F_2N_2OSi$: C, 53.76; H, 8.33; N, 9.65. Found: C, 53.61; H, 8.53; N, 9.43.

General procedure for the preparation of the compounds 24 and 25. KHF_2 (3.91 g, 0.05 mol) was added to a solution of pyrazole **22** or **23** (0.10 mol) in MeOH–H_2O (9 : 1) mixture (250 mL), and the reaction mixture was stirred overnight. After the reaction was complete (monitored by ^{1}H NMR analysis), MeOH was evaporated under reduced pressure. The residue was dissolved in EtOAc (150 mL) and washed with brine (2×70 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

(3-(Difluoromethyl)-1*H*-pyrazol-5-yl)methanol (24a). Yield 45.2 g (97 %) from 80.0 g of **22a**. Yellow liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (s, 1H), 6.91 (t, J = 54.8 Hz, 1H), 6.37 (s, 1H), 5.37 (t, J = 5.6 Hz, 1H), 4.52 (d, J = 5.6 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 146.1 (t, J = 28.3 Hz), 145.4, 112.1 (t, J = 230.9 Hz), 100.4, 54.5 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ –110.3 (d, J = 54.8 Hz) ppm. GC–MS (*m/z*): 148 (M^+), 131 (M^+ – OH). Anal. Calcd. for $C_5H_6F_2N_2O$: C, 40.55; H, 4.08; N, 18.91. Found: C, 40.48; H, 4.36; N, 18.52.

(3-(1,1-Difluoroethyl)-1*H*-pyrazol-5-yl)methanol (24c). Yield 2.39 g (95 %) from 4.28 g of **22c**. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (s, 1H), 4.69 (s, 2H), 1.93 (t, J = 18.4 Hz, 3H) ppm. OH and NH protons were exchanged with HDO. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 148.6 (t, J = 32.2 Hz), 145.3, 118.9 (t, J = 233.5 Hz), 101.0, 55.6, 24.1 (t, J = 27.8 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ –85.2 ppm. LC–MS (*m/z*): 161 ($M - H^+$). Anal. Calcd. for $C_6H_8F_2N_2O$: C, 44.45; H, 4.97; N, 17.28. Found: C, 44.24; H, 4.92; N, 17.57.

2-(3-(Difluoromethyl)-1*H*-pyrazol-5-yl)ethanol (24g). The product was synthesized from ynone **13g** (5.00 g, 19.1 mmol), which was first converted to 5-(2-((*tert*-

butyldimethylsilyl)oxy)ethyl)-3-(difluoromethyl)-1*H*-pyrazole (**22g**) by the general procedure for the preparation of the compounds **22**. The obtained crude intermediate **22g** was subjected to the next desilylation by the general procedure for the preparation of the compounds **24** and **25** without additional purification. Yield 2.76 g (82 %) from 5.00 g of **13g**. Colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.94 (s, 1H), 6.87 (t, J = 54.9 Hz, 1H), 6.29 (s, 1H), 4.79 (t, J = 5.1 Hz, 1H), 3.62 (td, J = 6.8, 5.1 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 146.1 (t, J = 28.4 Hz), 142.6, 112.2 (t, J = 230.7 Hz), 100.9, 60.1, 28.9 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ –110.2 (d, J = 54.9 Hz) ppm. Anal. Calcd. for $C_6H_8F_2N_2O$: C, 44.45; H, 4.97; N, 17.28. Found: C, 44.57; H, 5.29; N, 17.03.

1-(3-(Difluoromethyl)-1*H*-pyrazol-5-yl)ethanol (24h).[58] Yield 2.45 g (95 %) from 4.40 g of **22h**. White solid, mp = 61–63 °C (lit. 62–63 °C)[58]. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.08 (s, 1H), 6.90 (t, J = 54.9 Hz, 1H), 6.33 (s, 1H), 5.44 (d, J = 5.0 Hz, 1H), 4.80 (quint, J = 6.1 Hz, 1H), 1.39 (d, J = 6.4 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 149.9, 146.0 (t, J = 28.4 Hz), 112.2 (t, J = 230.9 Hz), 98.9, 61.3, 23.8 ppm. ^{19}F{^{1}H}

NMR (376 MHz, DMSO-d_6): δ –110.3 ppm. Anal. Calcd. for $C_6H_8F_2N_2O$: C, 44.45; H, 4.97; N, 17.28. Found: C, 44.84; H, 4.79; N, 17.35.

