Supporting Information

Synthesis, identification and structure-activity relationship analysis of GATA4 and NKX2-5 protein-protein interaction modulators

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Experimental Procedures (Chemistry)

All reactions were carried out using commercially available starting materials and reagents. Structures and synthesis of compounds SI1-136 are shown in Supporting Information. Compound 1 was purchased from Pharmatory Ltd (Oulu, Finland). Compounds SI120–130 and 59 were purchased from Enamine (Kiev, Ukraine), compounds 57, 70 and SI113 from ChemBridge (San Diego, California, USA), compounds 66, 69 and SI114-119 from ChemDiv (San Diego, California, USA) and compound SI133-136 from Maybridge (Leicestershire, UK). All chemicals, solvents and anhydrous solvents used in the syntheses were acquired from Sigma-Aldrich (Schnelldorf, Germany), Fluka (Buchs, Switzerland) and Alfa Aesar (Ward Hill, Massachusetts, USA). All moisture sensitive reactions were performed in flame-dried glassware under an inert argon atmosphere. The progress of chemical reactions was monitored by thin-layer chromatography on 0.2-mm silica gel plates (silica gel 60, F254, Merck KGaA, Darmstadt, Germany) and visualized by UV light or ninhydrin stain (1.5% by weight in ethanol), when applicable. Column chromatography was performed with automated Biotage high performance flash chromatography Sp4-system (Uppsala, Sweden) using a 0.1-mm path length flow cell UV-detector/recorder module (fixed wavelength 254 nm) and the indicated mobile phase. The melting points were recorded with an SMP40 automatic melting point apparatus (Bibby Scientific Limited, Staffordshire, UK) and are uncorrected. Nuclear magnetic resonance spectra (1H NMR and 13C NMR) were recorded on a Varian Mercury Plus 300 (Agilent Technologies, Santa Clara, California, United States) or a Bruker Ascend 400 – Avance III HD NMR spectrometer (Bruker Corporation, Billerica, MA, USA), 1H NMR spectra at 300 or 400 MHz and 13C NMR spectra at 75 or 101 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to the NMR solvent signals (CDCl3 7.26 and 77.16 ppm, DMSO-d6 2.50 and 39.50 ppm, for 1H and 13C NMR, respectively. When necessary, two–dimensional NMR experiments (COSY, NOESY, gHSQC, gHMBC) were conducted to support structure determination. Multiplicities are indicated by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), sept (septet). The additional letter “b” indicates a broad signal, such as bs (broad singlet). Multiplets (m) are either reported as a range of ppm values (m) or as a centered multiplet (m_c). Coupling constants J are quoted in Hertz (Hz). Exact mass and purity (>95%) of all tested compounds was confirmed by LC-MS analyses with a Waters Acquity® UPLC system (Waters, Milford, MA, USA) equipped with an Acquity UPLC® BEH C18 column (1.7 μm, 50 mm × 2.1 mm, Waters, Ireland), an Acquity PDA detector and a Waters Synapt G2 HDMS mass spectrometer (Waters, Milford, MA, USA) via an ESI ion source in positive mode. High resolution mass (HRMS-ESI) data was reported for the molecular ions [M+H]+.
General procedure I: HBTU-mediated amide coupling

Unless otherwise noted, equimolar amounts of carboxylic acid, aromatic amine and the indicated amount of \(N,N,N',N'-\text{tetramethyl-O-(1H-benzotriazol-1-yl)}\)uronium hexafluorophosphate (HBTU), typically between 1 and 3 equivalents, were dissolved under argon in anhydrous \(N,N\)-dimethylformamide (DMF). The given amount of \(N,N\)-diisopropylethylamine (DIPEA), typically between 1 and 3 equivalents, was added to the stirred reaction mixture at room temperature. Unless otherwise indicated, the work-up was started after the reaction mixture was stirred overnight. Either diethyl ether or ethyl acetate was added, and the organic phase was washed three times with water. When phase separation was slow, 5-30% of brine was added to the aqueous phase to aid separation. After drying the organic phase with anhydrous \(\text{Na}_2\text{SO}_4\), the solvents were removed with a rotary evaporator. The crude product was either directly recrystallized from the solvent mixtures indicated or subjected to automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in \(n\)-hexane, starting with 0% of ethyl acetate.

\[
\begin{align*}
\text{R}_1\text{COOH} + \text{R}_2\text{NH}_2 & \xrightarrow{a} \text{R}_1\text{CONHR}_2 \\
\end{align*}
\]

Scheme 1. Synthesis of amides with various northern (\(\text{R}_2\)) and southern (\(\text{R}_1\)) parts. Reagents and conditions. a) HBTU DIPEA, DMF, rt, 1-2 d.

General procedure II: Acyl chloride-mediated amide synthesis

When the required acyl chloride was not commercially available, it was prepared according to the following procedure. Unless otherwise noted, one equivalent of carboxylic acid was dissolved in anhydrous dichloromethane under argon. Three equivalents of a 2 M solution of oxalyl chloride in dichloromethane and a catalytic amount of anhydrous DMF (0.1 equiv) were added, and the reaction mixture was stirred for 2 h at room temperature. The solvent was removed with a rotary evaporator, and the residue was dissolved in anhydrous pyridine. The required amine was added, and the reaction mixture was stirred overnight at room temperature. Diethyl ether was added and the organic phase was washed three times with water. When phase separation was slow, 5-30% of brine was added to the aqueous phase to aid separation. The organic solvents were removed with a rotary evaporator. The crude product was either directly recrystallized from the solvent mixtures indicated or purified by automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in \(n\)-hexane, starting with 0% of ethyl acetate.

\[
\begin{align*}
\text{R}_1\text{COOH} & \xrightarrow{a} \text{R}_1\text{COCI} \\
\text{R}_1\text{COCI} & \xrightarrow{b} \text{R}_1\text{CONHR}_2 \\
\end{align*}
\]

Scheme 2. Synthesis of acyl chlorides and amides. Reagents and conditions. a) (COCl)\(_2\), DMF, DCM, rt, 2 h. b) \(\text{R}_2\text{NH}_2\), py, rt, overnight.
**General procedure III: Synthesis of Schiff bases**

Unless otherwise noted, equimolar amounts of aldehyde and amine were dissolved in anhydrous toluene under argon. The indicated amount of anhydrous \( \text{Na}_2\text{SO}_4 \), typically 2 equivalents, and the indicated amount of acetic acid, typically 0.25 equivalents, were added. Generally, the resulting mixture was stirred at room temperature overnight or, if indicated, heated under reflux conditions for an appropriate time. When no sufficient conversion was observed by TLC, a small amount of \( p \)-toluenesulfonic acid was added as indicated, and the reaction mixture was stirred at room temperature or heated for the given time. The reaction mixture was then concentrated with a rotary evaporator and purified by automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in \( n \)-hexane, starting with 0% of ethyl acetate.

\[
R^1\text{NH}_2 + R^2\text{CHO} \rightarrow R^2\text{N}^+\text{R}^1
\]

**Scheme 3.** Synthesis of Schiff bases with different northern (R\(^1\)NH\(_2\)) and southern (R\(^2\)CHO) parts. Reagents and conditions: AcOH, Na\(_2\)SO\(_4\) anhydr., toluene. a) rt, overnight. b) reflux, 9 h. c) 1. 70 °C, 100 °C, 5 h. 2. \( p \)-TsOH, 70 °C, 30 min. d) additional ethyl acetate, 70 °C, overnight. e) rt, overnight, 70 °C, 2 h. f) additional \( p \)-TsOH 70 °C, 2 h. g) additional \( p \)-TsOH, 70 °C, 4 h. h) 100 °C, 6 h. i) \( p \)-TsOH, 90 °C, 4 h, 70 °C, overnight. j) 70 °C, overnight.

**General procedure IV: Synthesis of ureas**

Unless otherwise noted, equimolar amounts of amine and isocyanate were dissolved in anhydrous toluene under argon, and the reaction mixture was stirred at room temperature overnight. The crude product was either directly recrystallized from the reaction mixture after addition of an appropriate amount of solvent. Alternatively, the solvent was removed with a rotary evaporator and the crude product was purified by automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in \( n \)-hexane, starting with 0% of ethyl acetate.

\[
\begin{align*}
\text{NH}_2 &+ \quad \text{O} = \text{N}^-\text{R}^1 \\
\text{O} = \text{N}^-\text{R}^1 &\rightarrow \quad \text{NH}^+\text{R}^1
\end{align*}
\]

**Scheme 4.** Synthesis of ureas. Reagents and conditions. a) Toluene, rt, overnight to 4 d.
General procedure V: Synthesis of carbothioamides from amides

Unless otherwise noted, one equivalent of the appropriate amide was dissolved in anhydrous toluene. Lawesson’s reagent, 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (0.6 equiv) was added and the resulting mixture was heated at reflux temperature for the time indicated or overnight. The reaction mixture was diluted with ethyl acetate and washed three times with water. The organic solvent was removed with a rotary evaporator and the crude product was purified by automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate.

Scheme 5. Synthesis of carbothioamides. Reagents and conditions. a) Lawesson’s reagent, toluene, reflux, 6 h to overnight.

General procedure VI: Hydrolysis of triazole esters and the subsequent HBTU-mediated amide coupling

Unless otherwise noted, one equivalent of triazole methyl ester was dissolved or suspended in an equimixture of THF, methanol and water. Lithium hydroxide monohydrate (1.5 equiv) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and the mixture was transferred to a separation funnel. Water was added and the mixture was acidified with 1 M hydrochloric acid. The phases were separated, the organic phase was washed neutral with portions of water and the solvent was removed with a rotary evaporator. After drying the crude intermediate, it was dissolved in anhydrous DMF under argon.

