Novel Microwave-Assisted One-Pot Synthesis of Isoxazoles by a Three-Component Coupling–Cycloaddition Sequence

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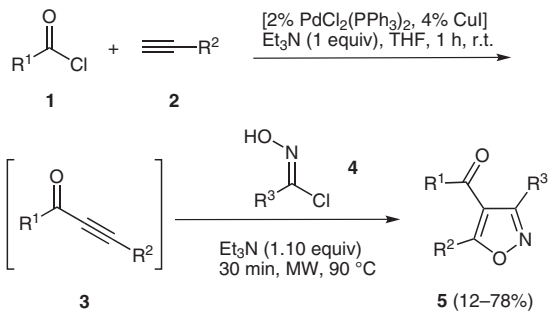
Abstract: The consecutive Sonogashira coupling of acid chlorides with terminal alkynes, followed by 1,3-dipolar cycloaddition under dielectric heating of in situ generated nitrile oxides from hydroximinoyl chlorides furnishes isoxazoles in moderate to good yields in the sense of a one-pot three-component reaction.

Key words: alkynes, cross-couplings, cycloaddition, isoxazole, microwave reaction

The biological activity of many substituted isoxazoles[1] is an important theme in medicinal chemistry. Isoxazoles are potent, selective agonists of human cloned dopamine D4 receptors[2] and exhibit $GABA_A$ antagonist,[3] analgesic,[4] anti-inflammatory,[4] ulcerogenic,[4] COX-2 inhibitory,[5] antinociceptive,[6] and anticancer[7] activity. Therefore, many synthetic approaches have been made to access the isoxazole core,[8] including reactions of hydroxylamine with 1,3-dicarbonyl compounds,[9] α,β-unsaturated carbonyl compounds,[10] and α,β-unsaturated nitriles.[11] The reaction of an oxime-derived dianion and an ester[12] or amide[13] also provides isoxazoles. In addition, [3+2] cycloadditions between alkynes and nitrile oxides have been reported.[14] Although these strategies are highly convergent, often strong bases or strong mineral acids are required, or prolonged heating to high temperatures is necessary. Other shortcomings are poor regioselectivities. Therefore, as part of our program on the design and development of new multicomponent synthesis of heterocycles initiated by Sonogashira coupling,[15,16] we have now focused on coupling–cycloaddition sequences as an entry to heterocycle sequences.[17] Here, we wish to report a concise, consecutive, three-component synthesis of 3,4,5-substituted isoxazoles with a flexible substitution pattern, applying dielectric heating (microwave irradiation) in the concluding pericyclic step.

The Sonogashira coupling of acid chlorides with terminal alkynes allows straightforward access to alkynones.[18] Recently, we reported that only one equivalent of triethylamine as the hydrochloric acid scavenging base proved to be most favorable for the successful coupling of even sensitive alkynes such as trimethylsilyl acetylene.[19] In turn, the resulting alkynones are highly reactive and readily react with all kinds of 1,3-dipoles, even in a one-pot fashion.[17] The 1,3-dipolar cycloaddition of aromatic nitrile oxides, a class of propargyl-type 1,3 dipoles is, in general, a suitable route to isoxazoles.[14] Since aromatic nitrile oxides are usually unstable compounds, it is necessary for them to be prepared in situ by dehydrochlorination of the corresponding hydroximinoyl chlorides with a suitable base. If triethylamine is the base, this step should be fully compatible with a preceding alkynone formation.

Therefore, after reacting acid chlorides **1** with terminal alkynes **2** under modified Sonogashira conditions for one hour at room temperature to furnish the expected alkynones **3**, subsequently, hydroximinoyl chlorides **4** and triethylamine are added. After heating for 30 minutes under dielectric heating, the isoxazoles **5** were obtained in moderate to excellent yields, often as crystalline solids (Scheme 1, Table 1–3).



Scheme 1 One-pot, three-component synthesis of isoxazoles

Initial attempts at performing the concluding cycloaddition step under conductive heating proved to be time-consuming (2–4 days) and were often inefficient; conventional heating for 12 hours (85 °C, oil bath) of the alkynone formed from **1c** and **2b** with **4a**, gave rise to formation of isoxazole **5c** only in 49%. One major drawback of the extended reaction times was that a side reaction of the in situ generated nitrile oxides gave rise to the formation of furoxan oxides **6**[20] (Scheme 2). Furoxane **6a**, for instance, was formed under conductive heating conditions in 32% yield, whereas dielectric heating diminished the amount of this side product to 14% (with respect to hydroximinoyl chloride **4a**).

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Table 1 Coupling–Cycloaddition Synthesis of Isoxazoles **5**; Variation of Acid Chlorides

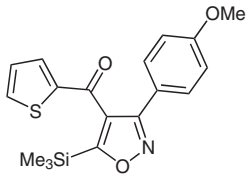
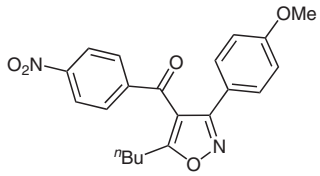
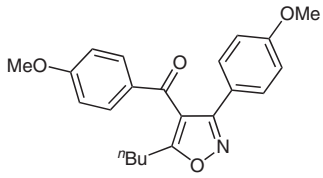
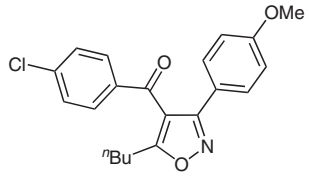
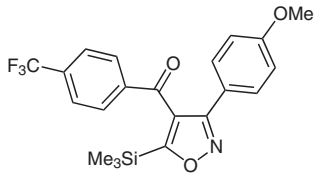
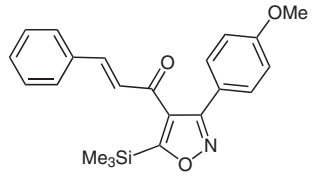
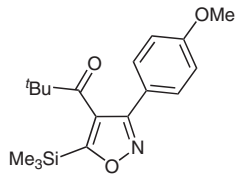
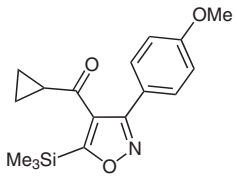
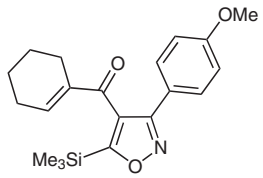
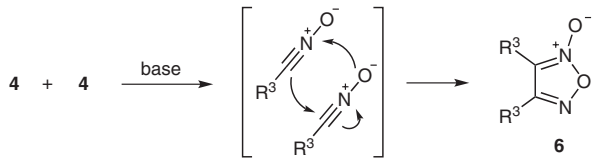
Entry	Acid chloride **1**	Alkyne **2**	Hydroximinoyl chloride **4**	Isoxazole **5** (yield, %)
1	**1a**: R^1 = 2-thienyl	**2a**: $R^2 = Me_3Si$	R^3 = 4-$MeOC_6H_4$ (**4a**)	 **5a** (77)
2	**1b**: R^1 = 4-$O_2NC_6H_4$	**2b**: R^2 = *n*-butyl	**4a**	 **5b** (56)
3	**1c**: R^1 = 4-$MeOC_6H_4$	**2b**	**4a**	 **5c** (64)
4	**1d**: R^1 = 4-ClC_6H_4	**2b**	**4a**	 **5d** (59)
5	**1e**: R^1 = 4-$F_3CC_6H_4$	**2a**	**4a**	 **5e** (56)
6	**1f**: R^1 = 2-styryl	**2a**	**4a**	 **5f** (12)
7	**1g**: R^1 = *t*-Bu	**2a**	**4a**	 **5g** (56)