(1-Methyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanol (25b). Yield 62.7 g (94 %) from 109 g of **23b**. White solid, mp 52–54 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.59 (s, 1H), 5.45 (t, J = 5.4 Hz, 1H), 4.54 (d, J = 5.4 Hz, 2H), 3.87 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 145.0, 138.9 (q, J = 37.1 Hz), 121.7 (q, J = 267.7 Hz), 103.6, 53.7, 37.1 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –60.9 ppm. LC–MS (*m/z*): 181 (M + H^+). Anal. Calcd. for $C_6H_7F_3N_2O$: C, 40.01; H, 3.92; N, 15.55. Found: C, 39.65; H, 3.83; N, 15.57.

2-(3-(Difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)ethanol (25g). The compound was synthesized from ynone **13g** (5.00 g, 19.1 mmol), which was first converted to 5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(difluoromethyl)-1-methyl-1*H*-pyrazole (**23g**) by the general procedure for the preparation of the compounds **23**. The obtained crude intermediate **23g** was subjected to the next desilylation by the general procedure for the preparation of the compounds **24** and **25** without additional purification. Yield 2.59 g (77 %) from 5.00 g of **13g**. Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.59 (t, J = 55.3

Hz, 1H), 6.30 (s, 1H), 3.86 (t, J = 6.4 Hz, 2H), 3.79 (s, 3H), 2.85 (t, J = 6.4 Hz, 2H), 2.34 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.9 (t, J = 28.7 Hz), 142.2, 111.1 (t, J = 233.5 Hz), 102.2 (t, J = 2.0 Hz), 60.2, 36.2, 28.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ – 112.0 (d, J = 55.3 Hz) ppm. Anal. Calcd. for $C_7H_{10}F_2N_2O$: C, 47.73; H, 5.72; N, 15.90. Found: C, 47.82; H, 5.50; N, 15.69.

1-(3-(Difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)ethanol (25h). Yield 2.46 g (97 %) from 4.18 g of **23h**. Yellow oil. ^1H NMR (400 MHz, DMSO-d_6): δ 6.89 (t, J = 54.8 Hz, 1H), 6.39 (s, 1H), 5.39 (d, J = 5.7 Hz, 1H), 4.87 – 4.79 (m, 1H), 3.85 (s, 3H), 1.42 (d, J = 6.4 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 148.4, 143.9 (t, J = 28.6 Hz), 111.8 (t, J = 231.2 Hz), 100.5, 60.1, 37.1, 22.5 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ – 110.7 ppm. Anal. Calcd. for $C_7H_{10}F_2N_2O$: C, 47.73; H, 5.72; N, 15.90. Found: C, 48.06; H, 5.59; N, 16.01.

(3-(Difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)methanol (25a).[59]

The compound was synthesized from ynone **13a** (100 g, 0.617 mol), which was first converted to 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(difluoromethyl)-1-methyl-1*H*-pyrazole (**23a**) by the general procedure for the preparation of the compounds **23**. The

reaction led to *ca*. 9:1 regioisomeric mixture of **23a** and **27a**, which was subjected to the next step without separation of the two isomers. Desilylation by the general procedure for the preparation of the compounds **24** and **25** resulted in *ca*. 9:1 regioisomeric mixture of **25a** and **26a**, which was subjected to separation by vacuum distillation. The isomer **25a** was isolated as a single product. Yield 89.0 g (89 %) from 100 g of **13a**. Yellow liquid, bp = 131–132 °C/1 mbar. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.90 (t, J = 54.9 Hz, 1H), 6.41 (s, 1H), 5.37 (t, J = 5.6 Hz, 1H), 4.51 (d, J = 5.6 Hz, 2H), 3.82 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 144.7, 144.5 (t, J = 28.7 Hz), 112.0 (t, J = 231.4 Hz), 102.9, 54.2, 36.8 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ –110.8 (d, J = 54.9 Hz) ppm. Anal. Calcd. for $C_6H_8F_2N_2O$: C, 44.45; H, 4.97; N, 17.28. Found: C, 44.26; H, 4.60; N, 17.54.