An equimolar amount of aromatic amine and the indicated amounts of HBTU (typically 1.3 equiv) and DIPEA (typically 2 equiv) were added to the above-mentioned solution of the crude carboxylic acid in DMF, and the reaction mixture was stirred at room temperature. Unless otherwise indicated, the work-up was started after the reaction mixture was stirred overnight. Either diethyl ether or ethyl acetate was added and the organic phase was washed three times with water. When phase separation was slow, 5-30% of brine was added to the aqueous phase. Organic solvents were removed with a rotary evaporator. The crude product was either directly recrystallized from the solvent mixtures indicated or subjected to automated preparative chromatography purification. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate.
Scheme 6. Hydrolysis of triazole esters and the subsequent HBTU-mediated amide coupling. Reagents and conditions.
a) 1. LiOH·H₂O, THF/MeOH/H₂O (1:1:1), rt, overnight. 2. N,N-diethyl-1,4-phenylenediamine, HBTU, DIPEA, DMF, rt, 1-2 d.

General procedure VII: HBTU-mediated ester synthesis

Unless otherwise noted, aromatic carboxylic acid, alcohol (3 equiv) and HBTU (1.3–1.5 equiv) were dissolved in anhydrous DMF under argon. DIPEA (2 equiv) was added and the reaction mixture was stirred at room temperature. After the reaction time indicated, either diethyl ether or ethyl acetate was added and the organic phase was washed three times with water. When phase separation was slow, 5-30% of brine was added to the aqueous phase. The organic solvents were removed with a rotary evaporator. The crude product was purified by automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate.

Scheme 7. HBTU-mediated ester synthesis. Reagents and conditions. a) R¹OH, HBTU, DIPEA, DMF, rt, 1-3 d.

General procedure VIII: Synthesis of 1,2,3-triazoles via 1,3-dipolar cycloaddition

Method A: Equimolar amounts of methyl phenylpropiolate, alkyl halide, tetra-n-butyrammoniumbromide, TBAB and sodium azide were dissolved in a two-phase system of equal volumes of toluene and water. The reaction mixture was either pre-stirred at room temperature as indicated, or irradiated directly in a microwave reactor (typically at 150 °C for 60 min). The phases were separated, and the aqueous phase was washed with toluene or ethyl acetate as indicated. The organic solvent was removed with a rotary evaporator. The crude product was purified by automated
preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate.

**Method B:** Equimolar amounts of methyl phenylpropiolate, alkyl halide and sodium azide were dissolved in absolute DMF. The reaction mixture was irradiated in a microwave reactor (typically at 140 °C for 70 min). The reaction mixture was diluted with ethyl acetate and washed three times with water. When phase separation was slow, 5-30% of brine was added to the aqueous phase. The organic solvents were removed with a rotary evaporator. The crude product was purified by automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate.

![Scheme 8](image_url)

**Scheme 8.** Synthesis of 1,2,3-triazoles via 1,3-dipolar cycloaddition. Reagents and conditions. a) R₁Br or R₁I, NaN₃, toluene, H₂O, TBAB, rt or MW (150 °C, 60 min) or b) R₁Br or R₁I, NaN₃, DMF, MW (140 °C, 70 min).

**General procedure IX: Reductive amination of aldehydes via Schiff bases**

Unless otherwise noted, anhydrous sodium sulphate (3 equiv) was flame-dried in an evacuated Schlenk flask. Absolute THF, acetic acid (0.25–1 equiv) as well as an equimolar amount of aromatic aldehyde and aromatic amine were added to the flask containing Na₂SO₄. The reaction mixture was stirred at room temperature for the indicated time, and a 1.0 M solution of sodium cyanoborohydride in THF (3-5 equiv) was added. The solution was stirred at room temperature until TLC indicated consumption of the starting materials and intermediate Schiff base (3-5 d). During this period of time additional sodium cyanoborohydride may be added (1-2 equiv). The reaction mixture was quenched with a diluted solution of sodium hydroxide in water or a saturated solution of sodium hydrogen carbonate in water. After 20-60 min ethyl acetate was added, and the organic phase was washed three times with a mixture of water and brine (typically 2:1). The organic solvents were removed with a rotary evaporator. The crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate containing triethylamine (1%) in n-hexane, starting with 0% of ethyl acetate-triethylamine mixture.
Scheme 9. Reductive amination of aldehydes via Schiff base. Reagents and conditions. a) 1. NaBH₃CN, Na₂SO₄, rt, 3 d, 2. additional NaBH₃CN, rt, overnight.

General procedure X: Ester synthesis by alkylation of aromatic carboxylic acids

Unless otherwise noted, the appropriate carboxylic acid was dissolved in absolute DMF under argon. Alkyl halide (3 equiv) and potassium carbonate (2 equiv) were added, and the reaction mixture was shaken in a sealed tube at room temperature (1-4 d). Ethyl acetate was added and the organic phase was washed three times with a mixture of water and brine (3:1). The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of the ethyl acetate.

Scheme 10. Alkylation of aromatic carboxylic acids to produce the corresponding esters. a) R²Br or R²I, K₂CO₃, DMF, rt, 1-4 d.
Preparation of compounds in Scheme 1 and other related compounds

\[N\text{-}[4\text{-}[\text{Ethyl}(2\text{-hydroxyethyl)amino}][\text{phenyl}]-5\text{-methyl}-3\text{-phenylisoxazole-4-carboxamide (4b)}\]

Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid (345 mg, 1.70 mmol), 4-amino-N-(2-hydroxyethyl)-N-ethylaniline sulfate 2b (473 mg, 1.70 mmol), HBTU (838 mg, 2.21 mmol, 1.3 equiv), DIPEA (1.18 mL, 6.80 mmol, 4 equiv), DMF (5 mL). Solvent for extraction: ethyl acetate. Recrystallization (MeOH/H\text{2}O 10+1) after chromatography on silica gel gave compound 4b (221 mg, 0.605 mmol, 36%) as beige crystals. M.p. 155.0–157.5 °C. \(^1\)H NMR (300 MHz, DMSO-\text{d}_6): \(\delta 10.10\) (s, 1H), 7.74–7.66 (m, 2H), 7.53–7.44 (m, 3H), 7.38 (m, 2H), 6.63 (m, 2H), 4.68 (t, 1H, \(^3\)J = 5.4 Hz), 3.51 (q, 2H, \(^3\)J = 6.0 Hz), 3.39–3.26 (m, 4H), 2.55 (s, 3H) 1.05 (t, 3H, \(^3\)J = 7.0 Hz) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\text{d}_6): \(\delta 169.4, 160.1, 159.1, 144.8, 130.1, 128.9, 128.2, 127.7, 127.1, 121.5, 113.6, 111.4, 58.4, 52.3, 44.7, 11.9, 11.9 ppm. HRMS calc. for C\text{21}H\text{24}N\text{3}O\text{3} [M+H]^+: 366.1818, found 366.1817.

\[N\text{-}[3\text{-Chloro-4-(diethylamino)phenyl}]-5\text{-methyl}-3\text{-phenylisoxazole-4-carboxamide (4c)}\]

Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid (0.100 g, 0.492 mmol), 2-chloro-N\text{3},N\text{3}-diethyl-1,4-phenylenediamine (116 mg, 0.492 mmol), HBTU (243 mg, 0.640 mmol, 1.3 equiv), DIPEA (0.257 mL, 1.48 mmol, 3 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (3:1). Recrystallization (MeOH/H\text{2}O 10+1) after chromatography on silica gel gave compound 4c (96.7 mg, 0.252 mmol, 51%) as white needles. M.p. 153.9–155.4 °C. \(^1\)H NMR (300 MHz, DMSO-\text{d}_6): \(\delta 10.44\) (s, 1H), 7.80 (d, 1H, \(^3\)J = 2.4 Hz), 7.73–7.65 (m, 2H), 7.54–7.41 (m, 4H), 7.18 (d, 1H, \(^3\)J = 8.7 Hz), 3.01 (q, 4H, \(^3\)J = 7.0 Hz), 2.58 (s, 3H), 0.94 (t, 3H, \(^3\)J = 7.0 Hz) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\text{d}_6): \(\delta 169.9, 160.1, 159.8, 143.2, 134.4, 130.0, 129.7, 128.8, 127.9, 127.7, 124.0, 121.2, 118.7, 113.1, 46.2, 12.0, 11.9 ppm. HRMS calc. for C\text{21}H\text{23}ClN\text{3}O\text{2} [M+H]^+: 384.1479, found 384.1481.

\[N\text{-}[4\text{-Isopropyl-3-methylphenyl}]-5\text{-methyl}-3\text{-phenylisoxazole-4-carboxamide (4e)}\]

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction mixture was diluted with ethyl acetate for the work-up and extracted in the following order: once with water containing 10% brine, once with a 2 M solution of sodium hydroxide in water, once with 2 M hydrochloric acid and several times with water until the water phase remained neutral. 5-Methyl-3-phenylisoxazole-4-carboxylic acid, 6, (82.1 mg, 0.404 mmol), 4-isopropyl-3-methylaniline hydrochloride (75.0 mg, 0.404 mmol), HBTU (383 mg, 1.01 mmol, 2.5 equiv), DIPEA (0.282 mL, 1.62 mmol, 4 equiv), DMF
(3 mL). Recrystallization (MeOH/H$_2$O 10+1) after automated chromatography on silica gel gave compound 4e (78.0 mg, 0.233 mmol, 58%) as fine white needles. M.p. 147.0–148.5 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.32 (s, 1H), 7.72–7.66 (m, 2H), 7.53–7.47 (m, 3H), 7.42–7.37 (m, 2H), 7.21–7.16 (m, 1H), 3.06 (sept, 1H, $^3$J = 6.8 Hz), 2.56 (s, 3H), 2.27 (s, 3H). 1.15 (d, 6H, $^3$J = 6.8 Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 169.7, 160.1, 159.7, 142.3, 136.0, 134.9, 130.1, 128.9, 128.1, 127.7, 124.9, 121.3, 117.7, 113.4, 28.3, 23.2, 19.1, 11.9 ppm. HRMS calc. for C$_{21}$H$_{23}$N$_2$O$_2$ [M+H]$^+$: 335.1760, found 335.1759.

