Graphical Abstract

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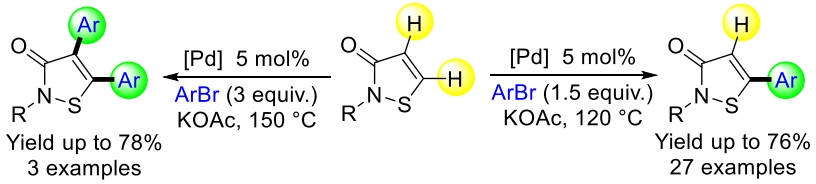

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Palladium-catalyzed direct C5-arylation or C4,C5-diarylation of 2-alkylisothiazol-3-ones

Oumaima Mhadhbi,[a,b,c] Linhao Liu,[a] Amal Benzai,[a] Besma Mellah,[c] Néji Besbes,[c] Jerome Ollivier,[a] Marie Cordier[a] and Henri Doucet[a,*]

[a] *Univ Rennes, CNRS, ISCR-UMR 6226, F-35000 Rennes, France.*
[b] *Faculté des Sciences de Tunis, Université de Tunis El Manar, Campus Universitaire El-Manar, 2092 El Manar Tunis, Tunisia.*
[c] *Laboratoire des Matériaux Composites et des Minéraux Argileux, Centre National de Recherches en Sciences des Matériaux, Technopole Bordj Cedria, Soliman, 8027, Tunisia.*

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ABSTRACT

The regioselectivity of the Pd-catalyzed direct arylation of unsubstituted 2-alkylisothiazol-3(2*H*)-ones was investigated. Conditions for the regioselective palladium-catalyzed direct C5-arylation of 2-alkylisothiazol-3-ones using aryl bromides as the coupling partners are reported. This procedure tolerates a wide variety of substituents such as nitro, nitrile, ester, chloro, fluoro, trifluoromethyl, trifluoromethoxy, difluoromethoxy at *para*-, *meta*- and also *ortho*-positions on the aryl bromide. Both methyl- and octyl-substituents at 2-position of alkylisothiazol-3-ones are tolerated. Moreover, at a more elevated temperature in the presence of a larger excess of the aryl bromide, the access to the C4,C5-diarylated alkylisothiazol-3-ones is also possible, revealing that the C4-position of isothiazol-3(2*H*)-ones is reactive for direct arylation when the C5-position is blocked. Therefore, this method provides a one pot access to a wide variety of isothiazolinone derivatives allowing to modify easily their biological properties.

1. Introduction

Methylisothiazolinone (MIT) and it's derivative chloromethylisothiazolinone (CMIT) are widely used as biocides killing most aerobic and anaerobic bacteria and can be found in many personal care products and cosmetics (Fig 1). However, they can cause contact dermatitis.[1] Therefore, the discovery of isothiazolinone derivatives causing less allergic reactions would be attractive.

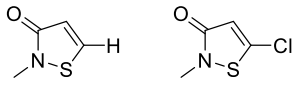
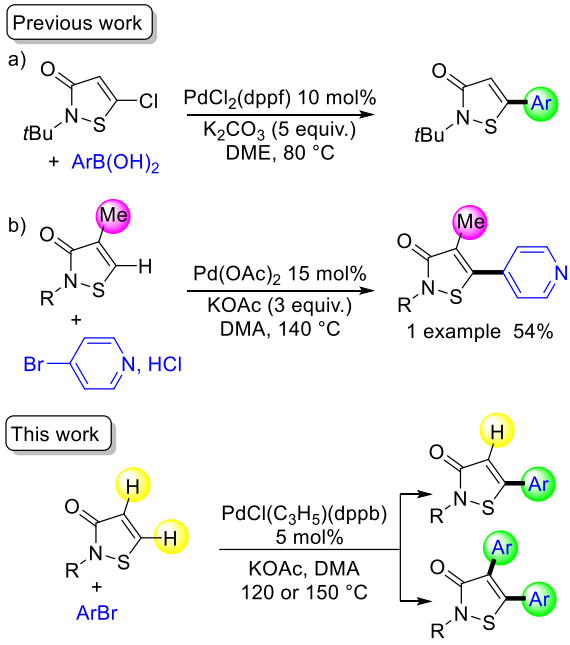


Figure 1. Structures of MethylIsoThiazolinone (MIT) and it's derivative ChloroMethylIsoThiazolinone (CMIT).

The so-called metal-catalyzed "direct arylation" of heteroarenes which proceeds *via* a C-H bond functionalization, pioneered by Ohta et al. now represents one of the most effective tool for the access to arylated heteroarenes.[2] This methodology has been applied to a wide range of 5-membered ring heteroaromatics such as pyrroles, indoles or thiophenes to access (hetero)biaryls using in many cases sustainable reaction conditions.[3-5] When this "direct arylation" methodology can be used for the late-stage functionalization of bioactive compounds, it provides a very appealing tool for a fast screening of the biological properties of a family of compounds containing a specific unit.

The synthesis of a few 5-arylisothiazol-3(2*H*)-ones from 2-(*tert*-butyl)-5-chloroisothiazol-3(2*H*)-one and arylboronic acids *via* Suzuki coupling has been described (Scheme 1, a).[6] Suzuki coupling has also been employed for the preparation of 5-arylated isothiazol-3-one 1-oxide and isothiazol-3-one 1,1-dioxide by reaction of the 5-chloro-substituted isothiazol-3-one 1-oxide[7] and isothiazol-3-one 1,1-dioxide[8] with arylboronic acids. By contrast, a single example of direct arylation of a C4-substituted 2-methylisothiazol-3(2*H*)-one using an heteroarene as the reaction partner has been described by Yin et al. in the course of their study on the preparation of saccharin derivatives as inhibitors of interferon-mediated inflammation (Scheme 1, b).[9] To the best of our knowledge, no examples of direct C4-arylations of isothiazol-3(2H)-ones and the reactivity in direct arylation of unsubstituted 2-alkylisothiazol-3(2H)-ones have been reported. Therefore, the reactivity and especially regioselectivity of the direct arylation (C4- vs C5-arylation) of unsubstituted 2-alkylisothiazol-3(2*H*)-ones needed to be investigated.

* Corresponding author. Tel.: +33 (0)2 23 23 63 84; e-mail: henri.doucet@univ-rennes1.fr



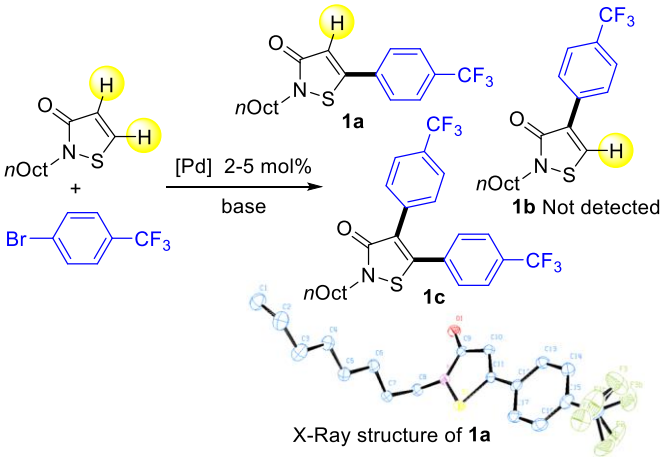
Scheme 1. Pd-catalyzed arylations of isothiazol-3(2*H*)-ones: Suzuki coupling and direct arylation.