(5-(Difluoromethyl)-1-methyl-1*H*-pyrazol-3-yl)methanol (27a). The compound was synthesized by the same procedure described for **25a**. The product was obtained as a single isomer after separation of *ca*. 9:1 regioisomeric mixture of **25a** and **27a** by vacuum distillation. Yield 6.00 g (6 %) from 100 g of **13a**. Yellow liquid, bp = 92–94 °C/1 mbar. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.26 (t, J = 53.7 Hz, 1H), 6.50 (s, 1H), 5.11 (t, J

= 5.8 Hz, 1H), 4.38 (d, *J* = 5.8 Hz, 2H), 3.84 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 152.0, 135.7 (t, *J* = 27.1 Hz), 109.3 (t, *J* = 232.8 Hz), 105.1 (t, *J* = 3.2 Hz), 56.9, 37.2 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ –113.7 (d, *J* = 53.7 Hz) ppm. Anal. Calcd. for $C_6H_8F_2N_2O$: C, 44.45; H, 4.97; N, 17.28. Found: C, 44.55; H, 4.99; N, 17.45.

5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(difluoromethyl)-1-methyl-1*H*-pyrazole (23a). An analytical sample of the compound was obtained by column chromatography (gradient hexanes–*t*-BuOMe as eluent) of the mixture of **23a** and **27a** (1.00 g), prepared by the protocol described for the compound **25a**. Colorless liquid. ^1H NMR (500 MHz, DMSO-d_6): δ 6.89 (t, *J* = 54.8 Hz, 1H), 6.43 (s, 1H), 4.73 (s, 2H), 3.82 (s, 3H), 0.87 (s, 9H), 0.07 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 144.0 (t, *J* = 28.8 Hz), 143.0, 111.5 (t, *J* = 231.4 Hz), 102.4, 55.6, 36.7, 25.5, 17.8, –5.7 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ –110.9 (d, *J* = 54.8 Hz) ppm. Anal. Calcd. for $C_{12}H_{22}F_2N_2OSi$: C, 52.15; H, 8.02; N, 10.14. Found: C, 52.46; H, 7.77; N, 10.02.

5-(Difluoromethyl)isoxazole-3-carboxylic acid (29a). To a solution of **21a** (67.0 g, 0.450 mol) in acetone (675 mL), a solution of CrO_3 (64.8 g, 0.648 mol) and conc. H_2SO_4 (55.8 mL) in H_2O (225 mL) was added slowly at 0 °C, and the reaction was stirred

overnight. After the reaction was complete (monitored by ^{1}H NMR analysis), the resulting mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (675 mL), then washed with H_2O (300 mL) and brine (2×300 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Yield 65.7 g (90 %) from 67.0 g of **21a**. White solid, mp = 77–79 °C (dec). ^{1}H NMR (400 MHz, D_2O): δ 7.03 (s, 1H), 6.95 (t, J = 52.8 Hz, 1H) ppm. $^{13}C\{^{1}H\}$ NMR (126 MHz, D_2O): δ 164.9 (t, J = 30.2 Hz), 161.5, 157.0, 107.0 (t, J = 237.8 Hz), 105.0 ppm. $^{19}F\{^{1}H\}$ NMR (376 MHz, D_2O): δ –119.7 ppm. LC–MS (*m/z*): 118 ($M - H^+ - CO_2$). Anal. Calcd. for $C_5H_3F_2NO_3$: C, 36.83; H, 1.85; N, 8.59. Found: C, 36.75; H, 1.59; N, 8.78.

2-(3-(Difluoromethyl)isoxazol-5-yl)acetic acid (35g). The compound was synthesized by the same procedure described for **29a**. Yield 2.01 g (43 %) from 4.30 g of **20g**. White solid, mp = 90–92 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.25 (br s, 1H), 6.76 (t, J = 53.5 Hz, 1H), 6.56 (s, 1H), 3.96 (s, 2H) ppm. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 173.0, 166.4, 159.2 (t, J = 30.1 Hz), 108.9 (t, J = 237.1 Hz), 101.0, 32.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ –115.7 (d, J = 53.5 Hz) ppm. Anal. Calcd. for $C_6H_5F_2NO_3$: C, 40.69; H, 2.85; N, 7.91. Found: C, 40.89; H, 2.58; N, 7.53.