$N$-[[1,1'-Biphenyl]-4-yl]-5-methyl-3-phenylisoxazole-4-carboxamide (4f)

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 2 d and the reaction mixture was diluted with ethyl acetate for the work-up and extracted in the following order: once with water, twice with a 2 M solution of sodium hydroxide in water, twice with 4 M hydrochloric acid and several times with water until the aqueous phase remained neutral. 5-Methyl-3-phenylisoxazole-4-carboxylic acid 6 (203 mg, 1.00 mmol), 4-aminobiphenyl (169 mg, 1.00 mmol), HBTU (455 mg, 1.20 mmol, 1.2 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (2 mL). Recrystallization, MeOH (10 mL)/2-propanol (5 mL)/ethyl acetate (5 mL), [without chromatography on silica gel] gave compound 4f (283 mg, 0.799 mmol, 80%) as fine white needles. M.p. 192.7–194.3 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.54 (s, 1H), 7.76–7.62 (m, 8H), 7.53–7.42 (m, 5H), 7.37–7.31 (m, 1H), 2.60 (s, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 169.8, 160.1, 159.9, 139.6, 138.0, 135.8, 130.4, 128.8, 128.0, 127.7, 127.1, 127.0, 126.3, 120.0, 113.3, 11.9 ppm. HRMS calc. for C$_{23}$H$_{23}$N$_2$O$_2$ [M+H]$^+$: 355.1447, found 355.1453.

5-Methyl-N-(4-oxo-2-phenyl-4H-chromen-6-yl)-3-phenylisoxazole-4-carboxamide (4g)

Synthesis according to the General procedure I. Deviating from the General procedure I, the crude product was first recrystallized from EtOAc/EtOH (2+1), and the mother liquor was purified by automated chromatography. The product obtained from chromatography on silica gel and the first recrystallization were combined and recrystallized again (EtOAc/EtOH 2+1). 5-Methyl-3-phenylisoxazole-4-carboxylic acid 6 (203 mg, 1.00 mmol), 6-aminoflavone (237 mg, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (2.5 mL). Solvent for extraction: ethyl acetate. Recrystallization (EtOAc/EtOH 2+1) after chromatography on silica gel gave compound 4g (278 mg, 0.658 mmol, 66%) as slightly yellow crystals. M.p. 228.0–229.4 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.71 (s, 1H), 8.41 (d, 1H, $^3$J = 2.7 Hz), 8.15–8.07 (m, 2H), 7.99 (dd, 1H, $^3$J = 9.1 Hz), 7.80 (d, 1H), 7.76–7.68 (m, 2H), 7.66–7.55, 7.54–7.46 (each m, each 3H), 7.03 (s, 1H), 2.63 (s, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 176.8, 170.2, 162.4, 160.2, 160.1, 152.1, 135.9, 131.7, 131.1, 130.1, 129.1, 128.8, 127.9, 127.7, 126.3, 126.2, 123.5, 119.6, 114.2, 113.0, 106.5, 11.9 ppm. HRMS calc. for C$_{28}$H$_{19}$N$_2$O$_4$ [M+H]$^+$: 423.1345, found 423.1347.
5-Methyl-N-[4-(2-morpholinoethoxy)phenyl]-3-phenylisoxazole-4-carboxamide (4h)

Synthesis according to the General procedure I. Deviating from the general procedure I, the reaction time was 3 h and reaction temperature was 60 °C. Deviating from the General procedure I, the reaction mixture was diluted with ethyl acetate for the work-up, and extracted twice with 2 M hydrochloric acid. The combined aqueous phases were made alkaline with a 2 M solution of sodium hydroxide in water and extracted twice with ethyl acetate. The combined organic phases were washed twice with a mixture of water and brine (10:1). 5-Methyl-3-phenylisoxazole-4-carboxylic acid (0.100 g, 0.492 mmol), 4-(2-morpholin-4-yethoxy)aniline (109 mg, 0.492 mmol), HBTU (373 mg, 0.984 mmol, 2 equiv), DIPEA (0.257 mL, 1.48 mmol, 3 equiv), DMF (5 mL). Recrystallization (MeOH/H₂O 10+1) [without chromatography on silica gel] gave compound 4h (102 mg, 0.250 mmol, 51%) as crystalline needles. M.p. 135.9–136.3 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 10.26 (s, 1H), 7.73–7.67 (m, 2H), 7.55–7.45 (m, 5H), 6.92 (m, 2H), 4.06 (t, 2H, J = 5.8 Hz), 3.58 (m, 4H), 2.67 (t, 2H, J = 5.8 Hz), 2.57 (s, 3H), 2.46 (m, 4H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 169.7, 160.1, 159.5, 155.0, 131.7, 130.1, 128.9, 128.1, 127.7, 121.1, 114.6, 113.4, 66.2, 65.5, 57.0, 53.6, 11.9 ppm. HRMS calc. for C₂₃H₂₆N₃O₄ [M+H]+: 408.1923, found 408.1920.

3-Cyanopropyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (10b)

Synthesis according to the General procedure X. Deviating from the General procedure X, the chromatography was omitted and the product was recrystallized from MeOH/H₂O (10+1). 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid 12 (40.1 mg, 0.124 mmol), bromobutanenitrile (12.4 µL, 0.124 mmol), K₂CO₃ (25.7 mg, 0.186 mmol, 1.5 equiv), DMF (1 mL). Reaction time: 2 d. Solvent for extraction: ethyl acetate and water. Recrystallization gave compound 10b (41.0 mg, 0.105 mmol, 85%) as colorless needles. M.p. 170.6–172.5 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 10.73 (s, 1H), 8.00 (m, 2H), 7.75 (m, 2H), 7.71–7.64 (m, 2H), 7.53–7.45 (m, 3H), 4.32 (t, 2H, J = 6.1 Hz), 2.68 (t, 2H, J = 7.1 Hz), 2.60 (s, 3H), 2.03 (m, 2H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 170.3, 165.1, 160.3, 160.2, 142.9, 130.4, 130.1, 128.8, 127.9, 127.7, 124.6, 120.2, 119.0, 113.0, 63.0, 24.2, 13.5, 11.9 ppm. HRMS calc. for C₂₂H₂₀N₃O₄ [M+H]^+: 390.1454, found 390.1458.
4-Cyanobutyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (10c)

Synthesis according to the General procedure X. Deviating from the General procedure X, the chromatography was omitted and the product was recrystallized from MeOH. 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid 12 (44.0 mg, 0.137 mmol), bromopentanenitrile (15.8 µL, 0.137 mmol), K₂CO₃ (28.4 mg, 0.206 mmol, 1.5 equiv), DMF (1 mL), Reaction time: 2 d. Solvent for extraction: ethyl acetate and water. Recrystallization gave compound 10c (43.2 mg, 0.107 mmol, 78%) as a white solid. M.p. 114.0–115.4 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 10.73 (s, 1H), 7.96 (m, 2H), 7.76 (m, 2H), 7.72–7.64 (m, 2H), 7.53–7.45 (m, 3H), 4.29 (t, 2H, ^3J = 6.1 Hz), 2.60 (s, 3H), 2.58 (t, 2H, ^3J = 6.8 Hz), 1.87–1.64 (m, 4H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 170.3, 165.1, 160.3, 160.2, 142.9, 130.2, 130.1, 128.8, 127.9, 127.7, 124.9, 120.5, 119.1, 113.0, 63.6, 27.3, 21.7, 15.9, 11.9 ppm. HRMS calc. for C₂₅H₂₁N₃O₄ [M+H]^+: 404.1610, found 404.1613.

2-(Dimethylamino)ethyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (10d)

Synthesis according to the General procedure VII. Deviating from the General procedure VII, the chromatography was performed with an increasing gradient of ethyl acetate containing TEA (1%) in n-hexane. 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid 12 (31.4 mg, 0.0974 mmol), 2-(dimethylamino)ethan-1-ol (29.4 µL, 0.292 mmol, 3 equiv), HBTU (48.0 mg, 0.127 mmol, 1.3 equiv), DIPEA (33.9 µL, 0.195 mmol, 2 equiv), DMF (1 mL). Reaction time: 3 d. Solvent for extraction: ethyl acetate and a mixture of water and brine (2:1). Chromatography on silica gel gave compound 10d (32.1 mg, 0.0816 mmol, 84%) as a yellowish solid. M.p. 95.8–99.5 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 10.73 (s, 1H), 7.95 (m, 2H), 7.76 (m, 2H), 7.72–7.64 (m, 2H), 7.53–7.45 (m, 3H), 4.34 (t, 2H, ^3J = 5.7 Hz), 2.64–2.58 (m, 5H), 2.21 (s, 6H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 170.3, 165.1, 160.3, 160.2, 142.8, 130.2, 130.1, 128.8, 127.9, 127.7, 124.9, 119.1, 113.0, 62.4, 57.2, 45.3, 11.9 ppm. HRMS calc. for C₂₃H₂₁N₃O₄ [M+H]^+: 394.1767, found 394.1772.