Table 1 Coupling–Cycloaddition Synthesis of Isoxazoles **5**; Variation of Acid Chlorides (continued)

Entry	Acid chloride **1**	Alkyne **2**	Hydroximinoyl chloride **4**	Isoxazole **5** (yield, %)
8	**1h**: R^1 = cyclopropyl	**2a**	**4a**	 **5h** (54)
9	**1i**: R^1 = cyclohexen-1-yl	**2a**	**4a**	 **5i** (39)



Scheme 2 Dimerization of nitrile oxides to furoxan oxides **6**

In addition to spectroscopic and analytical characterization, the structure of 3,4-bis(4-methoxyphenyl)-1,2,5-oxadiazole-2-oxide (**6a**) was corroborated by an X-ray crystal structure analysis (Figure 1).[21]

Hence, the synthesis was optimized by heating the reaction mixture under microwave irradiation. Thus, reaction times were reduced from three days to 30 minutes, while simultaneously increasing the yields, in some cases quite dramatically, and significantly reducing the amount of byproduct formation.

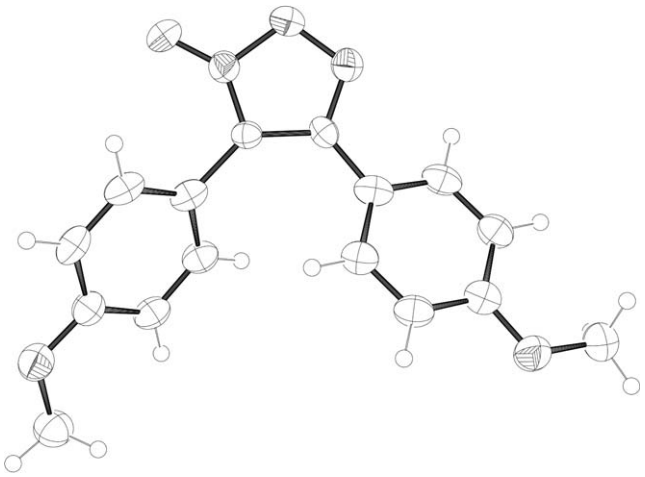


Figure 1 ORTEP plot of furoxan oxide **6a**

Table 2 Coupling–Cycloaddition Synthesis of Isoxazoles **5**; Variation of Alkynes

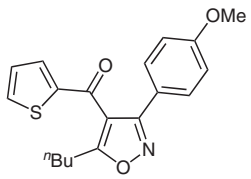
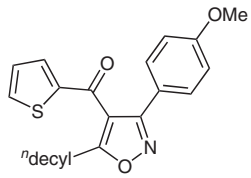
Entry	Acid chloride **1**	Alkyne **2**	Hydroximinoyl chloride **4**	Isoxazole **5** (yield, %)
1	**1a**	**2b**	**4a**	 **5j** (60)
2	**1a**	**2c**: R^2 = *n*-decyl	**4a**	 **5k** (42)

Table 2 Coupling–Cycloaddition Synthesis of Isoxazoles **5**; Variation of Alkynes (continued)

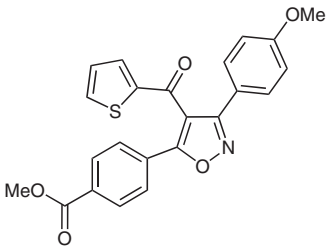
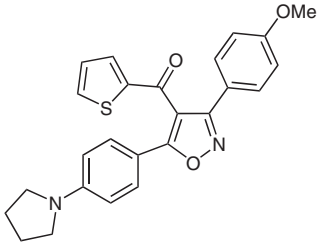
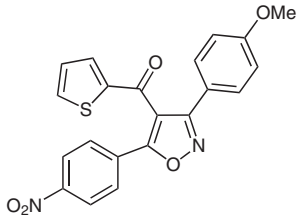
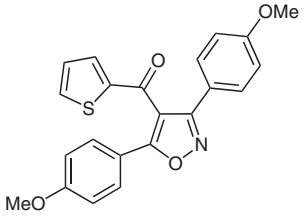
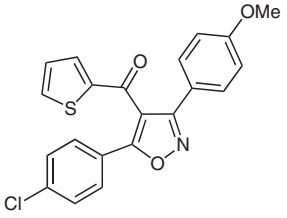
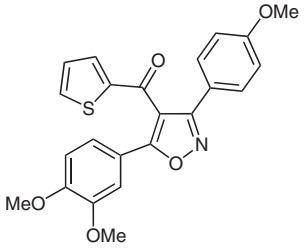
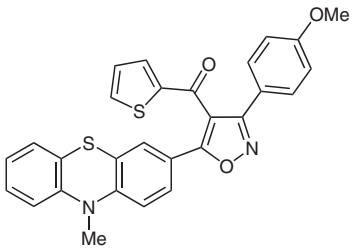
Entry	Acid chloride **1**	Alkyne **2**	Hydroximinoyl chloride **4**	Isoxazole **5** (yield, %)
3	**1a**	**2d**: R^2 = 4-$MeO_2CC_6H_4$	**4a**	 **5l** (72)
4	**1a**	**2e**: R^2 = 4-(1-pyrrolidinyl)C_6H_4	**4a**	 **5m** (48)
5	**1a**	**2f**: R^2 = 4-$O_2NC_6H_4$	**4a**	 **5n** (66)
6	**1a**	**2g**: R^2 = 4-$MeOC_6H_4$	**4a**	 **5o** (78)
7	**1a**	**2h**: R^2 = 4-ClC_6H_4	**4a**	 **5p** (70)
8	**1a**	**2i**: R^2 = 3,4-$(MeO)_2C_6H_4$	**4a**	 **5q** (44)

Table 2 Coupling–Cycloaddition Synthesis of Isoxazoles **5**; Variation of Alkynes (continued)

Entry	Acid chloride **1**	Alkyne **2**	Hydroximinoyl chloride **4**	Isoxazole **5** (yield, %)
9	**1a**	**2j**: R^2 = 3-(10-methyl)phenothiazinyl	**4a**	 **5r** (55)