Ethyl 5-(difluoromethyl)isoxazole-3-carboxylate (30). To a solution of **29a** (1.50 g, 7.85 mmol) in anhydrous EtOH (15 mL), conc H_2SO_4 (0.042 mL, 0.79 mmol) was added, and the solution was refluxed overnight. After the reaction was complete (monitored by ^1H NMR analysis), the mixture was concentrated *in vacuo*, and the residue was dissolved in EtOAc (15 mL). The organic phase was washed with aq $NaHCO_3$ (5 mL), and brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The compound was purified by distillation in *vacuo*. Yield 1.62 g (92%). Colorless oil, bp 46–49 °C / 1 mbar. ^1H NMR (400 MHz, DMSO-d_6): δ 7.41 (s, 1H), 7.40 (t, J = 53.8 Hz, 1H), 4.39 (q, J = 6.9, 2H), 1.33 (t, J = 6.9 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 165.0 (t, J = 29.1 Hz), 158.9, 156.8, 107.6 (t, J = 237 Hz), 106.0 (t, J = 3.6 Hz), 62.6, 14.0 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ –119.2 ppm. Anal. Calcd. for $C_7H_7F_2NO_3$: C, 43.99; H, 3.69; N, 7.33. Found: C, 44.04; H, 3.33; N, 7.67.

***tert*-Butyl 1-benzyl-2-(5-(difluoromethyl)isoxazole-3-carbonyl)hydrazinecarboxylate (33).** Ethyl 5-(difluoromethyl)isoxazole-3-carboxylate (**30**) (1.55 g, 8.12 mmol) and N_2H_4

in H_2O (3.90 mL, 20% wt, 24.4 mmol) were dissolved in EtOH (8 mL) and refluxed for 15 h. Then, the reaction mixture was concentrated *in vacuo* to dryness, and the residue was redissolved in THF (8 mL). PhCHO (0.90 g, 8.53 mol) was added to the solution of **31**, followed by the addition of $NaBH(OAc)_3$ (2.59 g, 12.2 mol) at 0 °C. To the resulting mixture, CH_3COOH (0.974 g, 16.2 mmol) was added, and the reaction was stirred at rt overnight. The solvent was removed by evaporation under reduced pressure, and the residue was partitioned between EtOAc (5 mL) and H_2O (5 mL). The organic layer was washed with aq $NaHCO_3$ (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL), and di-*tert*-butyl dicarbonate (2.24 mL, 9.74 mmol) and 4-dimethylaminopyridine (0.23 g, 1.9 mmol). The mixture was stirred at rt overnight, than washed with H_2O (4 mL), and brine (4 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by gradient reverse phase chromatography (gradient CH_3CN–H_2O as eluent). Yield 1.25 g (42%) from **30** (1.55 g). White solid, mp 88–90 °C. The compound was obtained as a mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.38 – 7.27 (m, 5H), 7.04 (s, 1H), 6.77 (t, J = 53.3 Hz, 1H), 4.76 (s, 2H), 1.49 (s, 9H) ppm.

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 165.0 (t, *J* = 31.5 Hz), 157.0, 156.9, 154.5, 136.3, 128.8, 128.5, 128.0, 106.8 (t, *J* = 240.4 Hz), 104.3, 82.5, 54.3 and 52.8, 28.2 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ –117.95 (d, *J* = 53.3 Hz) and –117.97 (d, *J* = 53.3 Hz) and –118.01 (d, *J* = 53.3 Hz) ppm. LC–MS (*m/z*): 366 ($M - H^+$). Anal. Calcd. for $C_{17}H_{19}F_2N_3O_4$: C, 55.58; H, 5.21; N, 11.44. Found: C, 55.81; H, 5.58; N, 11.63.