2-(Ethylthio)ethyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (SI1)

Synthesis according to the General procedure VII. 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid 12 (35.4 mg, 0.110 mmol), 2-(ethylthio)ethan-1-ol (57.2 µL 0.549 mmol, 5 equiv), HBTU (54.2 mg, 0.143 mmol, 1.3 equiv), DIPEA (38.3 µL, 0.220 mmol, 2 equiv), DMF (1 mL). Reaction time: 2 d. Solvent for extraction: diethyl ether
and water. Chromatography on silica gel gave compound SI1 (38.7 mg, 0.0976 mmol, 89%) as a white solid. M.p. 109.8–110.4 °C. 1H NMR (300 MHz, DMSO-d$_6$): δ 10.72 (s, 1H), 7.94 (m, 2H), 7.75 (m, 2H), 7.70–7.62 (m, 2H), 7.52–7.42 (m, 3H), 4.38 (t, 2H, 3J = 6.7 Hz), 2.86 (t, 2H, 3J = 6.7 Hz), 2.58 (q, 2H, 3J = 7.4 Hz), 2.58 (s, 3H), 1.18 (t, 3H, 3J = 7.4 Hz) ppm. 13C NMR (75 MHz, DMSO-d$_6$): δ 170.3, 165.0, 160.4, 160.2, 142.9, 130.3, 128.8, 127.9, 127.7, 124.7, 119.1, 113.0, 63.7, 29.3, 25.2, 14.7, 11.9 ppm. HRMS calc. for C$_{22}$H$_{23}$N$_2$O$_4$S [M+H]$^+$: 411.1379, found 411.1378.

**Furan-2-ylmethyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (SI2)**

Synthesis according to the General procedure VII. 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid 12 (32.2 mg, 0.100 mmol), furfurylalcohol (25.9 µL, 0.300 mmol, 3 equiv), HBTU (49.3 mg, 0.130 mmol, 1.3 equiv), DIPEA (34.8 µL, 0.200 mmol, 2 equiv), DMF (1 mL). Reaction time: 3 d. Solvent for extraction: diethyl ether and water. Chromatography on silica gel gave compound SI12 (29.7 mg, 0.0738 mmol, 74%) as a white solid. M.p. 133.7–135.1 °C. 1H NMR (300 MHz, DMSO-d$_6$): δ 10.73 (s, 1H), 7.94 (m, 2H), 7.75 (m, 2H), 7.71 (dd, 1H, 3J = 0.8 Hz, 3J = 1.9 Hz), 7.70–7.63 (m, 2H), 7.53–7.44 (m, 3H), 6.60 (dd, 1H, 3J = 3.3 Hz, 4J = 0.8 Hz), 6.49 (dd, 1H, 3J = 3.3 Hz, 3J = 1.9 Hz), 5.30 (s, 2H), 2.59 (s, 3H) ppm. 13C NMR (75 MHz, DMSO-d$_6$): δ 170.3, 164.7, 160.3, 160.2, 149.3, 143.7, 143.0, 130.3, 130.1, 128.8, 127.9, 127.7, 124.4, 119.1, 112.9, 110.9, 110.7, 58.0, 11.9 ppm. HRMS calc. for C$_{23}$H$_{19}$N$_2$O$_5$ [M+H]$^+$: 403.1294, found 403.1299.

**2-Oxopropyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (SI3)**

Synthesis according to the General procedure VII. Deviating from the General procedure VII, the chromatography was omitted and the product was recrystallized from MeOH. 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid 12 (34.0 mg, 0.105 mmol), hydroxyacetone (21.7 µL, 0.316 mmol, 3 equiv), HBTU (51.8 mg, 0.137 mmol, 1.3 equiv), DIPEA (36.6 µL, 0.210 mmol, 2 equiv), DMF (1 mL). Reaction time: 2 d. Solvent for extraction: diethyl ether and water. Recrystallization gave compound SI3 (28.5 mg, 0.0753 mmol, 72%) as a white solid. M.p. 199.9–201.5 °C. 1H NMR (300 MHz, DMSO-d$_6$): δ 10.76 (s, 1H), 7.99 (m, 2H), 7.78 (m, 2H), 7.72–7.65 (m, 2H), 7.53–7.45 (m, 3H), 4.99 (s, 2H), 2.60 (s, 3H), 2.16 ppm. 13C NMR (75 MHz, DMSO-d$_6$): δ 201.8, 170.3, 164.5, 160.4, 160.2, 143.1, 130.5, 130.1, 128.8, 127.9, 127.7, 124.1, 119.1, 113.0, 68.6, 25.9, 11.9 ppm. HRMS calc. for C$_{21}$H$_{19}$N$_2$O$_3$ [M+H]$^+$: 379.1294, found 379.1296.
**N,N-Diethyl-N-[4-(5-Methyl-3-phenylisoxazole-4-carboxamido)phenyl]hydroxylammonium 3-chlorobenzoate (SI4)**

\[ \text{SI4} \]

\[
\text{N-[4-(Diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide} \quad \text{1} \quad (349 \text{ mg, 1.00 mmol}) \]

was dissolved in a mixture of acetonitrile (5 mL) and acetone (3 mL). \( m \)-Chloroperoxybenzoic acid (77%, max. 288 mg, max. 1.28 mmol) was added to the solution. The reaction mixture was stirred for 30 min at room temperature, during which the product precipitated. Filtration gave compound SI4 (371 mg, 0.711 mmol, 71%) as white needles. M.p. 139.7–141.8 °C (decomp.). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \( \delta \) 10.80 (s, 1H), 7.93–7.76 (m, 5H), 7.73–7.66 (m, 2H), 7.58–7.42 (m, 5H), 4.03 (q, 4H, \(^3\)J = 7.0 Hz), 2.60 (s, 3H), 1.01 (t, 6H) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \( \delta \) 170.2, 167.6, 160.3, 141.3, 139.1, 137.3, 132.8, 130.9, 130.2, 130.0, 128.9, 128.8, 128.0, 127.8, 127.7, 122.4, 119.8, 113.1, 48.6, 12.0, 7.9 ppm. HRMS calc. for cation \( \text{C}_{21}\text{H}_{24}\text{N}_3\text{O}_3 \): 366.1809, found 366.1812.

**5-Methyl-3-phenyl-N-[4-(phenylamino)phenyl]isoxazole-4-carboxamide (SI5)**

Synthesis according to the General procedure I. The organic phase was washed twice with a mixture of water and brine (10:1). 5-Methyl-3-phenylisoxazole-4-carboxylic acid (1.00 g, 4.92 mmol), \( N \)-phenyl-\( p \)-phenylenediamine (1.09 g, 5.91 mmol, 1.2 equiv), HBTU (3.73 g, 9.84 mmol, 2 equiv), DIPEA (0.257 mL, 1.48 mmol, 3 equiv), DMF (20 mL). Deviating from the General procedure I, the automated chromatography started with 25% ethyl acetate in \( n \)-hexane and ended with 50% \( n \)-hexane in ethyl acetate. Recrystallization (MeOH/H\(\text{H}_2\text{O} \) 10+1) after automated chromatography on silica gel gave compound SI5 (1.00 g, 2.71 mmol, 55%) as fine white crystals. M.p. 142.9–146.5 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \( \delta \) 10.27 (s, 1H), 8.09 (s, 1H), 7.76–7.68 (m, 2H), 7.54–7.47 (m, 5H), 7.24–7.17 (m, 2H), 7.09–6.99 (m, 4H), 6.81–6.75 (m, 1H), 2.58 (s, 3H) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \( \delta \) 169.6, 160.2, 159.4, 143.8, 139.6, 131.3, 130.1, 129.2, 128.8, 128.2, 127.7, 121.1, 119.2, 117.5, 116.0, 113.5, 11.9 ppm. HRMS calc. for \( \text{C}_{23}\text{H}_{30}\text{N}_3\text{O}_2 \) [M+H]$: 370.1556, found 370.1558.
**N-[4-[Ethyl(phenyl)amino]phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide (SI6)**

5-Methyl-3-phenyl-N-[4-(phenylamino)phenyl]isoxazole-4-carboxamide SI5 (154 mg, 0.500 mmol) and potassium carbonate (104 mg, 0.750 mmol, 1.5 equiv) were dissolved in anhydrous DMF (3 mL) under argon and iodoethane (48.3 µL, 0.600 mmol, 1.2 equiv) was added to this solution. The reaction mixture was stirred for 2 d at room temperature. Diethyl ether was added, and the organic phase was washed three times with water. The organic solvents were removed with a rotary evaporator and the crude product was purified by automated chromatography on silica gel using a gradient of increasing ethyl acetate, starting with 100% n-hexane to yield compound SI6 (47.0 mg, 0.118 mmol, 24%) as a colorless resin.

1H NMR (300 MHz, DMSO-d6): δ 8.14 (s, 1H), 7.58–7.45 (m, 5H), 7.27–7.19 (m, 2H), 7.03–6.96 (m, 2H), 6.87–6.81 (m, 1H), 6.78–6.70 (m, 2H), 6.60–6.48 (m, 2H), 3.76 (q, 2H, J = 7.0 Hz), 2.36 (s, 3H), 1.09 (t, 3H) ppm.