Herein, we report *i*) on the regioselectivity of the direct arylation of unsubstituted 2-alkylisothiazol-3(2*H*)-ones; *ii*) reaction conditions for the palladium-catalyzed regioselective direct mono-arylation at C5-position of 2-alkylisothiazol-3(2*H*)-ones and on the substrate scope of the reaction; *iii*) reaction conditions for access to C4,C5-diarylated 2-alkylisothiazol-3(2*H*)-ones *via* a double C-H bond functionalization.

2. Results and Discussion

We initially examined the reactivity of 2-octanoylisothiazol-3(2*H*)-one based on our previous results on palladium-catalyzed direct arylation of 5-membered ring heteroarenes.[5] Using 1.5 equiv. of 4-(trifluoromethyl)bromobenzene in the presence of 5 mol% $PdCl(C_3H_5)(dppb)$[10] catalyst and KOAc as base at 120 °C in DMA, the C5-arylated imidazole **1a** was regioselectively obtained in 60% yield (Table 1, entry 1). The structure of **1a** was confirmed by X-Ray analysis.[11] The C5-selectivity might be due to coordination of the sulfur atom to palladium, and/or to electronic factors. The use of Cs_2CO_3 as base in place of KOAc didn't afford **1a**; whereas, the use of KOPiv gave a similar yield in **1a** (Table 1, entries 2 and 3). The yield in **1a** was not improved by using a longer reaction time (Table 1, entry 4) and decreased by 19% using xylene as the solvent (Table 1, entry 5), whereas both NMP and DMF were ineffective solvents (Table 1, entries 6 and 7). Phosphine-ligand free catalyst $Pd(OAc)_2$ (5 mol%) with KOAc base afforded **1a** in a very low 8% yield (Table 1, entry 8). A lower loading of $PdCl(C_3H_5)(dppb)$ catalyst (2 mol%) afforded **1a** in only 27% yield (Table 1, entry 9). In all cases, no formation of the regioisomer **1b** was detected by GC/MC analysis of the crude mixtures. In addition, although an excess (1.5 equiv.) of 4-(trifluoromethyl)bromobenzene was used for these reactions, no formation of a very significant amount of C4,C5-diarylated product **1c** was observed. Conversely, using a higher reaction temperature (150 °C), the formation of a larger amount of C4,C5-diarylated product **1c** as side-product was detected (Table 1, entry 10). Therefore, in order to obtained **1c** in high yield, we performed the reaction with a larger amount of 4-(trifluoromethyl)bromobenzene (3 equiv.) at 150 °C. Under these conditions, the desired C4,C5-diarylated 2-octanoylisothiazol-3(2*H*)-one **1c** was obtained in 78% yield (Table 1, entry 11).

Table 1. Influence of the reaction conditions for the palladium-catalysed direct coupling of 2-octanoylisothiazol-3(2*H*)-one with 4-(trifluoromethyl)bromobenzene.[a]



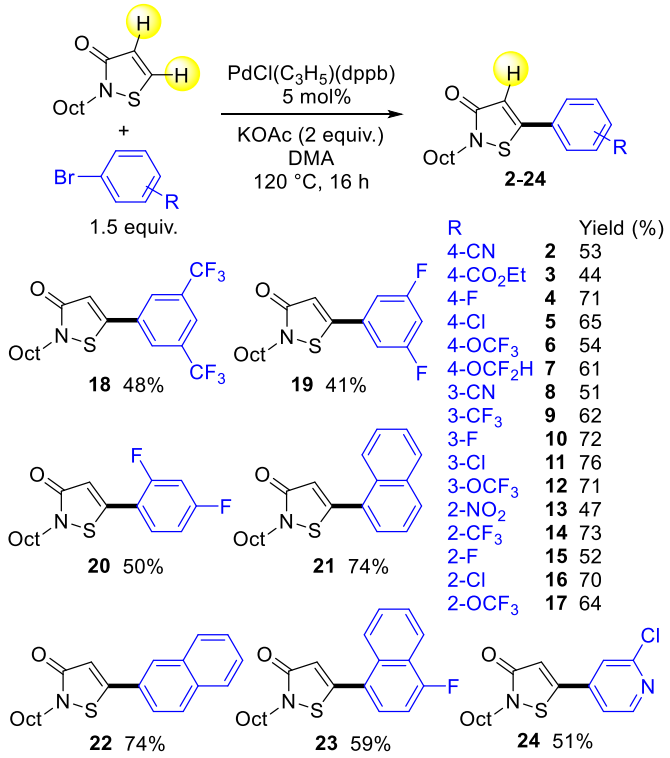
Entry	Catalyst (mol %)	Base	Solvent	Time (h)	Yield in **1a** (%)
1	$PdCl(C_3H_5)(dppb)$ (5)	KOAc	DMA	16	60
2	$PdCl(C_3H_5)(dppb)$ (5)	Cs_2CO_3	DMA	16	0
3	$PdCl(C_3H_5)(dppb)$ (5)	KOPiv	DMA	16	58
4	$PdCl(C_3H_5)(dppb)$ (5)	KOPiv	DMA	48	55
5	$PdCl(C_3H_5)(dppb)$ (5)	KOPiv	xylene	16	41
6	$PdCl(C_3H_5)(dppb)$ (5)	KOPiv	NMP	16	0
7	$PdCl(C_3H_5)(dppb)$ (5)	KOPiv	DMF	16	5
8	$Pd(OAc)_2$ (5)	KOAc	DMA	16	8
9	$PdCl(C_3H_5)(dppb)$ (2)	KOAc	DMA	16	27
10	$PdCl(C_3H_5)(dppb)$ (5)	KOAc	DMA	16	50[b]
11	$PdCl(C_3H_5)(dppb)$ (5)	KOAc	DMA	16	78[c]
12	$PdCl(C_3H_5)(dppb)$ (5)	KOAc	DMA	16	0[d]

Conditions: [a] 2-Octanoylisothiazol-3(2H)-one (1 mmol), 4-(trifluoromethyl)bromobenzene (1.5 mmol), base (2 mmol), 120 °C, isolated yields. [b] 150 °C, the formation of **1c** in significant amount was also observed. [c] 4-(trifluoromethyl)bromobenzene (3 mmol), KOAc (4 mmol), 150 °C, yield in **1c**. [d] using 4-(trifluoromethyl)chlorobenzene (1.5 mmol).

The influence of the aryl bromide substituents on the reactivity and selectivity for the C5-arylation of 2-octanoylisothiazol-3(2*H*)-one was examined using 5 mol% $PdCl(C_3H_5)(dppb)$ catalyst and KOAc base in DMA at 120 °C (Scheme 2). We first employed aryl bromides bearing electron-withdrawing *para*-substituents. Moderate yields were obtained using the electron-deficient aryl bromides 4-bromobenzonitrile and ethyl 4-bromobenzoate with the formation of products **2** and **3** in 53% and 44% yield, respectively. Conversely, 4-fluoro- and 4-chloro-substituents were well tolerated giving rise to products **4** and **5** in good yields. Moreover, the reaction with 1-bromo-4-chlorobenzene proceeded without cleavage of the C-Cl bond allowing further transformations. The bromobenzenes bearing OCF_3 and OCF_2H *para*-substituents gave the desired coupling products **6** and **7** in 54% and 61% yield, respectively.