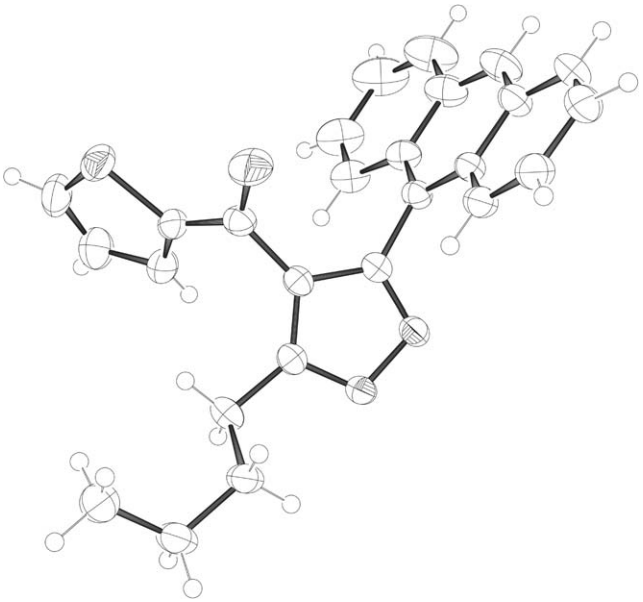
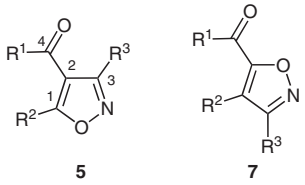


Figure 2 ORTEP plot of isoxazole **5w**

The structures of the isoxazoles **5** were unambiguously assigned by ^{1}H and ^{13}C NMR spectroscopy and, in addition, by X-ray crystal structure analysis of the isoxazole **5w** (Figure 2).[21]

In accordance with theory for kinetically controlled 1,3-dipolar cycloadditions,[20] in each case only one of the two possible regioisomers, i.e. isomer **5**, was formed. Not even traces of the regioisomers **7** could be detected. Substitution patterns were determined by NOESY NMR experiments and supported by an X-ray crystal structure analysis (Figure 3).



5 **7**

Figure 3 Possible regioisomers **5** and **6** of the isoxazoles

Table 3 Coupling–Cycloaddition Synthesis of Isoxazoles **5**; Variation of Hydroximinoyl Chlorides

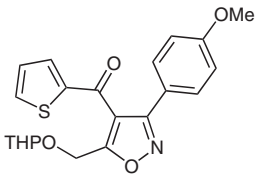
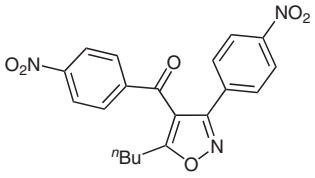
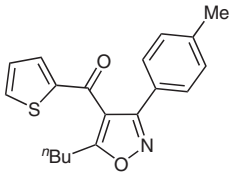
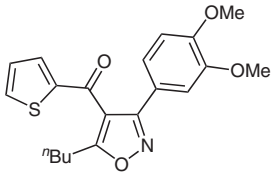
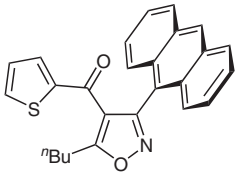
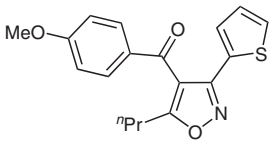
Entry	Acid chloride **1**	Alkyne **2**	Hydroximinoyl chloride **4**	Isoxazole **5** (yield, %)
1	**1a**	**2k**: R^2 = CH_2OTHP	**4a**	 **5s** (54)
2	**1b**	**2b**	R^3 = 4-$O_2NC_6H_4$ (**4b**)	 **5t** (67)

Table 3 Coupling–Cycloaddition Synthesis of Isoxazoles **5**; Variation of Hydroximinoyl Chlorides (continued)

Entry	Acid chloride **1**	Alkyne **2**	Hydroximinoyl chloride **4**	Isoxazole **5** (yield, %)
3	**1a**	**2b**	R^3 = 4-MeC_6H_4 (**4c**)	 **5u** (60)
4	**1a**	**2b**	R^3 = 3,4-$(MeO)_2C_6H_4$ (**4d**)	 **5v** (57)
5	**1a**	**2b**	R^3 = 10-anthranyl (**4e**)	 **5w** (68)
6	**1c**	**2l**: R^2 = *n*-propyl	R^3 = 2-thienyl (**4f**)	 **5x** (66)

As a consequence of 3,4,5-substitution, no peculiar resonances of the isoxazole core were found in the proton NMR spectra. However, the carbon signals of the isoxazole, as well as the carbonyl nuclei, could be readily assigned by 2D NMR spectroscopy and incremental calculations. Carbon atoms C-1 appeared in the carbon NMR spectra at about δ = 175 ppm. The quaternary C-2 resonances could be found at higher field (around δ = 115 ppm) as a consequence of the polarization caused by the electron-withdrawing effect of the carbonyl group. Finally, the imine-type nuclei emerged at about δ = 161 ppm. The signals around δ = 185 ppm could be unambiguously assigned to the nuclei of the carbonyl groups. According to the X-ray structure analysis, the aroyl moiety is distorted from coplanarity with respect to the isoxazole ring by 126°.

The scope of this one-pot coupling–cycloaddition isoxazole synthesis is fairly broad and can be performed under mild conditions and with excellent chemo- and regioselectivity. As a consequence of using acid chlorides as the halide coupling partner, amines and hydroxy groups need to be protected prior to the reaction. The use of the acid chlorides **1** is predominantly limited to (hetero)aromatic compounds and derivatives without β-hydrogens. With a few exceptions, cyclopropyl (Table 1, entry 8) or cyclohex-1-enyl substituents (entry 9) are tolerated in both steps of the sequence. Aliphatic alkynes can be employed as well as ethynylbenzenes with electron-donating or electron-withdrawing substituents (Table 2; **2d–i**). Even heterocyclic alkynes, such as the phenothiazine bearing alkyne **2j**, can be used as starting materials. Silylated alkynes also undergo the coupling procedure, indeed, trimethylsilyl acetylene (**1a**) proved to be very favorable (Table 2, entries 1–10). With respect to the 1,3-dipolar nitrile oxide, electron-rich, polycyclic, electron-deficient and heterocyclic substituents are all tolerated and react readily with the alkynones **3** (Table 3, entries 2–6).

In conclusion, we have established a straightforward, one-pot, three-component synthesis of 3,4,5-substituted isoxazoles in the sense of a consecutive coupling-cycloaddition sequence starting with room temperature coupling and subsequent dielectric heating for completion of the cycloaddition. Preparation of starting materials is very general and can be applied to a broad variety of substrates. Studies addressing this novel synthesis in order to enhance molecular diversity in material and pharmaceutically interesting targets are currently underway.

All reactions involving water-sensitive compounds were carried out in flame-dried Schlenk glassware under nitrogen atmosphere unless stated otherwise. Reagents and catalysts were purchased as reagent grade and used without further purification. Solvents were dried and

distilled according to standard procedures.[22] Aldoximes and the corresponding hydroximinoyl chlorides **4** were synthesized according to literature procedures.[23] Flash column chromatography: silica gel 60, mesh 230–400, Merck, Darmstadt. TLC: silica gel plates (60 F_{254} Merck, Darmstadt). ^{1}H-, ^{13}C-, DEPT-, NOESY-, COSY-, HMQC- and HMBC spectra were recorded with Bruker ARX 250, Bruker DRX 300 or Bruker DRX 500 spectrometers using $CDCl_3$ as solvent unless stated otherwise. The assignments of quaternary C, CH, CH_2 and CH_3 were made on the basis of DEPT spectra. Mass spectra were recorded with JEOL JMS-700 and Finnigan TSQ 700 spectrometers. The melting points (uncorrected) were measured with Stuart Scientific Melting Point Apparatus SMP3. Elemental analyses were carried out in the microanalytical laboratory of the Organisch-Chemisches Institut, Universität Heidelberg. Dielectric heating was performed in a SmithCreator (Personal Chemistry AB, Uppsala, Sweden) and a Discover™ (CEM GmbH, Kamp-Lintfort, Germany; Table 3, entries 2 and 6) single-mode microwave cavity, producing continuous irradiation at 2450 MHz.