1-(4-(3-Chlorophenyl)piperazin-1-yl)-2-(3-(difluoromethyl)isoxazol-5-yl)ethanone (37). Carbonyldiimidazole (708 mg, 4.38 mmol) was added to a solution of 2-(3-(difluoromethyl)isoxazol-5-yl)acetic acid (**35g**) (645 mg, 3.64 mmol) in THF (5 mL), and the solution was stirred for 2 h. Then 1-(3-chlorophenyl)piperazine (**36**) (788 mg, 4.00 mmol) was added, and the reaction mixture was stirred overnight. The obtained solution was concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 (10 mL), washed with 5% aq HCl (5 mL), $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Yield 1.19 g (92%). White solid, mp 89–92 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (t, *J* = 8.4 Hz, 1H), 6.92 – 6.85 (m, 2H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.74 (t, *J* = 53.8 Hz, 1H), 6.53 (s, 1H), 3.96 (s, 2H), 3.80 (s, 2H), 3.69 (s, 2H), 3.20 (s, 4H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ

168.2, 164.5, 159.0 (t, J = 29.8 Hz), 151.7, 135.0, 130.2, 120.2, 116.3, 114.5, 109.0 (t, J = 237.1 Hz), 100.5, 48.9, 48.6, 45.8, 41.8, 31.9 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ –115.9 ppm. LC–MS (*m/z*): 356/358 ($M + H^+$). Anal. Calcd. for $C_{16}H_{16}ClF_2N_3O_2$: C, 54.02; H, 4.53; N, 11.81; Cl, 9.96. Found: C, 54.22; H, 4.72; N, 11.64; Cl, 9.81.

5-(2-(4-(3-Chlorophenyl)piperazin-1-yl)ethyl)-3-(difluoromethyl)isoxazole (34). To a suspension of $LiAlH_4$ (146 mg, 3.84 mmol) in THF (10 mL), TMSCl (0.51 mL, 4.00 mmol) was added dropwise at 0 °C, and the reaction mixture was stirred for 30 min. Then, a solution of 1-(4-(3-chlorophenyl)piperazin-1-yl)-2-(3-(difluoromethyl)isoxazol-5-yl)ethanone (**37**) (1.19 g, 3.34 mmol) in THF (12 mL) was added dropwise at –5 °C, and the reaction was stirred overnight. After the reaction was complete (monitored by ^1H NMR analysis), H_2O (0.15 mL) was added dropwise at 0 °C. After that, a solution of NaOH (58.0 mg, 1.45 mmol) in H_2O (0.15 mL) was added dropwise at 10 °C, followed by the addition of another portion of H_2O (0.42 mL). Formed precipitate was filtered off, and the solution was concentrated under reduced pressure. The crude product was purified by gradient reverse phase chromatography (gradient CH_3CN–H_2O as eluent). Yield 810 mg (71 %). White solid, mp 78–81 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.16

(t, J = 8.1 Hz, 1H), 6.87 (s, 1H), 6.85 – 6.57 (m, 3H), 6.32 (s, 1H), 3.23 – 3.17 (m, 4H), 3.03 (t, J = 7.4 Hz, 2H), 2.78 (t, J = 7.4 Hz, 2H), 2.68 – 2.62 (m, 4H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6): δ 174.2, 158.5 (t, J = 28.6 Hz), 152.2, 133.8, 130.3, 118.0, 114.5, 113.6, 109.6 (t, J = 235.0 Hz), 98.9, 54.8, 52.1, 47.6, 23.9 ppm. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6): δ –116.3 ppm. LC–MS (*m/z*): 342/344 ($M + H^+$). Anal. Calcd. for $C_{16}H_{18}ClF_2N_3O$: C, 56.23; H, 5.31; N, 12.29; Cl, 10.37. Found: C, 55.85; H, 5.65; N, 12.14; Cl, 10.32.

ASSOCIATED CONTENT

Supporting Information. The following files are available free of charge:

copies of NMR spectra, results of X-Ray diffraction studies and procedures for the preparation of compounds **29**, **35**, and **38–52** (PDF)

crystallographic information files (CIF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

The work was funded by Enamine Ltd. and NIH grant GM133836 (to Prof. John J. Irwin and Y.S.M.). O.O.G. was also funded by Ministry of Education and Science of Ukraine

(Grant No. 19БФ037-03). The authors thank Prof. Andrey A. Tolmachev for his encouragement and support, and Eduard Rusanov for his help with X-ray diffraction studies.

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