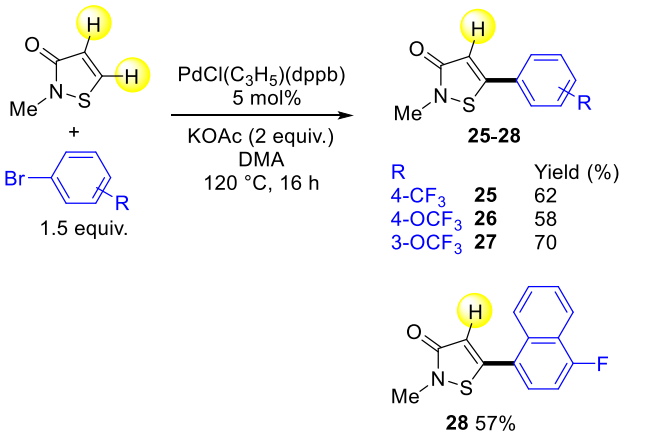
We also studied the influence some *meta*-substituents on the aryl bromide. Electron-withdrawing groups were tolerated. 4-Cyano substituted bromobenzene afforded the target product **8** in 51% yield. Trifluoromethyl-substituted aryl bromide leads to product **9** in 62% yield, while chloro, fluoro or trifluoromethoxy-substituted aryl bromides gave the expected products **10**-**12** in 71-76% yields.

Then, the reactivity of *ortho*-substituted aryl bromides was investigated. With the more sterically hindered aryl bromides, 2-(trifluoromethyl)bromobenzene, 2-chlorobromobenzene or 2-(trifluoromethoxy)bromobenzene, the arylated isothiazol-3(2*H*)-ones **14**, **16** and **17** were obtained in 64-73% yields. Again no cleavage of the C-Cl bond was observed. In the reaction of 2-bromonitrobenzene and 2-fluorobromobenzene, products **13** and **15** were obtained in lower yields. The disubstituted aryl bromides 3,5-bis(trifluoromethyl)bromobenzene, and 3,5- or 2,4-difluorobromobenzenes also reacted nicely to give the products **18**-**20** in moderate yields due to the formation of significant amounts of C4,C5-diarylated isothiazol-3(2*H*)-ones. Both 1-bromonaphthalene and 2-bromonaphthalene were also successfully coupled with 2-octanoylisothiazol-3(2*H*)-one affording the products **21**-**23** in 59-74% yields. The reaction with 4-bromo-2-chloropyridine afforded the product **24** in 51% yield. In the course of this reaction, no cleavage of the C-Cl bond leading to the formation of the 2,4-diheteroarylated pyridine was observed. It should be mentioned that in all cases, under these conditions, no formation of the regioisomer **b** was detected by GC/MS analysis of the crude mixtures.



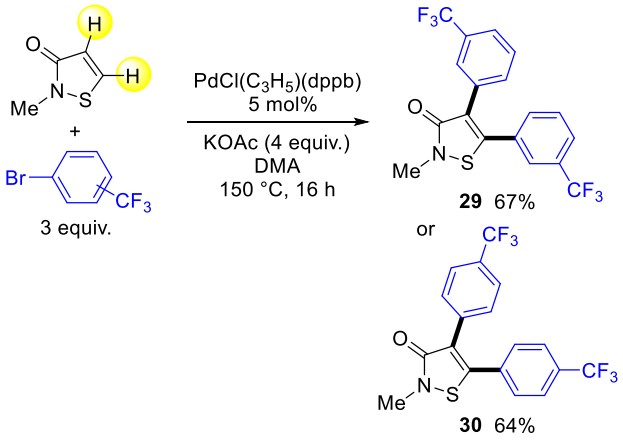
Scheme 2. Scope of the Pd-catalyzed direct C5-arylation of 2-octylisothiazol-3(2*H*)-one using various aryl bromides.

The reaction is not limited to the use of an octyl-substituted isothiazol-3(2*H*)-one. With 2-methylisothiazol-3(2H)-one which is employed as biocide (see Fig. 1) under the same reaction conditions, using 4-CF_3, 4-OCF_3 or 3-OCF_3 substituted aryl bromides and also 1-bromo-4-fluoronaphtalene as the coupling partners, the C5-arylated products **25**-**28** were obtained in similar yields than those obtained for the reactions using 2-octylisothiazol-3(2*H*)-one (Scheme 3).



Scheme 3. Scope of the Pd-catalyzed direct C5-arylation of 2-methylisothiazol-3(2H)-one using various aryl bromides.

Moreover, in the presence of a large excess of aryl bromide (3 equiv.) at 150 °C instead of 120 °C, the formation of C4,C5-diarylated isothiazol-3(2*H*)-ones in good yields is possible (Scheme 4). For example, using 3- or 4-(trifluoromethyl)bromobenzenes and 2-methylisothiazol-3(2*H*)-one as the substrates, the desired products **29** and **30** were obtained in 67% and 64% yield, respectively.



Scheme 4. Pd-catalyzed direct C4,C5-diarylations of 2-methylisothiazol-3(2H)-one.

3. Conclusion

In summary, we report herein on the reactivity and regioselectivity of unsubstituted 2-alkylisothiazol-3(2*H*)-ones in Pd-catalyzed direct arylation. At 120 °C the arylation occurred regioselectively at the C5-position of the isothiazol-3(2H)-one; whereas, the C-H bond at C4-position remained untouched. In addition, at 150 °C using 3 equiv. of aryl bromide, the C4,C5-diarylation was observed in good yields, revealing that the C4-position of isothiazol-3(2*H*)-ones is reactive for direct arylation when the C5-position is blocked. The reaction tolerated aryl bromides bearing useful functional groups such as nitro, nitrile, ester, chloro, fluoro, trifluoromethyl, trifluoromethoxy or difluoromethoxy. Therefore, this methodology which employs easily available substrates, catalyst and base, provides a very simple way to tune or modify their properties.

4. Experimental section

General: All reactions were carried out under an inert atmosphere with standard Schlenk techniques. HPLC grade DMA was used without purification. ^{1}H NMR spectra were recorded on Bruker GPX (400 MHz) spectrometer. Chemical shifts (δ) were reported in parts per million relative to residual chloroform (7.26 ppm for ^{1}H; 77.16 ppm for ^{13}C), constants were reported in Hertz. ^{1}H NMR assignment abbreviations were the following: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublet (dd), doublet of triplet (dt), triplet of doublet (td), quintuplet (quint.), doublet of doublet of doublet (ddd), and multiplet (m). ^{13}C NMR spectra were recorded at 100 MHz on the same spectrometer and reported in ppm. All reagents were weighed and handled in air.

Preparation of the PdCl(C_3H_5)(dppb) catalyst:[10] An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane was added, then the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The yellow powder was used without purification. ^{31}P NMR (162 MHz, $CDCl_3$) δ = 19.3 (s).