One-Pot, Three-Component Synthesis of Isoxazoles 5; General Procedure

In a 10 mL microwave tube, $PdCl_2(PPh_3)_2$ (15 mg, 0.02 mmol) and CuI (8 mg, 0.04 mmol) were dissolved in degassed THF (5 mL). To this orange solution, acid chloride **1** (1.00 mmol), alkyne **2** (1.00 mmol) and Et_3N (1.05 mmol) were added. The reaction mixture was stirred at r.t. for 1 h then aryl hydroximinoyl chloride **4** (1.00 mmol) and Et_3N (1.1 mmol) were added to the suspension and the reaction mixture was heated for 30 min at 90 °C under microwave conditions (sealed reaction vessel, ramp time 2 min, temperature measured by infra-red sensor, 1.9 bar). After cooling to r.t., the solvent was removed under reduced pressure and the crude products were purified by silica gel flash column chromatography (hexane–EtOAc, 50:1) to afford the analytically pure products.

[3-(4-Methoxyphenyl)-5-(trimethylsilyl)isoxazol-4-yl](thiophen-2-yl)methanone (5a)

Light-red crystals; mp 101 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.32 (s, 9 H), 3.76 (s, 3 H), 6.83 (d, ^3J = 8.8 Hz, 2 H), 6.96 (dd, ^3J = 4.9, 3.8 Hz, 1 H), 7.30 (dd, ^3J = 3.8 Hz, ^4J = 1.2 Hz, 1 H), 7.51 (d, ^3J = 8.8 Hz, 2 H), 7.65 (dd, ^3J = 4.9 Hz, ^4J = 1.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –2.1 (3 × CH_3), 55.1 (CH_3), 114.1 (2 × CH), 120.4 (C_q), 127.2 (C_q), 128.2 (CH), 129.7 (2 × CH), 135.5 (CH), 135.6 (CH), 144.8 (C_q), 158.8 (C_q), 160.7 (C_q), 179.8 (C_q), 183.3 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 357 (92) $[M]^+$, 314 (89), 240 (17), 208 (15), 141 (20), 133 (35), 111 (49), 90 (13), 73 (26), 32 (27), 28 (100) $[CO]^+$.

HRMS: *m*/*z* calcd for $C_{18}H_{19}NO_3SSi$: 357.0855; found: 357.0846.

Anal. Calcd for $C_{18}H_{19}NO_3SSi$: C, 60.47; H, 5.26; N, 3.92. Found: C, 60.21; H, 5.60; N, 3.80.

[5-*n*-Butyl-3-(4-methoxyphenyl)isoxazol-4-yl](4-nitrophenyl)methanone (5b)

Light-yellow crystals; mp 98 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.3 Hz, 3 H), 1.40 (m, 2 H), 1.77 (q, ^3J = 7.6 Hz, 2 H), 2.93 (t, ^3J = 7.4 Hz, 2 H), 3.74 (s, 3 H), 6.73 (d, ^3J = 8.9 Hz, 2 H), 7.28 (d, ^3J = 8.9 Hz, 2 H), 7.77 (d, ^3J = 8.9 Hz, 2 H), 8.10 (d, ^3J = 8.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (CH_3), 22.3 (CH_2), 26.6 (CH_2), 29.6 (CH_2), 55.3 (CH_3), 114.1 (2 × CH), 114.5 (C_q), 119.9 (C_q), 123.5 (2 × CH), 130.0 (2 × CH), 130.3 (2 × CH), 142.1 (C_q), 150.1 (C_q), 160.9 (C_q), 161.1 (C_q), 178.3 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 380 (100) $[M]^+$, 351 (31), 296 (25), 202 (10), 174 (27), 150 (68), 104 (15), 28 (16).

Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.76. Found: C, 66.36; H, 5.29; N, 7.33.

[5-*n*-Butyl-3-(4-methoxyphenyl)isoxazol-4-yl](4-methoxyphenyl)methanone (5c)

Yellow resin.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 7.3 Hz, 3 H), 1.33 (m, 2 H), 1.69 (q, ^3J = 7.5 Hz, 2 H), 2.79 (t, ^3J = 7.5 Hz, 2 H), 3.75 (s, 3 H), 3.81 (s, 3 H), 6.79 (d, ^3J = 8.9 Hz, 2 H), 6.82 (d, ^3J = 8.9 Hz, 2 H), 7.44 (d, ^3J = 8.9 Hz, 2 H), 7.73 (d, ^3J = 8.9 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6 (CH_3), 22.2 (CH_2), 26.3 (CH_2), 29.6 (CH_2), 55.2 (CH_3), 55.5 (CH_3), 113.8 (CH), 114.0 (CH), 114.5 (2 × CH), 115.1 (C_q), 120.7 (C_q), 129.8 (2 × CH), 130.4 (C_q), 132.0 (2 × CH), 160.7 (C_q), 161.0 (C_q), 164.0 (C_q), 175.1 (C_q), 189.0 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 366 (21) $[M + H]^+$, 365 (77) $[M]^+$, 364 (30) $[M – H]^+$, 336 (19), 322 (35), 238 (59), 228 (20), 223 (23), 136 (18), 135 (100), 107 (14), 77 (16).

HRMS: *m*/*z* calcd for $C_{22}H_{23}NO_4$: 365.1627; found: 365.1635.

[5-*n*-Butyl-3-(4-methoxyphenyl)isoxazol-4-yl](4-chlorophenyl)methanone (5d)

Colorless crystals; mp 83 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 7.3 Hz, 3 H), 1.35 (m, 2 H), 1.72 (q, ^3J = 7.7 Hz, 2 H), 2.84 (t, ^3J = 7.4 Hz, 2 H), 3.76 (s, 3 H), 6.78 (d, ^3J = 8.8 Hz, 2 H), 7.28 (d, ^3J = 8.6 Hz, 2 H), 7.36 (d, ^3J = 8.8 Hz, 2 H), 7.63 (d, ^3J = 8.6 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (CH_3), 22.3 (CH_2), 26.5 (CH_2), 29.6 (CH_2), 55.3 (CH_3), 114.0 (2 × CH), 114.7 (C_q), 120.3 (C_q), 128.8 (2 × CH), 129.9 (2 × CH), 130.9 (2 × CH), 135.7 (C_q), 139.9 (C_q), 160.8 (C_q), 161.0 (C_q), 176.6 (C_q), 189.1 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 372 (6) $[^{37}Cl: M + H]^+$, 371 (29) $[^{37}Cl: M]^+$, 370 (27) $[^{35}Cl: M + H]^+$, 369 (83) $[^{35}Cl: M]^+$, 368 (24) $[^{35}Cl: M – H]^+$, 340 (27), 326 (11), 285 (17), 174 (19), 149 (13), 141 (43), 139 (100), 113 (10), 111 (28).