13C NMR (75 MHz, DMSO-d6): δ 168.1, 162.0, 159.3, 142.6, 142.4, 132.3, 130.1, 129.1, 128.8, 128.2, 127.7, 127.0, 120.2, 117.2, 115.8, 111.7, 43.7, 12.5, 11.4 ppm. HRMS calc. for C25H24N3O2 [M+H]+: 398.1869, found 398.1859.

**N-(6-Butoxypyridin-3-yl)-5-methyl-3-phenylisoxazole-4-carboxamide (SI7)**

Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid 6 (75.0 mg, 0.369 mmol), 5-amino-2-butoxypyridine hydrochloride (74.8 mg, 0.369 mmol), HBTU (0.210 g, 0.554 mmol, 1.5 equiv), DIPEA (0.257 mL, 1.48 mmol, 4 equiv), DMF (2 mL). Solvent for extraction: ethyl acetate. Recrystallization (MeOH) without chromatography on silica gel gave compound SI7 (87.0 mg, 0.248 mmol, 67%) as white needles. M.p. 159.6–161.0 °C.

1H NMR (300 MHz, DMSO-d6): δ 10.42 (s, 1H), 8.35 (d, 1H, J = 2.7 Hz), 7.90 (dd, 1H, J = 2.7 Hz, J = 8.9 Hz), 7.73–7.66 (m, 2H), 7.53–7.45 (m, 3H), 6.81 (d, 1H, J = 8.9 Hz), 4.22 (t, 2H, J = 6.6 Hz), 2.59 (s, 3H), 1.73–1.62 (m, 2H), 1.47–1.34 (m, 2H), 0.92 (t, 3H, J = 7.4 Hz) ppm.

13C NMR (75 MHz, DMSO-d6): δ 169.9, 160.1, 160.0, 159.9, 138.3, 132.0, 130.0, 129.0, 128.8, 127.9, 127.7, 112.9, 110.3, 65.1, 30.5, 18.7, 13.6, 11.9 ppm. HRMS calc. for C20H22N3O3 [M+H]+: 352.1661, found 352.1664.
**N-[4-(Benzylxoy)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide (SI8)**

Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid 6 (203 mg, 1.00 mmol), 4-(benzylxoy)aniline hydrochloride (236 mg, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.523 mL, 2.00 mmol, 2 equiv), DMF (4 mL). Solvent for extraction: diethyl ether. Recrystallization (EtOH) without chromatography on silica gel gave compound **SI8** (289 mg, 0.751 mmol, 75%) as white needles. M.p. 155.1–157.3 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.26 (s, 1H), 7.74–7.67 (m, 2H), 7.56–7.29 (m, 10H), 7.00 (m, 2H), 5.09 (s, 2H), 2.57 (s, 3H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 169.6, 160.1, 159.5, 154.8, 137.0, 131.8, 130.0, 128.7, 128.3, 128.1, 127.7, 127.6, 127.5, 121.2, 114.9, 113.3, 69.3, 11.8 ppm. HRMS calc. for C\(_{24}\)H\(_{21}\)N\(_3\)O\(_3\) [M+H]^+: 385.1552, found 385.1554.

**5-Methyl-N-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-phenylisoxazole-4-carboxamide (SI9)**

Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid 6 (203 mg, 1.00 mmol), 2-amino-1-methylbenzimidazole (147 mg, 1.00 mmol), HBTU (455 mg, 1.20 mmol, 1.2 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (4 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H\(_2\)O 10+1) after chromatography on silica gel gave compound **SI9** (133 mg, 0.400 mmol, 40%) as white crystals. M.p. 156.7–158.4 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 12.55 (s, 1H), 7.68–7.68 (m, 2H), 7.51–7.39 (m, 5H), 7.73–7.66 (m, 2H), 7.27–7.16 (m, 2H), 3.38 (s, 3H), 2.84 (s, 3H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 172.6, 168.9, 162.5, 159.9, 151.7, 130.0, 129.7, 129.3, 128.8, 128.7, 127.7, 122.6, 122.5, 115.1, 111.9, 109.3, 27.9, 13.4 ppm. HRMS calc. for C\(_{19}\)H\(_{17}\)N\(_4\)O\(_2\) [M+H]^+: 333.1352, found 333.1358.

**5-Methyl-N-(4-methyl-5-nitropyridin-2-yl)-3-phenylisoxazole-4-carboxamide (SI10)**

Synthesis according to the General procedure II. Deviating from the General procedure II, the oxalyl chloride solution was stirred at room temperature for 1 h and DIPEA was added to the pyridine solution. 5-Methyl-3-phenylisoxazole-4-carboxylic acid 6 (508 mg, 2.50 mmol), 4-methyl-5-nitropyridin-2-amine (383 mg, 2.50 mmol), a 2 M solution of oxalyl chloride in DCM (3.13 mL, 6.25 mmol, 2.5 equiv), DMF (20.9 μL, 0.250 mmol, 1.0 equiv), DCM (5 mL), DIPEA (0.653 mL, 3.75 mmol, 1.5 equiv), pyridine (5 mL). Solvent for extraction: ethyl acetate. Recrystallization (MeOH/H\(_2\)O 20+1) after chromatography on silica gel gave compound **SI10** (72.0 mg, 0.213 mmol, 8.5%) as white needles. M.p. 174.4–175.3 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 11.46 (s, 1H), 8.99 (s, 1H), 8.22 (s, 1H), 7.67–7.60 (m, 2H), 7.53–7.45 (m, 3H), 2.62, 2.60 (s, 3H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 171.4, 161.3, 160.5,
5-Methyl-3-phenyl-N-[4-(phenylcarbamoyl)phenyl]isoxazole-4-carboxamide (SI11)

Synthesis according to the General procedure I. Deviating from the General procedure I, the ethyl acetate phase obtained from extraction was filtered, and the filtrate was purified by automated chromatography. The products obtained from chromatography and filtration were combined and recrystallized again (EtOAc/EtOH 1+1). 5-Methyl-3-phenylisoxazole-4-carboxylic acid 6 (406 mg, 2.00 mmol), 4-amino-N-phenylbenzamide (425 mg, 2.00 mmol), HBTU (986 mg, 2.60 mmol, 1.3 equiv), DIPEA (0.697 mL, 4.00 mmol, 2 equiv), DMF (5 mL). Solvent for extraction: ethyl acetate. Recrystallization (EtOH/EtOAc 11+1) after chromatography on silica gel gave compound SI11 (0.220 g, 0.554 mmol, 28%) as a white solid. M.p. 248.4–249.6 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.79 (s, 1H), 10.19 (s, 1H), 8.04–7.97 (m, 2H), 7.84–7.75 (m, 4H), 7.74–7.66 (m, 2H), 7.54–7.45 (m, 3H), 7.39–7.29 (m, 2H), 7.13–7.05 (m, 1H), 2.62 (s, 3H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 170.1, 164.7, 160.2, 160.2, 141.4, 139.2, 130.0, 128.7, 128.6, 128.4, 128.0, 127.7, 123.4, 120.3, 118.9, 113.1, 69.4, 11.5 ppm. HRMS calc. for C24H20N3O3 [M+H]+: 398.1505, found 398.1504.

5-Methyl-3-phenyl-N-(quinolin-3-yl)isoxazole-4-carboxamide (SI12)

Synthesis according to the General procedure I. 5-Methyl-3-(2-nitrophenyl)isoxazole-4-carboxylic acid (203 mg, 1.00 mmol), 3-aminoquinoline (144 mg, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate. Recrystallization (EtOH/H2O 10+1) after chromatography on silica gel gave compound SI12 (146 mg, 0.443 mmol, 44%) as white needles. M.p. 202.1–203.2 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.86 (s, 1H), 8.92 (d, 1H, J = 2.5 Hz), 8.75 (d, 1H), 8.01–7.94 (m, 2H), 7.76–7.56 (m, 4H), 7.53–7.45 (m, 3H), 2.65 (s, 3H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 170.4, 160.7, 160.3, 144.6, 144.5, 132.2, 130.1, 128.8, 128.5, 128.2, 127.9, 127.8, 127.7, 127.6, 127.1, 123.1, 112.8, 12.0 ppm. HRMS calc. for C20H16N3O2 [M+H]+: 330.1243, found 330.1246.
N-[3-Chloro-4-(2,2,2-trifluoroethoxy)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide (SI13)

Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid (21.3 mg, 0.105 mmol), 3-chloro-4-(2,2,2-trifluoroethoxy)aniline (23.6 mg, 0.105 mmol), HBTU (51.8 mg, 0.137 mmol, 1.3 equiv), DIPEA (36.6 µL, 0.210 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether and water. Recrystallization (MeOH/H2O 10+1) after chromatography on silica gel gave compound SI13 (30.5 mg, 0.0742 mmol, 71%) as white needles. M.p. 166.4–168.4 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.48 (s, 1H), 7.83 (d, 1H, 4J = 2.4 Hz), 7.54–7.42 (m, 2H), 7.28 (d, 1H, 3J = 9.0 Hz), 4.82 (q, 2H, 3J = 8.8 Hz), 2.59 (s, 3H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 170.0, 160.2, 159.9, 148.8, 133.8, 130.1, 128.8, 127.9, 127.7, 123.7 (d=q, J = 278.4 Hz), 121.6, 121.3, 119.5, 115.5, 113.0, 65.8 (q, J = 34.3 Hz), 11.9 ppm. HRMS calc. for C19H15ClF3N2O3 [M+H]+: 411.0723, found 411.0723.