Synthesis of C5-arylated and C4,C5-diarylated 2-alkylisothiazol-3-ones: To a 25 mL oven dried Schlenk tube, aryl bromide (1.5 or 3 mmol) (see schemes 2-4), 2-alkylisothiazol-3(2*H*)-one (1 mmol), KOAc (0.196 g, 2 or 4 mmol) (see schemes 2-4), DMA (2 mL) and PdCl(C_3H_5)(dppb) (30.5 mg, 0.05 mmol) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 120 or 150 °C (see schemes 2-4) (oil bath temperature) for 16 hours. After cooling the reaction at room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the C5-arylated 2-alkylisothiazol-3-ones **1a** and **2**-**27** and C4,C5-diarylated 2-alkylisothiazol-3-ones **1c**, **28** and **29**.

2-Octanoyl-5-(4-(trifluoromethyl)phenyl)isothiazol-3(2*H*)-one (1a)

Following the general procedure, 4-(trifluoromethyl)bromobenzene (0.338 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **1a** in 60% (0.214 g) as a white solid: mp 79-81 °C.

^{1}H NMR (400 MHz, DMSOd_6): δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.88 (d, *J* = 8.2 Hz, 2H), 6.96 (s, 1H), 3.76 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H).

^{19}F NMR (376 MHz, DMSOd_6): δ -61.4.

^{13}C NMR (100 MHz, DMSOd_6): δ 167.4, 152.4, 133.1, 130.1 (q, *J* = 32.2 Hz), 126.1, 125.8 (q, *J* = 3.7 Hz), 123.1 (q, *J* = 271.5 Hz), 111.5, 42.4, 30.7, 28.7, 28.0, 27.9, 25.4, 21.5, 13.4.

HRMS calcd for $[M+Na]^+$ $C_{18}H_{22}F_3NOSNa$ 380.1266, found: 380.1268.

2-Octanoyl-4,5-bis(4-(trifluoromethyl)phenyl)isothiazol-3(2*H*)-one (1c)

Following the general procedure, 4-(trifluoromethyl)bromobenzene (0.676 g, 3 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **1c** in 78% (0.391 g) as a white solid: mp 76-78 °C.

^{1}H NMR (400 MHz, DMSOd_6): δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 3.87 (t, *J* = 7.1 Hz, 2H), 1.68 (quint., *J* = 6.8 Hz, 2H), 1.40-1.20 (m, 10H), 0.84 (t, *J* = 6.8 Hz, 3H).

^{19}F NMR (376 MHz, DMSOd_6): δ -61.1, -61.4.

^{13}C NMR (100 MHz, DMSOd_6): δ 165.4, 149.2, 135.6, 133.6, 129.9, 129.8 (q, *J* = 32.2 Hz), 128.7, 127.7 (q, *J* = 32.0 Hz), 125.8 (q, *J* = 3.6 Hz), 124.6 (q, *J* = 3.6 Hz), 123.8 (q, *J* = 271.5 Hz), 123.7 (q, *J* = 271.5 Hz), 121.0, 43.1, 30.7, 28.5, 28.0, 27.9, 25.4, 21.5, 13.4.

HRMS calcd for $[M+Na]^+$ $C_{25}H_{25}F_6NOSNa$ 524.1453, found: 524.1461.

4-(2-Octanoyl-3-oxo-2,3-dihydroisothiazol-5-yl)benzonitrile (2)

Following the general procedure, 4-bromobenzonitrile (0.273 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **2** in 53% (0.166 g) as a white solid: mp 66-68 °C.

^{1}H NMR (400 MHz, DMSOd_6): δ 7.99 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.5 Hz, 2H), 6.98 (s, 1H), 3.76 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.84 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, DMSOd_6): δ 167.4, 152.3, 133.4, 132.8, 126.1, 117.7, 112.6, 111.8, 42.5, 30.7, 28.7, 28.0, 27.9, 25.4, 21.6, 13.5.

HRMS calcd for $[M+Na]^+$ $C_{18}H_{22}N_2OSNa$ 337.1345, found: 337.1345.

Ethyl 4-(2-octanoyl-3-oxo-2,3-dihydroisothiazol-5-yl)benzoate (3)

Following the general procedure, ethyl 4-bromobenzoate (0.343 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **3** in 44% (0.159 g) as a white solid: mp 84-86 °C.

^{1}H NMR (400 MHz, DMSOd_6): δ 8.05 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 6.93 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.75 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.30-1.20 (m, 10H), 0.84 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, DMSOd_6): δ 168.4, 165.4, 153.8, 134.3, 132.1, 130.5, 126.5, 112.1, 61.6, 43.4, 31.6, 29.6, 29.0, 28.9, 26.3, 22.5, 14.6, 14.4.

HRMS calcd for $[M+Na]^+$ $C_{20}H_{27}NO_3SNa$ 384.1603, found: 384.1604.

5-(4-Fluorophenyl)-2-octanoylisothiazol-3(2*H*)-one (4)

Following the general procedure, 1-bromo-4-fluorobenzene (0.262 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **4** in 71% (0.218 g) as a white solid: mp 76-78 °C.

^{1}H NMR (400 MHz, DMSOd_6): δ 7.73 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.36 (t, *J* = 8.8 Hz, 2H), 6.77 (s, 1H), 3.73 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.31-1.22 (m, 10H), 0.84 (t, *J* = 6.8 Hz, 3H).

^{19}F NMR (376 MHz, DMSOd_6): δ -109.4.

^{13}C NMR (100 MHz, DMSOd_6): δ 167.7, 162.9 (d, *J* = 249.2 Hz), 153.1, 127.6 (d, *J* = 8.8 Hz), 125.9 (d, *J* = 3.3 Hz), 116.0 (d, *J* = 22.2 Hz), 109.6, 40.3, 30.2, 28.7, 28.0, 27.9, 25.4, 21.5, 13.4.

HRMS calcd for $[M+Na]^+$ $C_{17}H_{22}FNOSNa$ 330.1298, found: 330.1302.

5-(4-Chlorophenyl)-2-octanoylisothiazol-3(2*H*)-one (5)

Following the general procedure, 1-bromo-4-chlorobenzene (0.287 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **5** in 65% (0.210 g) as a white solid: mp 53-55 °C.

^{1}H NMR (400 MHz, DMSOd_6): δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 6.83 (s, 1H), 3.75 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, DMSOd_6): δ 167.5, 152.9, 135.0, 128.9, 128.1, 127.0, 110.1, 42.3, 30.6, 28.6, 28.0, 27.9, 25.3, 21.5, 13.4.
HRMS calcd for [M+Na]$^+$ $C_{17}H_{22}ClNOSNa$ 346.1003, found: 346.1001.

2-Octanoyl-5-(4-(trifluoromethoxy)phenyl)isothiazol-3(2*H*)-one (6)
Following the general procedure, 1-bromo-4-(trifluoromethoxy)benzene (0.262 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **6** in 54% (0.201 g) as a colorless oil.
^{1}H NMR (400 MHz, DMSOd_6): δ 7.80 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 6.83 (s, 1H), 3.74 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H).
^{19}F NMR (376 MHz, DMSOd_6): δ -56.7.
^{13}C NMR (100 MHz, DMSOd_6): δ 167.5, 152.6, 149.3, 128.5, 127.4, 120.7, 119.4 (q, *J* = 257.3 Hz), 110.5, 42.3, 30.7, 28.7, 28.0, 27.9, 25.4, 21.5, 13.4.
HRMS calcd for [M+Na]$^+$ $C_{18}H_{22}F_3NO_2SNa$ 396.1216, found: 396.1216.