HRMS: *m*/*z* calcd for $C_{21}H_{20}{}^{37}ClNO_3$: 371.1097; found: 371.1127.

HRMS: *m*/*z* calcd for $C_{21}H_{20}{}^{35}ClNO_3$: 369.1127; found: 369.1142.

[3-(4-Methoxyphenyl)-5-(trimethylsilyl)isoxazol-4-yl][4-(trifluoromethyl)phenyl)methanone (5e)

Light-red crystals; mp 108 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.35 (s, 9 H), 3.73 (s, 3 H), 6.74 (d, ^3J = 8.4 Hz, 2 H), 7.30 (d, ^3J = 8.4 Hz, 2 H), 7.54 (d, ^3J = 8.6 Hz, 2 H), 7.76 (d, ^3J = 8.6 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –2.0 (3 × CH_3), 55.2 (CH_3), 114.1 (2 × CH), 120.1 (C_q), 123.3 (q, $^1J_{C–F}$ = 272.8 Hz, C_q), 125.4 (q, $^3J_{C–F}$ = 3.8 Hz, CH), 127.0 (C_q), 129.9 (2 × CH), 130.0 (CH), 134.5 (q, $^2J_{C–F}$ = 32.7 Hz, C_q), 140.1 (q, $^5J_{C–F}$ = 1.2 Hz, C_q), 159.5 (C_q), 160.8 (C_q), 182.5 (C_q), 190.4 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 420 (30) $[M + H]^+$, 419 (58) $[M]^+$, 377 (30), 376 (100), 302 (39), 270 (32), 173 (26), 145 (18), 73 (29).

Anal. Calcd for $C_{21}H_{20}F_3NO_3Si$: C, 60.13; H, 4.81; N, 3.34. Found: C, 59.81; H, 4.76; N, 3.37.

(*E*)-1-[3-(4-Methoxyphenyl)-5-(trimethylsilyl)isoxazol-4-yl]-3-phenylprop-2-en-1-one (5f)

Colorless crystals; mp 124 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.44 (s, 9 H), 3.83 (s, 3 H), 6.71 (dd, ^3J = 15.9, 0.6 Hz, 1 H), 6.97 (d, ^3J = 8.3 Hz, 2 H), 7.22–7.31 (m, 5 H), 7.50–7.58 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –2.2 (3 × CH_3), 55.4 (CH_3), 114.3 (2 × CH), 120.8 (C_q), 125.7 (CH), 128.4 (CH), 128.9 (2 × CH), 129.2 (C_q), 130.6 (CH), 130.7 (CH), 134.3 (C_q), 144.4 (CH), 159.6 (C_q), 161.0 (C_q), 183.5 (C_q), 187.2 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 378 (20) $[M + H]^+$, 377 (65) $[M]^+$, 362 (22), 248 (14), 335 (25), 334 (100), 162 (10), 151 (13), 133 (10), 131 (12), 86 (16), 84 (24), 77 (16), 73 (26).

HRMS: *m*/*z* calcd for $C_{22}H_{23}NO_5Si$: 377.1447; found: 377.1440.

1-[3-(4-Methoxyphenyl)-5-(trimethylsilyl)isoxazol-4-yl]-2,2-dimethylpropan-1-one (5g)
Colorless crystals; mp 136 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.34 (s, 9 H), 0.96 (s, 9 H), 3.83 (s, 3 H), 6.94 (d, ^3J = 8.9 Hz, 2 H), 7.44 (d, ^3J = 8.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.5 (3 × CH_3), 27.3 (CH_3), 45.4 (C_q), 55.3 (CH_3), 114.3 (2 × CH), 122.0 (C_q), 128.1 (C_q), 129.7 (2 × CH), 158.3 (C_q), 160.9 (C_q), 175.8 (C_q), 209.4 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 331 (15) $[M]^+$, 275 (12), 274 (61), 247 (13), 246 (69), 101 (11), 73 (100).

HRMS: *m*/*z* calcd for $C_{18}H_{25}NO_3Si$: 331.1604; found: 331.1601.

Cyclopropyl[3-(4-methoxyphenyl)-5-(trimethylsilyl)isoxazol-4-yl)methanone (5h)
Colorless crystals; mp 137 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.38 (s, 9 H), 0.80 (m, 2 H), 1.18 (s, 2 H), 1.82 (m, 1 H), 3.85 (s, 3 H), 6.98 (d, ^3J = 8.7 Hz, 2 H), 7.56 (d, ^3J = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –2.2 (3 × CH_3), 13.1 (2 × CH_2), 21.5 (CH), 55.3 (CH_3), 114.1 (2 × CH), 120.9 (C_q), 130.1 (C_q), 130.6 (2 × CH), 159.8 (C_q), 161.0 (C_q), 182.7 (C_q), 197.7 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 315 (35) $[M]^+$, 300 (20), 273 (21), 272 (100), 198 (27), 99 (10), 73 (40).

HRMS: *m*/*z* calcd for $C_{17}H_{21}NO_3Si$: 315.1291; found: 315.1293.

Cyclohexenyl[3-(4-methoxyphenyl)-5-(trimethylsilyl)isoxazol-4-yl]methanone (5i)
Colorless crystals; mp 124 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.31 (s, 9 H), 1.46–1.61 (m, 4 H), 1.97–2.02 (m, 2 H), 2.28–2.33 (m, 2 H), 3.80 (s, 3 H), 6.48–6.52 (m, 1 H), 6.89 (d, ^3J = 8.8 Hz, 2 H), 7.43 (d, ^3J = 8.8 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –2.0 (3 × CH_3), 21.3 (CH_2), 21.6 (CH_2), 23.0 (CH_2), 26.1 (CH_2), 55.2 (CH_3), 114.0 (2 × CH), 120.9 (C_q), 127.2 (C_q), 129.7 (2 × CH), 140.8 (C_q), 146.7 (CH), 159.3 (C_q), 160.5 (C_q), 178.6 (C_q), 192.8 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 356 (16) $[M + H]^+$, 355 (54) $[M]^+$, 340 (30), 313 (23), 312 (100), 238 (17), 206 (12), 139 (10), 121 (10), 73 (40), 32 (10).

HRMS: *m*/*z* calcd for $C_{20}H_{25}NO_3Si$: 355.1604; found: 355.1617.