5-Methyl-N-(8-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)-3-phenylisoxazole-4-carboxamide (SI14)

Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid: (33.3 mg, 0.164 mmol), 7-amino-alpha-tetralone (26.4 mg, 0.164 mmol), HBTU (80.9 mg, 0.213 mmol, 1.3 equiv), DIPEA (57.1 µL, 0.328 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (1:1). Recrystallization (MeOH/water 10+1) after chromatography on silica gel gave compound SI14 (22.5 mg, 0.0650 mmol, 40%) as a brown solid. M.p. 176.5–178.2 °C. 1H NMR (300 MHz, CDCl3): δ 7.78 (dd, 1H, 4J = 2.4 Hz, 3J = 8.3 Hz), 7.68–7.53 (m, 5H), 7.43 (d, 1H, 4J = 2.4 Hz), 7.20 (d, 1H), 7.17 (s, 1H), 2.90 (t, 2H, J = 6.1 Hz), 2.60 (t, 2H, J = 7.1 Hz), 2.15–2.04 (m, 2H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 197.8, 175.5, 160.0, 140.9, 136.1, 133.1, 131.2, 129.8, 129.7, 129.3, 128.0, 125.5, 117.7, 111.3, 39.1, 29.3, 23.4, 13.3 ppm. HRMS calc. for C21H19N2O3 [M+H]+: 347.1396, found 347.1404.
Nitrosonium tetrafluoroborate (213 mg, 1.61 mmol) was dissolved in absolute acetonitrile (10 mL) and cooled to 0 °C in an ice bath. N-[4-[Ethyl(isopropyl)amino]phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide 4i (584 mg, 1.61 mmol) was added as a solid to the above-mentioned solution, and the reaction mixture was stirred for 2 h at 0 °C. Methanol (5 mL), glacial acetic acid (10 mL) and zinc powder (315 mg, 4.82 mmol) were added to the reaction mixture. The reaction mixture was stirred for 15 min at 0 °C and 6 h at room temperature. The reaction mixture was filtered through Celite® and the solvent was removed with a rotary evaporator. The residual acetic acid was removed by co-distillation with toluene with a rotary evaporator, and the solid residue was dissolved in ethyl acetate. Celite® was washed with methanol and water and the filtrate was combined with the ethyl acetate solution in a separatory funnel. The phases were separated, and the organic layer was washed several times with small portions of water until the aqueous phase remained neutral. The organic solvents were removed with a rotary evaporator, and the product mixture was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to give compound SI15 (21.0 mg, 0.561 mmol, 3%) as a brownish solid. M.p. 200.2–202.7 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 10.34 (s, 1H), 7.86 (d, 1H, 3J = 1.9 Hz), 7.76–7.68 (m, 2H), 7.60 (d, 1H, 3J = 8.7 Hz), 7.55–7.43 (m, 3H), 7.32 (d, 1H), 4.70 (sept, 1H, 3J = 6.9 Hz), 2.59 (s, 3H), 2.55 (s, 3H), 1.54 (d, 6H, J = 6.9 Hz) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 169.6, 160.1, 159.6, 151.9, 142.9, 132.4, 130.3, 130.1, 128.8, 128.2, 127.7, 114.5, 113.5, 111.3, 109.9, 47.3, 21.0, 14.4, 11.9 ppm. HRMS calc. for C₂₂H₂₃FN₄ [M+H]+: 375.1821, found 375.1831.

(5-Methyl-3-phenylisoxazol-4-yI)(5-nitroindolin-1-yl)methanone (SI16)
Synthesis according to the General procedure I. Deviating from the General procedure I, HATU, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, was used instead of HBTU and after the work-up, the ethereal phase was washed twice with water, 6 times with a small amount of 4 M hydrochloric acid and several times with water until the aqueous phase remained neutral. The crude product was recrystallized once from methanol and once from 2-propanol/ethyl acetate/MeOH (10+4+3). 5-Methyl-3-phenylisoxazole-4-carboxylic acid 6 (508 mg, 2.50 mmol), 5-nitroindoline (493 mg, 3.00 mmol, 1.2 equiv), HATU (1.14 g, 3.00 mmol, 1.2 equiv), DIPEA (1.31 mL, 7.50 mmol, 3 equiv), DMF (8 mL). Solvent for extraction: diethyl ether. Recrystallization (twice) [without chromatography on silica gel] gave compound SI16 (339 mg, 0.970 mmol, 39%) as yellow crystals. M.p. 171.2–172.4 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 8.30–8.02 (m, 3H), 7.65–7.56 (m, 2H), 7.53–7.43 (m, 3H), 3.91 (bt, 2H), 3.09 (t, 2H, \(^3\)\(J = 8.3\) Hz), 2.56 (s, 3H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 161.5, 161.3, 159.4, 147.5, 143.4, 135.1, 130.5, 129.3, 127.8, 127.0 (2\(\times\)), 124.2, 120.7, 111.9, 49.9, 26.8, 11.7 ppm. HRMS calc. for C\(_{19}\)H\(_{16}\)N\(_3\)O\(_4\) [M+H]\(^+\): 330.1494, found 330.1494.

Preparation of compounds in Scheme 2 and other related compounds

\((E)\) and \((Z)\)-Methyl \(N\)-[4-(diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carbimidothioate (24a)

\(N\)-[4-(Diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carbothioamide 23 (75.0 mg, 0.205 mmol) was dissolved in a mixture of acetonitrile (2.5 mL) and DMSO (2 mL). Lithium carbonate (22.7 mg, 0.308 mmol) and iodomethane (19.2 \(\mu\)L, 0.308 mmol) were added. The reaction mixture was heated at 38 °C overnight and diluted with ethyl acetate. The organic phase was washed three times with water. The solvent was removed with a rotary evaporator, and the crude product mixture was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in \(n\)-hexane, starting with 0% of ethyl acetate to give compound 24a (55.0 mg, 0.146 mmol, 71%) as a yellow oil. The \(^1\)H NMR spectra show a mixture of isomers (A and B). The ratio of integrals is approximately 1:3, the isomer B being the minor one. The \(^{13}\)C NMR spectra show only a few visible signals of the isomer B. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 7.79–7.72 (m, 2H, isomer B), 7.60–7.52 (m, 3H, isomer B), 7.50–7.38 (m, 5H), 6.83 (m, 2H, isomer B), 6.69 (m, 2H, isomer B), 6.40–6.30 (m, 4H), 3.33 (q, 4H, \(^3\)\(J = 7.0\) Hz, isomer B), 3.20 (q, 4H, \(^3\)\(J = 7.0\) Hz), 2.57 (s, 3H, isomer B), 2.51 (s, 3H), 2.39 (s, 3H), 1.95 (s, 3H, isomer B), 1.09 (t, 6H, isomer B), 1.00 (t, 6H) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 168.4, 159.3, 154.4, 144.4, 137.3, 129.9, 128.9, 128.7, 127.8, 127.4, 126.8, 121.8, 121.4, 111.8, 111.0, 111.7, 43.6, 3.14, 12.4, 12.3, 11.5 ppm. HRMS calc. for C\(_{22}\)H\(_{26}\)N\(_3\)OS [M+H]\(^+\): 380.1797, found 380.1801.
(Z) & (E)-2-Fluoroethyl N-[4-(diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carbimidothioate (24b)

N-[4-(Diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carbothioamide 23 (64.0 mg, 0.175 mmol) was dissolved in absolute DMF (2.5 mL) under argon. A 60% suspension of sodium hydride in mineral oil (8.4 mg, 0.210 mmol, 1.2 equiv) was added, and the reaction mixture was stirred for 2 h at 0 °C. 1-Bromo-2-fluoroethane (15.7 μL, 0.210 mmol) was added, and the reaction mixture was stirred for 3 d at room temperature. The reaction mixture was diluted with ethyl acetate. The organic phase was washed three times with water. The solvent was removed with a rotary evaporator and the crude product mixture was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to give compound 24b (56.8 mg, 0.138 mmol, 79%) as a yellow resin. The 1H NMR spectra show a mixture of isomer A and isomer B. The ratio of integrals is approximately 1:4.6, with the isomer B being the minor one. In the 13C NMR spectra only a few signals of the isomer B are visible. 1H NMR (300 MHz, DMSO-d6): δ 7.79–7.71 (m, 2H, isomer B), 7.60–7.51 (m, 3H, isomer B), 7.50–7.36 (m, 5H), 6.83 (m, 2H, isomer B), 6.70 (m, 2H, isomer B), 6.41–6.32 (m, 4H), 4.69 (dt, 2H, 3J = 47.2 Hz, 2J = 6.1 Hz), 4.26 (dt, 2H, 3J = 47.1 Hz, 2J = 5.7 Hz), 3.60 (m, 2H), 3.33 (q, 4H, 3J = 7.0 Hz, isomer B), 3.21 (q, 4H, 3J = 7.0 Hz), 2.81 (dt, 2H', 3J = 24.1 Hz, 3J = 5.7 Hz, isomer B), 2.58 (s, 3H, isomer B), 2.40 (s, 3H), 1.10 (s, 6H, isomer B), 1.00 (s, 6H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 210.1, 168.0, 162.4, 159.4, 145.9, 130.3, 129.9, 128.7, 126.8, 121.4, 111.7, 111.7, 109.5, 81.3 (d, 3J = 167.5 Hz), 43.6, 29.7 (d, 3JHF = 21.5 Hz), 12.2, 11.4 ppm. HRMS calc. for C23H27FN3OS [M+H]+: 412.1859, found 412.1859.