5-(4-(Difluoromethoxy)phenyl)-2-octanoylisothiazol-3(2*H*)-one (7)
Following the general procedure, 1-bromo-4-(difluoromethoxy)benzene (0.333 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **7** in 61% (0.216 g) as a white solid: mp 61-63 °C.
^{1}H NMR (400 MHz, DMSOd_6): δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.35 (t, *J* = 73.6 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.78 (s, 1H), 3.73 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H).
^{19}F NMR (376 MHz, DMSOd_6): δ -82.9.
^{13}C NMR (100 MHz, DMSOd_6): δ 167.6, 153.1, 152.2 (t, *J* = 3.4 Hz), 127.1, 126.0, 118.6, 115.5 (t, *J* = 258.4 Hz), 109.6, 42.3, 30.6, 30.3, 28.7, 28.0, 27.9, 25.3, 13.4.
HRMS calcd for [M+Na]$^+$ $C_{18}H_{23}F_2NO_2SNa$ 378.1310, found: 378.1306.

3-(2-Octanoyl-3-oxo-2,3-dihydroisothiazol-5-yl)benzonitrile (8)
Following the general procedure, 3-bromobenzonitrile (0.273 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **8** in 51% (0.160 g) as a white solid: mp 70-72 °C.
^{1}H NMR (400 MHz, DMSOd_6): δ 8.25 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.71 (t, *J* = 7.9 Hz, 1H), 6.94 (s, 1H), 3.75 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.84 (t, *J* = 6.8 Hz, 3H).
^{13}C NMR (100 MHz, DMSOd_6): δ 167.4, 152.1, 133.7, 130.4, 130.1, 129.7, 128.9, 117.5, 112.1, 111.2, 42.0, 30.7, 28.7, 28.0, 27.9, 25.3, 21.5, 13.4.
HRMS calcd for [M+Na]$^+$ $C_{18}H_{22}N_2OSNa$ 337.1345, found: 337.1346.

2-Octanoyl-5-(3-(trifluoromethyl)phenyl)isothiazol-3(2*H*)-one (9)
Following the general procedure, 3-(trifluoromethyl)bromobenzene (0.338 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **9** in 62% (0.221 g) as a white solid: mp 84-86 °C.
^{19}F NMR (376 MHz, DMSOd_6): δ -61.2.
^{1}H NMR (400 MHz, DMSOd_6): δ 8.03 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.00 (s, 1H), 3.73 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.84 (t, *J* = 6.8 Hz, 3H).
^{13}C NMR (100 MHz, DMSOd_6): δ 167.5, 152.5, 131.3, 131.1, 130.6 (q, *J* = 32.2 Hz), 130.2, 127.8 (q, *J* = 3.8 Hz), 123.1 (q, *J* = 271.5 Hz), 121.9 (q, *J* = 3.6 Hz), 111.2, 42.4, 30.7, 28.7, 28.0, 27.9, 25.3, 21.5, 13.4.
HRMS calcd for [M+Na]$^+$ $C_{18}H_{22}F_3NOSNa$ 380.1266, found: 380.1265.

5-(3-Fluorophenyl)-2-octanoylisothiazol-3(2*H*)-one (10)
Following the general procedure, 1-bromo-3-fluorobenzene (0.262 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **10** in 72% (0.221 g) as a white solid: mp 61-63 °C.
^{1}H NMR (400 MHz, DMSOd_6): δ 7.62 (dt, *J* = 8.6, 1.5 Hz, 1H), 7.58-7.51 (m, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.36 (td, *J* = 8.6, 2.5 Hz, 1H), 6.88 (s, 1H), 3.73 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.83 (t, *J* = 6.8 Hz, 3H).
^{19}F NMR (376 MHz, DMSOd_6): δ -111.7.
^{13}C NMR (100 MHz, DMSOd_6): δ 168.4, 163.0 (d, *J* = 245.2 Hz), 153.8, 131.4 (d, *J* = 8.5 Hz), 131.1 (d, *J* = 8.6 Hz), 121.2, 117.2 (d, *J* = 21.2 Hz), 112.2 (d, *J* = 23.4 Hz), 110.7, 43.3, 31.6, 29.6, 29.0, 28.9, 26.3, 22.5, 14.4.
HRMS calcd for [M+Na]$^+$ $C_{17}H_{22}FNOSNa$ 330.1298, found: 330.1302.

5-(3-Chlorophenyl)-2-octanoylisothiazol-3(2*H*)-one (11)
Following the general procedure, 1-bromo-3-chlorobenzene (0.287 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **11** in 76% (0.246 g) as a white solid: mp 56-58 °C.
^{1}H NMR (400 MHz, DMSOd_6): δ 7.80 (t, *J* = 1.7 Hz, 1H), 7.60-7.48 (m, 3H), 6.88 (s, 1H), 3.73 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.83 (t, *J* = 6.8 Hz, 3H).
^{13}C NMR (100 MHz, DMSOd_6): δ 167.4, 152.5, 133.7, 131.2, 130.7, 130.2, 124.9, 123.7, 110.7, 42.3, 30.7, 28.7, 28.0, 27.9, 25.4, 21.5, 13.4.
HRMS calcd for [M+Na]$^+$ $C_{17}H_{22}ClNOSNa$ 346.1003, found: 346.1005.

2-Octanoyl-5-(3-(trifluoromethoxy)phenyl)isothiazol-3(2*H*)-one (12)
Following the general procedure, 1-bromo-3-(trifluoromethoxy)benzene (0.262 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **12** in 71% (0.265 g) as a white solid: mp 68-70 °C.
^{1}H NMR (400 MHz, DMSOd_6): δ 7.73 (s, 1H), 7.67-7.61 (m, 2H), 7.52 (d, *J* = 7.0 Hz, 1H), 6.92 (s, 1H), 3.73 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H).
^{19}F NMR (376 MHz, DMSOd_6): δ -56.8.
^{13}C NMR (100 MHz, DMSOd_6): δ 167.5, 152.3, 148.4, 131.4, 131.0, 124.2, 122.6, 119.5 (q, *J* = 257.1 Hz), 118.0, 111.0, 42.3, 30.6, 28.6, 28.0, 27.9, 25.3, 21.5, 13.3.
HRMS calcd for [M+Na]$^+$ $C_{18}H_{22}F_3NO_2SNa$ 396.1216, found: 396.1216.

5-(2-Nitrophenyl)-2-octanoylisothiazol-3(2*H*)-one (13)
Following the general procedure, 1-bromo-2-nitrobenzene (0.303 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **13** in 47% (0.157 g) as a yellow oil.
^{1}H NMR (400 MHz, DMSOd_6): δ 8.14 (d, *J* = 7.9 Hz, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 6.40 (s, 1H), 3.76 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.86 (t, *J* = 6.8 Hz, 3H).
^{13}C NMR (100 MHz, DMSOd_6): δ 166.5, 150.5, 147.5, 133.1, 131.1, 131.0, 124.2, 124.0, 114.0, 42.3, 30.6, 28.7, 28.0, 27.9, 25.3, 21.5, 13.4.