[5-*n*-Butyl-3-(4-methoxyphenyl)isoxazol-4-yl](thiophen-2-yl)methanone (5j)
Yellow resin.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 7.4 Hz, 3 H), 1.36 (m, 2 H), 1.73 (q, ^3J = 7.6 Hz, 2 H), 2.86 (t, ^3J = 7.4 Hz, 2 H), 3.77 (s, 3 H), 6.83 (d, ^3J = 8.9 Hz, 2 H), 6.96 (dd, ^3J = 4.9, 3.9 Hz, 1 H), 7.31 (dd, ^3J = 3.9 Hz, ^4J = 1.1 Hz, 1 H), 7.49 (d, ^3J = 8.9 Hz, 2 H), 7.64 (dd, ^3J = 4.9 Hz, ^4J = 1.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (CH_3), 22.2 (CH_2), 26.4 (CH_2), 29.6 (CH_2), 55.3 (CH_3), 114.1 (2 × CH), 115.1 (C_q), 120.6 (C_q), 128.2 (CH), 129.8 (2 × CH), 135.1 (CH), 135.3 (CH), 144.2 (C_q), 160.5 (C_q), 160.8 (C_q), 175.3 (C_q), 182.1 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 341 (91) $[M]^+$, 312 (11), 257 (26), 242 (18), 228 (28), 174 (14), 149 (22), 111 (100).

HRMS: *m*/*z* calcd for $C_{19}H_{19}NO_3S$: 341.1086; found: 341.1088.

[5-*n*-Decyl-3-(4-methoxyphenyl)isoxazol-4-yl](thiophen-2-yl)methanone (5k)
Colorless crystals; mp 109 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, ^3J = 6.6 Hz, 3 H), 1.16–1.37 (m, 14 H), 1.66–1.79 (m, 2 H), 2.84 (t, ^3J = 7.5 Hz, 2 H), 3.75 (s, 3 H), 6.81 (d, ^3J = 8.4 Hz, 2 H), 6.93 (dd, ^3J = 4.9, 3.8 Hz, 1 H), 7.23 (dd, ^3J = 4.9, 1.2 Hz, 1 H), 7.48 (d, ^3J = 8.4 Hz, 2 H), 7.62 (dd, ^3J = 3.8, 1.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.6 (CH_2), 26.5 (CH_2), 27.5 (CH_2), 29.0 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 55.1 (CH_3), 114.0 (2 × CH), 115.0 (C_q), 120.5 (C_q), 128.1 (CH), 129.7 (2 × CH), 135.0 (CH), 135.1 (CH), 144.1 (C_q), 160.4 (C_q), 160.7 (C_q), 175.2 (C_q), 182.0 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 426 (29) $[M + H]^+$, 425 (100) $[M]^+$, 424 (11), 312 (22), 257 (13), 111 (32).

HRMS: *m*/*z* calcd for $C_{25}H_{31}NO_3S$: 425.2025; found: 425.2004.

Anal. Calcd for $C_{25}H_{31}NO_3S$: C, 70.55; H, 7.34; N, 3.29. Found: C, 70.23; H, 7.44; N, 3.32.

Methyl 4-[3-(4-Methoxyphenyl)-4-(thiophene-2-carbonyl)isoxazol-5-yl]benzoate (5l)
Colorless crystals; mp 147 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 3.90 (s, 3 H), 6.85–6.94 (s, 3 H), 7.36 (dd, ^3J = 3.9, 1.0 Hz, 1 H), 7.58–7.66 (m, 3 H), 7.81 (d, ^3J = 8.5 Hz, 2 H), 8.05 (d, ^3J = 8.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.3 (CH_3), 55.2 (CH_3), 114.3 (2 × CH), 115.1 (C_q), 120.1 (C_q), 127.2 (2 × CH), 128.5 (CH), 129.5 (2 × CH), 130.0 (2 × CH), 130.4 (C_q), 131.9 (C_q), 135.7 (CH), 136.3 (CH), 144.0 (C_q), 161.1 (C_q), 161.4 (C_q), 166.0 (C_q), 167.2 (C_q), 182.6 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 420 (15) $[M + H]^+$, 419 (58) $[M]^+$, 390 (12), 268 (15), 244 (13), 242 (13), 216 (47), 164 (10), 163 (100), 149 (12), 135 (30), 111 (85), 103 (14), 32 (14), 28 (56).

HRMS: *m*/*z* calcd for $C_{23}H_{17}NO_5S$: 419.0827; found: 419.0816.

Anal. Calcd for $C_{23}H_{17}NO_5S$: C, 65.86; H, 4.09; N, 3.34. Found: C, 65.65; H, 4.22; N, 3.29.

{3-(4-Methoxyphenyl)-5-[4-(pyrrolidin-1-yl)phenyl]isoxazol-4-yl}(thiophen-2-yl)methanone (5m)
Yellow crystals; mp 141 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96–2.01 (m, 4 H), 3.25–3.31 (m, 4 H), 3.78 (s, 3 H), 6.48 (d, ^3J = 8.8 Hz, 2 H), 6.86 (d, ^3J = 8.6 Hz, 2 H), 6.87–6.92 (m, 1 H), 7.36–7.41 (m, 1 H), 7.55–7.64 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4 (2 × CH_2), 47.4 (2 × CH_2), 55.2 (CH_3), 111.0 (C_q), 111.4 (2 × CH), 113.3 (C_q), 114.1 (2 × CH), 121.0 (C_q), 128.3 (CH), 128.8 (2 × CH), 129.5 (2 × CH), 135.34 (CH), 135.39 (CH), 144.7 (C_q), 149.2 (C_q), 160.7 (C_q), 161.2 (C_q), 169.8 (C_q), 183.7 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 420 (15) $[M + H]^+$, 419 (58) $[M]^+$, 340 (94), 281 (44), 191 (16), 170 (15), 139 (36), 111 (100), 74 (16), 41 (24), 40 (29), 39 (47).

Anal. Calcd for $C_{25}H_{22}N_2O_3S$: C, 69.75; H, 5.15; N, 6.51. Found: C, 69.44; H, 5.29; N, 6.39.

[3-(4-Methoxyphenyl)-5-(4-nitrophenyl)isoxazol-4-yl](thiophen-2-yl)methanone (5n)
Colorless crystals; mp 139 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 6.89 (d, ^3J = 8.9 Hz, 2 H), 6.96 (dd, ^3J = 4.7, 3.9 Hz, 1 H), 7.37 (dd, ^3J = 3.9, 1.0 Hz, 1 H), 7.60 (d, ^3J = 8.7 Hz, 2 H), 7.70 (dd, ^3J = 4.9, 1.0 Hz, 1 H), 7.96 (d, ^3J = 8.7 Hz, 2 H), 8.27 (d, ^3J = 8.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (CH_3), 114.4 (2 × CH), 116.1 (C_q), 119.8 (C_q), 124.2 (2 × CH), 128.3 (2 × CH), 128.8 (CH), 129.6 (2 × CH), 132.2 (C_q), 136.0 (CH), 136.8 (CH), 143.8 (C_q), 148.8 (C_q), 161.3 (C_q), 161.6 (C_q), 165.9 (C_q), 182.3 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 408 (11), 407 (27), 406 (100) $[M]^+$, 378 (15), 377 (13), 216 (11), 162 (14), 151 (15), 150 (11), 113 (11), 112 (10), 111 (100), 104 (10).

HRMS: *m*/*z* calcd for $C_{21}H_{14}N_2O_5S$: 406.0623; found: 406.0613.

Anal. Calcd for $C_{21}H_{14}N_2O_5S$: C, 62.06; H, 3.47; N, 6.89. Found: C, 61.90; H, 3.59; N, 6.75.