N-[4-(Diethylamino)phenyl]-N,5-dimethyl-3-phenylisoxazole-4-carboxamide (25a)

N-[4-(Diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide 1 (175 mg, 0.500 mmol) was dissolved in anhydrous DMF (2.5 mL) under argon, cooled to 0 °C in an ice bath, and a 60% dispersion of sodium hydride in mineral oil (30.0 mg, 0.750 mmol, 1.5 equiv) was added. After 1 h, iodomethane (37.4 μL, 0.600 mmol, 1.2 equiv) was added. The ice bath was removed, and the reaction mixture was stirred at room temperature for 4 d. Water and ethyl acetate were added, the phases were separated, and the organic phase was washed twice with water. The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel using a gradient of increasing ethyl acetate, starting with 100% n-hexane to yield compound 25a (139 mg, 0.382 mmol, 76%) as a white solid. M.p. 88.9–93.3 °C. 1H NMR (300 MHz, DMSO-d6): δ 7.56–7.43 (m, 5H), 6.51 (m, 2H), 6.32 (m, 2H), 3.25 (s, 3H), 3.23 (q, 4H, 3J = 7.0 Hz), 2.33 (s, 3H), 1.01 (s, 6H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 168.0, 162.4, 159.4, 145.9, 130.3, 129.9, 128.7,
N-[4-(Diethylamino)phenyl]-N-(2-fluoroethyl)-5-methyl-3-phenylisoxazole-4-carboxamide (25b)

N-[4-(Diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide 1 (175 mg, 0.500 mmol) was dissolved in absolute DMF (2.5 mL) under argon. A 60% suspension of sodium hydride in mineral oil (24.0 mg, 0.600 mmol, 1.2 equiv) was added, and the reaction mixture was stirred for 2 h at room temperature. 1-Bromo-2-fluoroethane (56.0 μL, 0.750 mmol, 1.5 equiv) was added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with diethyl ether. The organic phase was washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to give compound 25b (157 mg, 0.397 mmol, 79%) as a colorless oil. 1H NMR (300 MHz, DMSO-d6): δ 7.56–7.44 (m, 5H), 6.54 (m, 2H), 6.32 (m, 2H), 4.57 (dt, 2H, J = 47.5 Hz, J = 5.0 Hz), 4.03 (dt, 2H, J = 26.2 Hz, J = 5.0 Hz), 3.23 (q, 4H, J = 7.0 Hz), 2.33 (s, 3H), 1.01 (t, 6H, J = 7.0 Hz) ppm. 13C NMR (75 MHz, DMSO-d6): δ 167.8, 163.1, 159.2, 146.2, 130.0, 128.4, 128.3, 128.1, 127.6, 127.2, 127.1, 112.8, 110.7, 52.3, 43.4, 12.2, 11.4 ppm. HRMS calc. for C23H27FN3O2 [M+H]+: 396.2087, found 396.2084.

N-Benzyl-N-[4-(diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide (25c)

N-[4-(Diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide 1 (0.100 g, 0.286 mmol) was dissolved in anhydrous DMF (2.5 mL) under argon and cooled to 0 °C. A 60% dispersion of sodium hydride in mineral oil (13.7 mg, 0.343 mmol, 1.2 equiv) was added. After 1.5 h, benzyl bromide (0.102 mL, 0.858 mmol, 3 equiv) was added. The cooling bath was removed after 2 h, and the reaction mixture was stirred at room temperature overnight. Ethyl acetate was added, and the organic phase was washed three times with a mixture of water and brine (3:1). The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel using a gradient of increasing ethyl acetate, starting with 100% n-hexane to yield compound 25c (102 mg, 0.232 mmol, 81%) as white crystals. M.p. 129.8-133.0 °C. 1H NMR (300 MHz, DMSO-d6): δ 7.55–7.40 (m, 5H), 7.34–7.19 (m, 5H), 6.35 (m, 2H), 6.23 (m, 2H), 4.93 (bs, 2H), 3.18 (q, 4H, J = 7.0 Hz), 2.36 (s, 3H), 0.97 (t, 6H, J = 7.0 Hz) ppm. 13C NMR (75 MHz, DMSO-d6): δ 167.8, 162.9, 159.4, 146.1, 137.2, 130.0, 128.7, 128.4, 128.3, 128.3, 128.1, 127.6, 127.2, 127.1, 112.8, 110.7, 52.3, 43.4, 12.2, 11.5 ppm. HRMS calc. for C28H30N3O2 [M+H]+: 440.2338, found 440.2338.
N-[4-(Diethylamino)phenyl]-N,5-dimethyl-3-phenylisoxazole-4-carbothioamide (26)

Synthesis according to the General procedure V. Deviating from the General procedure V, the solvent of the reaction mixture was removed with a rotary evaporator prior chromatography without purification by extraction. N-[4-(Diethylamino)phenyl]-N,5-dimethyl-3-phenylisoxazole-4-carboxamide 25a (50.0 mg, 0.138 mmol), Lawesson’s reagent (33.4 mg, 0.0825 mmol, 0.6 equiv), toluene (1 mL). Reaction time: 8 h. Chromatography on silica gel gave compound 26 (44.5 mg, 0.117 mmol, 85%) as a yellow solid. M.p. 126.5–127.7 °C. 1H NMR (300 MHz, DMSO-d6): δ 7.54–7.43 (m, 3H), 7.42–7.36 (m, 2H), 6.35 (m, 2H), 6.26 (m, 2H), 3.69 (s, 3H), 3.23 (m, 4H), 2.43 (s, 3H), 1.00 (t, 6H, 3J = 7.0 Hz) ppm. 13C NMR (75 MHz, DMSO-d6): δ 188.8, 167.1, 157.2, 146.2, 132.5, 129.8, 128.6, 128.4, 126.9, 125.3, 119.4, 110.6, 45.0, 43.6, 12.1, 11.3 ppm. HRMS calc. for C22H26N3O2 [M+H]+: 380.1797, found 380.1799.

4-(Diethylamino)-N-(5-methyl-3-phenylisoxazol-4-yl)benzamide (27)

Synthesis according to the General procedure II. 4-(Diethylamino)benzoic acid 29 (111 mg, 0.574 mmol), a 2 M solution of oxalyl chloride in DCM (1.72 mL, 3.44 mmol, 6 equiv), 5-methyl-3-phenylisoxazol-4-amine 28 (0.100 g, 0.574 mmol), DCM (1 mL), pyridine (2 mL). Recrystallization (MeOH/H2O 10+1) after chromatography on silica gel gave compound 27 (70.0 mg, 0.200 mmol, 35%) as white crystals. M.p. 189.8–191.0 °C. 1H NMR (300 MHz, DMSO-d6): δ 9.47 (s, 1H), 7.80 (m, 2H), 7.75–7.68 (m, 2H), 7.49–7.43 (m, 3H), 6.70 (m, 2H), 3.41 (q, 4H, 3J = 7.0 Hz), 2.34 (s, 3H), 1.12 (t, 6H, 3J = 7.0 Hz) ppm. 13C NMR (75 MHz, DMSO-d6): δ 165.9, 165.9, 159.4, 149.9, 129.7, 129.4, 128.7, 128.4, 127.0, 118.7, 113.4, 110.1, 43.7, 12.3, 10.7 ppm. HRMS calc. for C21H24N2O2 [M+H]+: 350.1869, found 350.1874.

tert-Butyl (5-methyl-3-phenylisoxazol-4-yl)carbamate (SI17)

5-Methyl-3-phenylisoxazole-4-carboxylic acid 6 (8.00 g, 39.4 mmol) was dissolved in tert-butanol (70 mL) under argon. Triethylamine (5.49 mL, 39.4 mmol) and diphenylphosphoryl azide (8.51 mL,
39.4 mmol) were added, and the reaction mixture was heated at reflux temperature for 2 h. After cooling to room temperature, ethyl acetate was added and the organic phase was washed three times with water. The combined aqueous phases were extracted once with ethyl acetate and the combined ethyl acetate phases were washed twice with a 1 M solution of sodium hydroxide in water and with small portions of water until the aqueous phase remained neutral. The organic solvents were removed with a rotary evaporator and recrystallized twice (MeOH/H2O 10+1). The solvent of the mother liquor was removed with a rotary evaporator, and the residue was purified by automated chromatography on silica gel with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate. The combined material from crystallizations and chromatography was recrystallized (MeOH/H2O 10+1) to give compound SI17 (6.77 g, 24.7 mmol, 63%) as white needles. M.p. 116.8–119.9 °C.

1H NMR (300 MHz, CDCl3): δ 7.72–7.65 (m, 2H), 7.54–7.40 (m, 3H), 5.65 (bs, 1H), 2.41 (s, 3H), 1.56 (bs, 9H) ppm.

13C NMR (75 MHz, CDCl3): δ 165.88, 159.43, 154.14, 129.92, 128.95, 128.66, 127.74, 112.87, 81.28, 28.27, 11.28 ppm. HRMS calc. for C15H19N2O3 [M+H]+: 275.1396, found 275.1396.