HRMS calcd for $[M+Na]^+$ $C_{17}H_{22}N_2O_3SNa$ 357.1243, found: 357.1241.

2-Octanoyl-5-(2-(trifluoromethyl)phenyl)isothiazol-3(2*H*)-one (14)

Following the general procedure, 2-(trifluoromethyl)bromobenzene (0.338 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **14** in 73% (0.261 g) as a colorless oil.

^{1}H NMR (400 MHz, DMSOd_6): δ 7.91 (d, J = 7.5 Hz, 1H), 7.79 (t, J = 7.5 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.63 (d, J = 7.3 Hz, 1H), 6.33 (s, 1H), 3.76 (t, J = 7.1 Hz, 2H), 1.64 (quint., J = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.83 (t, J = 6.8 Hz, 3H).

^{19}F NMR (376 MHz, DMSOd_6): δ -57.9.

^{13}C NMR (100 MHz, DMSOd_6): δ 166.8, 151.9, 132.6, 131.4, 130.5, 128.2, 127.0 (q, J = 30.2 Hz), 126.5 (q, J = 5.4 Hz), 124.0 (d, J = 273.0 Hz), 115.0, 42.6, 30.8, 28.8, 28.2, 28.1, 25.4, 21.7, 13.5.

HRMS calcd for $[M+Na]^+$ $C_{18}H_{22}F_3NOSNa$ 380.1266, found: 380.1263.

5-(2-Fluorophenyl)-2-octanoylisothiazol-3(2*H*)-one (15)

Following the general procedure, 1-bromo-2-fluorobenzene (0.262 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **15** in 52% (0.160 g) as a white solid: mp 57-59 °C.

^{1}H NMR (400 MHz, DMSOd_6): δ 7.95 (td, J = 7.9, 1.5 Hz, 1H), 7.61-7.54 (m, 1H), 7.41 (dd, J = 11.9, 8.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 6.88 (s, 1H), 3.75 (t, J = 7.1 Hz, 2H), 1.64 (quint., J = 6.8 Hz, 2H), 1.31-1.22 (m, 10H), 0.84 (t, J = 6.8 Hz, 3H).

^{19}F NMR (376 MHz, DMSOd_6): δ -111.7.

^{13}C NMR (100 MHz, DMSOd_6): δ 166.8, 158.6 (d, J = 250.3 Hz), 147.4 (d, J = 3.8 Hz), 132.3 (d, J = 9.0 Hz), 127.8 (d, J = 2.7 Hz), 125.1 (d, J = 3.1 Hz), 116.8 (d, J = 11.9 Hz), 116.0 (d, J = 21.5 Hz), 110.9 (d, J = 2.5 Hz), 42.3, 30.7, 28.6, 28.0, 27.9, 25.4, 21.5, 13.4.

HRMS calcd for $[M+Na]^+$ $C_{17}H_{22}FNOSNa$ 330.1298, found: 330.1299.

5-(2-Chlorophenyl)-2-octanoylisothiazol-3(2*H*)-one (16)

Following the general procedure, 1-bromo-2-chlorobenzene (0.287 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **16** in 70% (0.227 g) as a white solid: mp 49-51 °C.

^{1}H NMR (400 MHz, DMSOd_6): δ 7.86 (dd, J = 7.4, 1.4 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.56-7.46 (m, 2H), 6.78 (s, 1H), 3.75 (t, J = 7.1 Hz, 2H), 1.64 (quint., J = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.84 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, DMSOd_6): δ 166.6, 150.8, 131.3, 130.5, 130.2, 129.7, 127.8, 127.5, 113.3, 42.2, 30.6, 28.7, 28.0, 27.9, 25.4, 21.5, 13.4.

HRMS calcd for $[M+Na]^+$ $C_{17}H_{22}ClNOSNa$ 346.1003, found: 346.1006.

2-Octanoyl-5-(2-(trifluoromethoxy)phenyl)isothiazol-3(2*H*)-one (17)

Following the general procedure, 1-bromo-2-(trifluoromethoxy)benzene (0.262 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **17** in 64% (0.239 g) as a colorless oil.

^{1}H NMR (400 MHz, DMSOd_6): δ 8.03 (dd, J = 7.9, 1.4 Hz, 1H), 7.65 (td, J = 8.5 , 1.7 Hz, 1H), 7.59-7.52 (m, 2H), 6.89 (s, 1H), 3.75 (t, J = 7.1 Hz, 2H), 1.64 (quint., J = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.85 (t, J = 6.8 Hz, 3H).

^{19}F NMR (376 MHz, DMSOd_6): δ -56.1.

^{13}C NMR (100 MHz, DMSOd_6): δ 166.6, 147.8, 144.5, 131.9, 128.9, 127.8, 122.2, 120.6, 119.4 (q, J = 259.6 Hz), 112.3, 42.2, 30.6, 28.6, 28.0, 27.9, 25.3, 21.5, 13.4.

HRMS calcd for $[M+Na]^+$ $C_{18}H_{22}F_3NO_2SNa$ 396.1216, found: 396.1215.

5-(3,5-Bis(trifluoromethyl)phenyl)-2-octanoylisothiazol-3(2*H*)-one (18)

Following the general procedure, 1-bromo-3,5-bis(trifluoromethyl)benzene (0.440 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **18** in 48% (0.204 g) as a white solid: mp 106-108 °C.

^{1}H NMR (400 MHz, DMSOd_6): δ 8.32 (s, 2H), 8.26 (s, 1H), 7.15 (s, 1H), 3.77 (t, J = 7.1 Hz, 2H), 1.64 (quint., J = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.84 (t, J = 6.8 Hz, 3H).

^{19}F NMR (376 MHz, DMSOd_6): δ -61.2.

^{13}C NMR (100 MHz, DMSOd_6): δ 167.2, 151.0, 131.9, 131.1 (q, J = 33.5 Hz), 126.3 (q, J = 2.7 Hz), 123.8 (q, J = 4.2 Hz), 122.4 (q, J = 273.0 Hz), 112.8, 42.5, 30.4, 28.7, 28.0, 27.9, 25.3, 21.6, 13.4.

HRMS calcd for $[M+Na]^+$ $C_{19}H_{21}F_6NOSNa$ 448.1140, found: 448.1142.

5-(3,5-Difluorophenyl)-2-octanoylisothiazol-3(2*H*)-one (19)

Following the general procedure, 1-bromo-3,5-difluorobenzene (0.288 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **19** in 41% (0.133 g) as a white solid: mp 74-76 °C.

^{1}H NMR (400 MHz, DMSOd_6): δ 7.49 (dd, J = 8.3, 2.1 Hz, 2H), 7.43 (tt, J = 8.5, 2.1 Hz, 1H), 6.93 (s, 1H), 3.73 (t, J = 7.1 Hz, 2H), 1.62 (quint., J = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.83 (t, J = 6.8 Hz, 3H).