[3,5-Bis(4-methoxyphenyl)isoxazol-4-yl](thiophen-2-yl)methanone (5o)
Colorless crystals; mp 138 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 3.80 (s, 3 H), 6.84–6.93 (m, 5 H), 7.36 (dd, ^3J = 3.9, 1.2 Hz, 1 H), 7.60 (d, ^3J = 8.9 Hz, 2 H), 7.61 (dd, ^3J = 4.9, 1.1 Hz, 1 H), 7.71 (d, ^3J = 9.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (CH_3), 55.4 (CH_3), 112.8 (C_q), 114.2 (2 × CH), 114.4 (2 × CH), 119.3 (C_q), 120.6 (C_q), 128.5 (CH), 129.1 (2 × CH), 129.6 (2 × CH), 135.7 (CH), 135.9 (CH), 144.4 (C_q), 160.9 (C_q), 161.3 (C_q), 161.6 (C_q), 168.7 (C_q), 183.2 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 391 (36) $[M]^+$, 216 (15), 136 (11), 135 (100), 111 (21), 77 (12), 59 (11).

HRMS: *m*/*z* calcd for $C_{22}H_{17}NO_4S$: 391.0878; found: 391.0871.

Anal. Calcd for $C_{22}H_{17}NO_4S$: C, 67.50; H, 4.38; N, 3.58. Found: C, 67.28; H, 4.44; N, 3.55.

[5-(4-Chlorophenyl)-3-(4-methoxyphenyl)isoxazol-4-yl](thiophen-2-yl)methanone (5p)
Colorless crystals; mp 126 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 6.88 (d, ^3J = 8.9 Hz, 2 H), 6.93 (dd, ^3J = 4.9, 3.8 Hz, 1 H), 7.34–7.40 (m, 3 H), 7.65 (dd, ^3J = 4.9, 1.1 Hz, 1 H), 7.59 (d, ^3J = 8.9 Hz, 2 H), 7.70 (d, ^3J = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.2 (CH_3), 114.3 (2 × CH), 114.4 (C_q), 120.2 (C_q), 125.1 (C_q), 128.5 (CH), 128.6 (2 × CH), 129.3 (2 × CH), 129.5 (2 × CH), 135.8 (CH), 136.3 (CH), 137.1 (C_q), 144.0 (C_q), 161.0 (C_q), 161.4 (CH), 167.4 (C_q), 182.7 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 397 (16) [^{37}Cl: $M]^+$, 396 (10) $[M + H]^+$, 395 (47) [^{35}Cl – $M]^+$, 244 (14), 220 (11), 216 (36), 149 (10), 141 (23), 139 (70), 113 (13), 111 (100).

HRMS: *m*/*z* calcd for $C_{21}H_{14}ClNO_3S$: 395.0383; found: 395.0395.

Anal. Calcd for $C_{21}H_{14}ClNO_3S$: C, 67.50; H, 4.38; N, 3.58. Found: C, 67.44; H, 4.59; N, 3.56.

[5-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)isoxazol-4-yl](thiophen-2-yl)methanone (5q)
Colorless crystals; mp 151 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H), 3.78 (s, 3 H), 3.84 (s, 3 H), 6.80–6.90 (m, 4 H), 7.23 (d, ^4J = 2.0 Hz, 1 H), 7.30–7.37 (m, 2 H), 7.55–7.61 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.1 (CH_3), 55.72 (CH_3), 55.76 (CH_3), 110.1 (CH), 111.0 (CH), 112.8 (C_q), 114.1 (2 × CH), 119.1 (C_q), 120.4 (C_q), 120.8 (CH), 128.4 (CH), 129.4 (2 × CH), 135.5 (CH), 135.8 (CH), 144.2 (C_q), 148.9 (C_q), 151.0 (C_q), 160.8 (CH), 161.2 (C_q), 168.4 (C_q), 183.1 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 422 (33), 421 (100) $[M]^+$, 420 (20), 357 (20), 356 (36), 163 (19), 135 (18), 133 (11), 121 (18).

HRMS: *m*/*z* calcd for $C_{23}H_{19}NO_5S$: 421.0984; found: 421.0985.

[3-(4-Methoxyphenyl)-5-(10-methyl-10*H*-phenothiazin-3-yl)isoxazol-4-yl](thiophen-2-yl)methanone (5r)
Orange crystals; mp 172 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.30 (s, 3 H), 3.76 (s, 3 H), 6.68–6.77 (m, 2 H), 6.83–6.95 (m, 4 H), 7.05–7.17 (m, 2 H), 7.36 (dd, ^3J = 3.8, 1.1 Hz, 1 H), 7.48–7.63 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.3 (CH_3), 55.1 (CH_3), 112.9 (C_q), 113.8 (CH), 114.1 (2 × CH), 114.3 (CH), 120.4 (C_q), 120.6 (C_q), 122.3 (C_q), 123.0 (CH), 123.9 (C_q), 125.5 (CH), 126.99 (CH), 127.07 (CH), 127.6 (CH), 128.4 (CH), 129.5 (2 × CH), 135.6 (CH), 135.9 (CH), 144.1 (C_q), 144.4 (C_q), 147.8 (C_q), 160.8 (C_q), 161.2 (CH), 167.8 (C_q), 182.9 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 497 (19), 496 (63) $[M]^+$, 241 (17), 240 (100), 239 (15), 224 (13), 216 (28), 213 (22), 212 (73), 210 (13), 197 (25), 196 (19), 153 (11), 111 (11).

HRMS: *m*/*z* calcd for $C_{28}H_{20}N_2O_3S_2$: 496.0915; found: 496.0925.

{3-(4-Methoxyphenyl)-5-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]isoxazol-4-yl}(thiophen-2-yl)methanone (5s)
Colorless crystals; mp 133 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.71 (m, 6 H), 3.41–3.49 (m, 1 H), 3.41–3.49 (m, 1 H), 3.62–3.71 (m, 1 H), 3.76 (s, 3 H), 4.60–4.68 (s, 2 H), 4.83 (d, ^3J = 13.7 Hz, 1 H), 6.84 (d, ^3J = 8.9 Hz, 2 H), 7.00 (dd, ^3J = 4.9, 3.9 Hz, 1 H), 7.43 (dd, ^3J = 3.8, 1.1 Hz, 1 H), 7.53 (d, ^3J = 8.9 Hz, 2 H), 7.67 (dd, ^3J = 4.9, 1.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5 (CH_2), 25.1 (CH_2), 29.8 (CH_2), 55.2 (CH_3), 59.1 (CH_2), 61.6 (CH_2), 98.4 (CH), 114.1 (2 × CH), 116.5 (C_q), 120.1 (C_q), 128.2 (CH), 129.6 (2 × CH), 135.3 (CH), 135.6 (CH), 144.3 (C_q), 160.4 (C_q), 160.9 (C_q), 169.7 (C_q), 181.3 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 400 (22) $[M + H]^+$, 343 (12), 315 (13), 300 (12), 299 (59), 298 (97), 286 (16), 271 (10), 270 (19), 266 (21), 257 (14), 175 (10), 174 (45), 111 (71), 97 (30), 85 (32).

HRMS: *m*/*z* calcd for $C_{21}H_{21}NO_5S$: 399.1140; found: 399.1115.