^{19}F NMR (376 MHz, DMSOd_6): δ -107.8.

^{13}C NMR (100 MHz, DMSOd_6): δ 167.3, 162.3 (dd, J = 247.6, 13.6 Hz), 151.7 (t, J = 3.1 Hz), 132.5 (t, J = 10.5 Hz), 111.7, 108.9 (d, J = 7.9 Hz), 105.6 (t, J = 25.9 Hz), 42.4, 30.7, 28.7, 28.0, 27.9, 25.3, 21.5, 13.4.

HRMS calcd for $[M+Na]^+$ $C_{17}H_{21}F_2NOSNa$ 348.1204, found: 348.1207.

5-(2,4-Difluorophenyl)-2-octanoylisothiazol-3(2*H*)-one (20)

Following the general procedure, 1-bromo-2,4-difluorobenzene (0.288 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **20** in 50% (0.163 g) as a yellow oil.

^{1}H NMR (400 MHz, DMSOd_6): δ 8.02 (dm, J = 8.9 Hz, 1H), 7.52 (ddd, J = 11.8, 9.1, 2.5 Hz, 1H), 7.30 (td, J = 8.2, 2.3 Hz, 1H), 6.85 (s, 1H), 3.74 (t, J = 7.1 Hz, 2H), 1.64 (quint., J = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.84 (t, J = 6.8 Hz, 3H).

^{19}F NMR (376 MHz, DMSOd_6): δ -105.1, -107.9.

^{13}C NMR (100 MHz, DMSOd_6): δ 166.7, 162.6 (dd, J = 252.1, 13.0 Hz), 158.7 (dd, J = 252.8, 12.7 Hz), 146.4 (d, J = 4.1 Hz), 129.3 (dd, J = 10.3, 4.4 Hz), 113.6 (dd, J = 12.3, 3.9 Hz), 112.4 (dd, J = 22.0, 3.2 Hz), 110.9, 104.6 (t, J = 26.4 Hz), 42.2, 30.6, 28.6, 28.0, 27.9, 25.3, 21.5, 13.4.

HRMS calcd for $[M+Na]^+$ $C_{17}H_{21}F_2NOSNa$ 348.1204, found: 348.1205.

5-(Naphthalen-1-yl)-2-octanoylisothiazol-3(2*H*)-one (21)

Following the general procedure, 1-bromonaphthalene (0.311 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **21** in 74% (0.251 g) as a yellow oil.

^{1}H NMR (400 MHz, DMSOd_6): δ 8.15-8.04 (m, 3H), 7.69-7.59 (m, 4H), 6.60 (s, 1H), 3.80 (t, J = 7.1 Hz, 2H), 1.68 (quint., J = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.85 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, DMSOd_6): δ 167.1, 153.0, 132.8, 130.1, 129.4, 128.2, 127.2, 127.1, 126.8, 126.3, 124.9, 123.7, 114.3, 42.6, 30.7, 28.7, 28.0, 27.9, 25.4, 21.5, 13.4.
HRMS calcd for $[M+Na]^+$ $C_{21}H_{25}NOSNa$ 362.1549, found: 362.1545.

5-(Naphthalen-2-yl)-2-octanoylisothiazol-3(2*H*)-one (22)
Following the general procedure, 2-bromonaphthalene (0.311 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **22** in 74% (0.251 g) as a yellow oil.
^{1}H NMR (400 MHz, DMSOd_6): δ 8.25 (s, 1H), 8.07-7.95 (m, 3H), 7.80 (dd, J = 8.6, 1.7 Hz, 1H), 7.63-7.57 (m, 2H), 6.92 (s, 1H), 3.76 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.84 (t, *J* = 6.8 Hz, 3H).
^{13}C NMR (100 MHz, DMSOd_6): δ 167.7, 154.2, 133.3, 132.1, 128.6, 128.0, 127.3, 127.1, 126.7, 126.6, 124.5, 122.4, 109.9, 42.3, 30.7, 28.7, 28.0, 27.9, 25.4, 21.5, 13.4.
HRMS calcd for $[M+Na]^+$ $C_{21}H_{25}NOSNa$ 362.1549, found: 362.1549.

5-(4-Fluoronaphthalen-1-yl)-2-octanoylisothiazol-3(2*H*)-one (23)
Following the general procedure, 1-bromo-4-fluoronaphthalene (0.338 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **23** in 59% (0.210 g) as a colorless oil.
^{1}H NMR (400 MHz, DMSOd_6): δ 7.18-7.12 (m, 2H), 7.76-7.71 (m, 2H), 7.66 (dd, *J* = 8.0, 5.4 Hz, 1H), 7.44 (dd, *J* =10.4, 8.0 Hz, 1H), 6.56 (s, 1H), 3.78 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.84 (t, *J* = 6.8 Hz, 3H).
^{19}F NMR (376 MHz, DMSOd_6): δ -119.1.
^{13}C NMR (100 MHz, DMSOd_6): δ 167.0, 158.8 (d, *J* = 254.4 Hz), 152.2, 131.0 (d, *J* = 5.1 Hz), 128.2, 127.3 (d, *J* = 9.3 Hz), 127.0 (d, *J* = 1.6 Hz), 124.1 (d, *J* = 2.4 Hz), 123.7 (d, *J* = 4.3 Hz), 122.6 (d, *J* = 16.6 Hz), 120.0 (d, *J* = 5.5 Hz), 114.5, 109.0 (d, *J* = 20.6 Hz), 42.4, 30.7, 28.7, 28.0, 27.9, 25.4, 21.5, 13.4.
HRMS calcd for $[M+Na]^+$ $C_{21}H_{24}FNOSNa$ 380.1455, found: 380.1454.

5-(2-Chloropyridin-4-yl)-2-octanoylisothiazol-3(2*H*)-one (24)
Following the general procedure, 4-bromo-2-chloropyridine (0.288 g, 1.5 mmol) and 2-octanoylisothiazol-3(2*H*)-one (0.227 g, 1 mmol), affords **24** in 51% (0.165 g) as a white solid: mp 176-178 °C.
^{1}H NMR (400 MHz, DMSOd_6): δ 8.54 (d, *J* = 5.2 Hz, 1H), 7.89 (d, *J* = 1.2 Hz, 1H), 7.65 (td, *J* = 5.2, 1.2 Hz, 1H), 7.10 (s, 1H), 3.76 (t, *J* = 7.1 Hz, 2H), 1.64 (quint., *J* = 6.8 Hz, 2H), 1.30-1.20 (m, 10H), 0.84 (t, *J* = 6.8 Hz, 3H).
^{13}C NMR (100 MHz, DMSOd_6): δ 168.0, 152.0, 151.6, 151.1, 140.7, 120.8, 119.7, 114.3, 43.6, 31.6, 29.6, 29.0, 28.9, 26.3, 22.5, 14.4.
HRMS calcd for $[M+Na]^+$ $C_{16}H_{21}ClN_2OSNa$ 347.0955, found: 347.0557.

2-Methyl-5-(4-(trifluoromethyl)phenyl)isothiazol-3(2*H*)-one (25)
Following the general procedure, 4-(trifluoromethyl)bromobenzene (0.338 g, 1.5 mmol) and 2-methylisothiazol-3(2*H*)-one (0.115 g, 1 mmol), affords **25** in 62% (0.160 g) as a white solid: mp 171-173 °C.
^{1}H NMR (400 MHz, DMSOd_6): δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.88 (d, *J* = 8.2 Hz, 2H), 6.96 (s, 1H), 3.30 (s, 3H).
^{19}F NMR (376 MHz, DMSOd_6): δ -61.4.
^{13}C NMR (100 MHz, DMSOd_6): δ 167.6, 152.4, 133.1, 130.1 (q, *J* = 32.2 Hz), 126.1, 125.8 (q, *J* = 3.8 Hz), 123.1 (q, *J* = 271.4 Hz), 111.3, 29.5.
HRMS calcd for $[M+Na]^+$ $C_{11}H_8F_3NOSNa$ 282.1071, found: 282.1070.

2-Methyl-5-(4-(trifluoromethoxy)phenyl)isothiazol-3(2*H*)-one (26)
Following the general procedure, 1-bromo-4-(trifluoromethoxy)benzene (0.262 g, 1.5 mmol) and 2-methylisothiazol-3(2*H*)-one (0.115 g, 1 mmol), affords **26** in 58% (0.159 g) as a white solid: mp 63-65 °C.
^{1}H NMR (400 MHz, DMSOd_6): δ 7.80 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 6.83 (s, 1H), 3.27 (s, 3H).
^{19}F NMR (376 MHz, DMSOd_6): δ -56.7.
^{13}C NMR (100 MHz, DMSOd_6): δ 167.7, 152.6, 149.3, 128.5, 127.4, 121.3, 119.4 (q, *J* = 257.3 Hz), 110.3, 29.4.
HRMS calcd for $[M+Na]^+$ $C_{11}H_8F_3NO_2SNa$ 298.0125, found: 298.0122.

2-Methyl-5-(3-(trifluoromethoxy)phenyl)isothiazol-3(2*H*)-one (27)
Following the general procedure, 1-bromo-3-(trifluoromethoxy)benzene (0.262 g, 1.5 mmol) and 2-methylisothiazol-3(2*H*)-one (0.115 g, 1 mmol), affords **27** in 70% (0.192 g) as a white solid: mp 73-75 °C.
^{1}H NMR (400 MHz, DMSOd_6): δ 7.73 (s, 1H), 7.67-7.61 (m, 2H), 7.56-7.50 (m, 1H), 6.94 (s, 1H), 3.29 (s, 3H).
^{19}F NMR (376 MHz, DMSOd_6): δ -56.8.
^{13}C NMR (100 MHz, DMSOd_6): δ 167.6, 152.3, 148.4 (q, *J* = 3.5 Hz), 131.4, 131.0, 124.3, 122.6, 119.5 (q, *J* = 257.1 Hz), 118.1, 110.8, 29.4.
HRMS calcd for $[M+Na]^+$ $C_{11}H_8F_3NO_2SNa$ 298.0125, found: 298.0122.

2-Methyl-5-(4-fluoronaphtalen-1-yl)isothiazol-3(2*H*)-one (28)
Following the general procedure, 1-bromo-4-fluoronaphtalene (0.338 g, 1 mmol) and 2-methylisothiazol-3(2*H*)-one (0.115 g, 1 mmol), affords **28** in 57% (0.147 g) as a white solid: mp 121-123 °C.
^{1}H NMR (400 MHz, DMSOd_6): δ 8.22-8.14 (m, 2H), 7.80-7.73 (m, 2H), 7.68 (dd, *J* = 8.0, 5.4 Hz, 1H), 7.47 (dd, *J* = 10.5, 8.0 Hz, 1H), 6,58 (s, 1H), 3.36 (s, 3H).
^{19}F NMR (376 MHz, DMSOd_6): δ -119.4.
^{13}C NMR (100 MHz, DMSOd_6): δ 167.9, 159.0 (d, *J* = 254.3 Hz), 152.3, 131.6 (d, J = 5.3 Hz), 128.9, 128.0 (d, *J* = 9.3 Hz), 127.7, 124.8 (d, *J* = 2.7 Hz), 124.3 (d, *J* = 4.4 Hz), 123.1 (d, *J* = 16.6 Hz), 120.6 (d, *J* = 5.6 Hz), 114.9, 109.6 (d, *J* = 20.8 Hz), 29.9.
HRMS calcd for $[M+Na]^+$ $C_{14}H_{10}FNOSNa$ 282.0359, found: 282.0358.

2-Methyl-4,5-bis(3-(trifluoromethyl)phenyl)isothiazol-3(2*H*)-one (29)
Following the general procedure, 1-bromo-3-(trifluoromethoxy)benzene (0.524 g, 3 mmol) and 2-methylisothiazol-3(2*H*)-one (0.115 g, 1 mmol), affords **29** in 67% (0.270 g) as a white solid: mp 106-108 °C.
^{1}H NMR (400 MHz, DMSOd_6): δ 7.84 (d, *J* = 7.5 Hz, 1H), 7.70-7.63 (m, 3H), 7.61-7.55 (m, 4H), 3.41 (s, 3H).
^{19}F NMR (376 MHz, DMSOd_6): δ -61.5, -61.6.
^{13}C NMR (100 MHz, DMSOd_6): δ 165.7, 148.9, 133.0, 132.4, 132.0, 130.5, 130.1, 129.3 (q, *J* = 32.2 Hz), 128.9, 128.5 (q, *J* = 32.2 Hz), 126.4 (q, *J* = 3.6 Hz), 125.6 (q, *J* = 3.9 Hz), 124.6 (q, *J* = 3.9 Hz), 124.0 (q, *J* = 3.6 Hz), 123.0 (q, *J* = 271.4 Hz), 122.9 (q, *J* = 271.4 Hz), 120.8, 30.2.
HRMS calcd for $[M+H]^+$ $C_{18}H_{12}F_6NOS$ 404.0538, found: 404.0541.

2-Methyl-4,5-bis(4-(trifluoromethyl)phenyl)isothiazol-3(2*H*)-one (30)

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Following the general procedure, 1-bromo-4-(trifluoromethoxy)benzene (0.524 g, 3 mmol) and 2-methylisothiazol-3(2*H*)-one (0.115 g, 1 mmol), affords **30** in 64% (0.258 g) as a white solid: mp 111-113 °C.
^{1}H NMR (400 MHz, DMSOd_6): δ 7.82 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 3.41 (s, 3H).
^{19}F NMR (376 MHz, DMSOd_6): δ -61.1, -61.4.
^{13}C NMR (100 MHz, DMSOd_6): δ 165.6, 149.2, 135.6, 133.6, 129.9, 129.8 (q, J = 32.2 Hz), 128.8, 127.6 (q, J = 32.2 Hz), 125.8 (q, J = 3.6 Hz), 124.7 (q, J = 3.7 Hz), 123.4 (q, J = 271.4 Hz), 123.2 (q, J = 271.4 Hz), 120.9, 29.9.
HRMS calcd for $[M+Na]^+$ $C_{18}H_{11}F_6NOSNa$ 426.0358, found: 426.0360.

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Supplementary Material

Copies of the ^{1}H, ^{13}C and ^{19}F NMR for all compounds.