Anal. Calcd for $C_{21}H_{21}NO_5S$: C, 63.14; H, 5.30; N, 3.51. Found: C, 62.93; H, 5.45; N, 3.44.

[5-*n*-Butyl-3-(4-nitrophenyl)isoxazol-4-yl](4-nitrophenyl)methanone (5t)
Colorless crystals; mp 97 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 7.3 Hz, 3 H), 1.30–1.43 (m, 2 H), 1.76 (q, ^3J = 7.6 Hz, 2 H), 2.90 (t, ^3J = 7.4 Hz, 2 H), 6.71 (d, ^3J = 8.9 Hz, 2 H), 7.25 (d, ^3J = 8.9 Hz, 2 H), 7.74 (d, ^3J = 8.9 Hz, 2 H), 8.07 (d, ^3J = 8.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.3 (CH_2), 27.8 (CH_2), 30.1 (CH_2), 114.0 (2 × CH), 114.8 (C_q), 119.3 (C_q), 123.4 (2 × CH), 130.0 (2 × CH), 130.2 (2 × CH), 142.4 (C_q), 150.3 (C_q), 160.8 (C_q), 161.1 (C_q), 178.5 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 395 (100) $[M]^+$, 366 (27), 245 (19), 150 (68), 85 (12), 28 (11).

Anal. Calcd for $C_{20}H_{17}N_3O_6$: C, 60.76; H, 4.33; N, 10.63. Found: C, 60.39; H, 4.47; N, 10.46.

(5-*n*-Butyl-3-*p*-tolylisoxazol-4-yl)(thiophen-2-yl)methanone (5u)
Yellow resin.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 7.4 Hz, 3 H), 1.29–1.42 (m, 2 H), 1.66–1.79 (m, 2 H), 2.30 (s, 3 H), 2.86 (t,

^3J = 7.9 Hz, 2 H), 6.93 (dd, ^3J = 4.9, 3.8 Hz, 1 H), 7.11 (d, ^3J = 8.3 Hz, 2 H), 7.29 (dd, ^3J = 3.8, 1.2 Hz, 1 H), 7.43 (d, ^3J = 8.3 Hz, 2 H), 7.62 (dd, ^3J = 4.9, 1.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5 (CH_3), 21.3 (CH_3), 22.2 (CH_2), 26.3 (CH_2), 29.5 (CH_2), 115.2 (C_q), 125.3 (C_q), 128.2 (2 × CH), 128.1 (CH), 129.3 (2 × CH), 135.0 (CH), 135.1 (CH), 139.9 (C_q), 144.1 (C_q), 160.8 (C_q), 175.3 (C_q), 182.0 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 326 (21) $[M + H]^+$, 325 (92) $[M]^+$, 324 (21), 296 (22), 283 (15), 241 (10), 212 (21), 111 (100) $[C_4H_3SCO]^+$.

HRMS: *m*/*z* calcd for $C_{19}H_{19}NO_2S$: 325.1136; found: 325.1115.

[5-*n*-Butyl-3-(3,4-dimethoxyphenyl)isoxazol-4-yl](thiophen-2-yl)methanone (5v)

Colorless crystals; mp 147 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, ^3J = 7.3 Hz, 3 H), 1.26–1.38 (m, 2 H), 1.63–1.74 (m, 2 H), 2.84 (t, ^3J = 7.4 Hz, 2 H), 3.73 (s, 3 H), 3.80 (s, 3 H), 6.74 (d, ^3J = 8.2 Hz, 1 H), 6.92 (dd, ^3J = 4.9, 3.8 Hz, 1 H), 7.05–7.12 (s, 2 H), 7.27 (dd, ^3J = 3.8, 1.1 Hz, 1 H), 7.61 (dd, ^3J = 4.9, 1.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4 (CH_3), 22.1 (CH_2), 26.2 (CH_2), 29.5 (CH_2), 55.7 (2 × CH_3), 110.9 (CH), 111.0 (CH), 115.0 (C_q), 120.6 (C_q), 121.3 (CH), 128.2 (CH), 135.0 (CH), 135.1 (CH), 144.1 (C_q), 148.8 (C_q), 150.2 (C_q), 160.4 (C_q), 175.4 (C_q), 182.1 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 372 (19) $[M + H]^+$, 371 (100) $[M]^+$, 287 (10), 162 (11), 111 (29).

HRMS: *m*/*z* calcd for $C_{20}H_{21}NO_4S$: 371.1191; found: 371.1215.

[3-(Anthracen-9-yl)-5-*n*-butylisoxazol-4-yl](thiophen-2-yl)methanone (5w)

Colorless crystals; mp 112 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 (t, ^3J = 7.4 Hz, 3 H), 1.51 (m, 2 H), 1.93 (q, ^3J = 7.6 Hz, 2 H), 3.14 (t, ^3J = 7.4 Hz, 2 H), 6.40 (dd, ^3J = 4.9, 3.9 Hz, 1 H), 6.95 (dd, ^3J = 3.9 Hz, ^4J = 1.1 Hz, 1 H), 7.22 (dd, ^3J = 4.9 Hz, ^4J = 1.1 Hz, 1 H), 7.41–7.50 (m, 4 H), 7.89–7.97 (m, 4 H), 8.43 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7 (CH_3), 22.5 (CH_2), 26.8 (CH_2), 29.7 (CH_2), 118.8 (C_q), 121.6 (C_q), 125.2 (CH), 125.3 (CH), 126.9 (CH), 129.3 (CH), 130.9 (C_q), 130.9 (C_q), 133.1 (CH), 134.1 (CH), 143.1 (C_q), 159.1 (C_q), 176.7 (C_q), 181.2 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 411 (100) $[M]^+$, 327 (15), 219 (14), 194 (13), 111 (26), 32 (11), 28 (39).

HRMS: *m*/*z* calcd for $C_{26}H_{21}NO_2S$: 411.1293; found: 411.1303.

(4-Methoxyphenyl)[5-*n*-propyl-3-(thiophen-2-yl)isoxazol-4-yl]methanone (5x)

Colorless crystals; mp 152 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 7.3 Hz, 3 H), 1.70 (s, 2 H), 2.68 (t, ^3J = 7.4 Hz, 2 H), 3.88 (s, 3 H), 6.75 (d, ^3J = 4.0 Hz, 1 H), 6.92 (d, ^3J = 8.8 Hz, 2 H), 7.01 (d, ^3J = 4.0 Hz, 1 H), 7.80 (d, ^3J = 8.8 Hz, 2 H), 8.08–8.14 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (CH_3), 20.9 (CH_2), 28.6 (CH_2), 55.6 (CH_3), 114.0 (C_q), 114.1 (2 × CH), 126.6 (CH), 127.8 (C_q), 128.9 (CH), 130.3 (C_q), 132.1 (2 × CH), 155.2 (C_q), 164.4 (C_q), 174.9 (C_q), 188.2 (C_q).

MS (EI, 70 eV): *m*/*z* (%) = 328 (11) $[M + H]^+$, 327 (100) $[M]^+$, 266 (10), 151 (11), 79 (29).

Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28. Found: C, 65.99; H, 5.54; N, 4.12.

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