N-Allyl-N-[4-(diethylamino)benzyl]-5-methyl-3-phenylisoxazol-4-amine (30b)

A mixture of N-[4-(diethylamino)benzyl]-5-methyl-3-phenylisoxazol-4-amine 33 (23.0 mg, 0.0686 mmol), allyl iodide (7.50 µL, 0.0823 mmol, 1.2 equiv) and cesium carbonate (31.3 mg, 0.0960 mmol, 1.4 equiv) in absolute DMF (0.20 mL) was stirred for 3 d at room temperature under argon. The

A solution of tert-butyl (5-methyl-3-phenylisoxazol-4-yl)carbamate SI17 (5.259 g, 19.17 mmol) in trifluoroacetic acid (20 mL) was stirred at room temperature overnight. Diethyl ether and water were added and the resulting solution was made basic with a 10 M solution of sodium hydroxide in water. Phases were separated and the aqueous phase was extracted with diethyl ether. The organic phase was washed three times with water and the solvent was removed with the rotary evaporator. The resulting crude product mixture was subjected to a purification by an automated high performance flash chromatography (n-hexane/EtOAc 0→100%) to yield 5-methyl-3-phenylisoxazol-4-amine 28 (1.728 g, 9.92 mmol, 52%). 1H NMR (300 MHz, DMSO-d6): δ 7.99–7.75 (m, 2H), 7.54–7.40 (m, 3H), 3.96 (s, 1H), 2.34 (s, 3H). 13C NMR (75 MHz, DMSO-d6): δ 155.69, 153.39, 129.44, 129.44, 129.08, 128.65, 128.65, 127.15, 121.96, 9.88. HRMS calc. for C10H11N2O [M+H]+: 175.0871, found 175.0891.
reaction mixture was diluted with ethyl acetate and washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to give compound 30b (12.1 mg, 0.0322 mmol, 47%) as a brownish oil. 

1H NMR (300 MHz, CDCl3): δ 8.00–7.92 (m, 2H), 7.48–7.39 (m, 3H), 6.96 (m, 2H). 6.58 (m, 2H), 5.83 (ddt, 1H, 3J = 6.4 Hz, 3J = 10.3 Hz, 3J = 17.1 Hz), 5.17–5.06 (m, 2H), 3.91 (s, 2H), 5.50 (d, 1H, 3J = 7.0 Hz), 2.18 (s, 3H), 1.14 (t, 6H, 3J = 7.0 Hz) ppm. 13C NMR (75 MHz, CDCl3): δ 163.8, 160.0, 147.4, 135.5, 130.4, 130.1, 129.4, 128.5, 128.1, 125.4, 124.3, 117.6, 111.9, 57.1, 55.6, 44.5, 12.7, 12.3 ppm. HRMS calc. for C24H30N3O [M+H]+: 376.2389, found 376.2386.

N-[4-(Diethylamino)benzyl]-2,2,2-trifluoro-N-(5-methyl-3-phenylisoxazol-4-yl)acetamide (30c)

A mixture of N-[4-(diethylamino)benzyl]-5-methyl-3-phenylisoxazol-4-amine 33 (20.7 mg, 0.0617 mmol), trifluoroacetic anhydride (13.1 μL, 0.0926 mmol, 1.5 equiv) and DMAP (11.3 mg, 0.0926 mmol, 1.5 equiv) in absolute pyridine (0.30 mL) was stirred for 2 d at room temperature under argon. The reaction mixture was diluted with ethyl acetate and washed once with a saturated solution of sodium hydrogen carbonate in water and twice with water. The solvent was removed with a rotary evaporator and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to give compound 30c (16.9 mg, 0.0392 mmol, 63%) as a yellowish oil. 

1H NMR (300 MHz, CDCl3): δ 7.76–7.69 (m, 2H), 7.53–7.43 (m, 3H), 6.95 (m, 2H), 6.54 (m, 2H), 5.50 (d, 1H, 3J = 13.6 Hz), 3.69 (d, 1H), 3.33 (q, 4H, 3J = 7.0 Hz), 1.70 (s, 3H), 1.14 (t, 6H, 3J = 7.0 Hz) ppm. 13C NMR (75 MHz, CDCl3): δ 160.1, 158.4, 157.8 (q, J = 35.2 Hz), 148.2, 131.4, 130.6, 129.3, 127.6, 127.0, 120.6, 116.2 (q, J = 288.6 Hz), 113.9, 111.9, 53.6, 44.5, 12.6, 10.2 ppm. HRMS calc. for C23H25F3N3O2 [M+H]+: 432.1899, found 432.1899.

3-(4-Cyanophenyl)-1-[4-(diethylamino)benzyl]-1-(5-methyl-3-phenylisoxazol-4-yl)urea (30d)

A mixture of N-[4-(diethylamino)benzyl]-5-methyl-3-phenylisoxazol-4-amine 33 (21.7 mg, 64.7 μmol) and 4-isocyanatobenzonitrile (10.3 mg, 0.0712 mmol, 1.1 equiv) in absolute THF (0.30 mL) was stirred for 4 d at room temperature under argon. The solvent was removed with a rotary evaporator, and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to give compound 30d (25.3 mg, 0.0528 mmol, 82%) as a white solid. M.p. 199.2–201.7 °C. 1H NMR (300 MHz,
DMSO-d$_6$: $\delta$ 8.84 (s, 1H), 7.70–7.63 (m, 4H), 7.58–7.50 (m, 2H), 7.50–7.41 (m, 3H), 6.90 (m, 2H), 6.51 (m, 2H), 5.00 (d, 1H, $^2J = 14.0$ Hz), 3.83 (d, 1H), 3.27 (q, 4H, $^3J = 7.0$ Hz), 1.88 (s, 3H), 1.04 (t, 6H, $^3J = 7.0$ Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 168.0, 158.7, 154.0, 147.0, 144.3, 132.5, 130.3, 129.9, 128.9, 127.8, 126.7, 120.0, 119.1, 115.3, 111.3, 103.8, 51.1, 43.5, 12.2, 10.2 ppm. HRMS calc. for C$_{29}$H$_{29}$N$_5$O$_2$ [M+H]$^+$: 480.2400, found 480.2400.

$N^1$-[3-(2,6-Dichlorophenyl)-5-methylisoxazol-4-yl)methyl]-$N^4$,$N^4$-diethylbenzene-1,4-diamine (SI18)

![Chemical structure](image)

4-(Chloromethyl)-3-(2,6-dichlorophenyl)-5-methylisoxazole (86.5 mg, 0.313 mmol) was dissolved under argon in absolute DMF (2 mL). N,N-diethyl-p-phenylenediamine 17 (78.0 µL, 0.469 mmol, 1.5 equiv) and cesium carbonate (163 mg, 0.501 mmol, 1.6 equiv) were added, and the reaction mixture was shaken for 4 d at room temperature. The reaction mixture was diluted with ethyl acetate and washed three times with a mixture of water and brine (3:1). The solvent was removed with a rotary evaporator, and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate gave compound SI18 (66.4 mg, 0.164 mmol, 52%) as a red-brown oil. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 7.63–7.50 (m, 3H), 6.52, 6.36 (each m, each 2H), 4.88 (t, 1H, $^3J = 5.8$ Hz), 3.80 (d, 2H, $^3J = 5.8$ Hz), 3.09 (q, 4H, $^3J = 7.0$ Hz), 2.48 (s, 3H), 1.95 (t, 6H, $^3J = 7.0$ Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 167.2, 158.7, 140.2, 140.1, 134.6, 132.2, 128.4, 127.4, 116.3, 113.7, 113.2, 44.8, 36.9, 12.3, 11.1 ppm. HRMS calc. for C$_{21}$H$_{25}$Cl$_2$N$_3$O [M+H]$^+$: 404.1296, found 404.1292.
**N-[4-(Diethylamino)phenyl]-3,5-dimethylisoxazole-4-sulfonamide (SI19)**

\[ \text{N,N-Diethyl-p-phenylenediamine 17 (63.5 \mu L, 0.382 mmol) was dissolved in anhydrous pyridine (3 mL) under argon and cooled to 0 °C. 3,5-Dimethylisoxazole-4-sulfonyl chloride (74.7 mg, 0.382 mmol) was added. After 30 min the ice bath was removed, and the reaction mixture was stirred at room temperature overnight. Pyridine was removed by co-distillation with toluene (3 \times 20 mL) with a rotary evaporator. Automated chromatography on silica gel starting with 100% n-hexane and ending after an increasing gradient with 100% ethyl acetate gave compound SI19 (81.0 mg, 0.250 mmol, 66%) as brownish resin.} \]

\[ ^1H \text{ NMR (300 MHz, DMSO-d}_6\text{: } \delta 9.60 \text{ (s, 1H), 6.83 (m, 2H), 6.59 (m, 2H), 3.28 (q, 4H, } ^3J = 7.0 \text{ Hz), 2.28, 2.13 (s, 3H), 1.04 (t, 6H, } ^3J = 7.0 \text{ Hz) ppm.} \]

\[ ^13C \text{ NMR (75 MHz, DMSO-d}_6\text{: } \delta 172.7, 157.3, 146.0, 125.9, 123.5, 115.2, 111.9, 43.6, 12.1, 11.8, 10.2 \text{ ppm. HRMS calc. for } C_{15}H_{22}N_3O_3S [M+H]^+: 324.1382, \text{ found } 324.1391. \]

**N,N-Diethylaniline (SI20)**

\[ \text{N,N-Diethylaniline (112 mg, 1.00 mol) was dissolved in ethanol (3 mL). To this solution, sodium acetate (0.410 g, 5.00 mmol, 5 equiv) was added, and the solution was cooled to 0 °C in an ice bath. A solution of sodium nitrite (69.0 mg, 1.00 mmol) in water (0.5 mL) was prepared and cooled to 0 °C. 3,5-Dimethylisoxazol-4-amine (112 mg, 1.00 mol) was dissolved in an equimixture of concentrated hydrochloric acid and water (1 mL) and cooled to 0 °C in an ice bath. To this solution, the sodium nitrite solution was added slowly during a period of 20 min. The reaction mixture was stirred for another 20 min, and the resulting mixture was added during a period of 7 min to the N,N-diethylaniline solution. The reaction mixture was stirred for 2 h. Diethyl ether was added, and the organic phase was washed once with a 0.5 M solution of sodium hydroxide in water and twice with water. The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel using a gradient of increasing ethyl acetate, starting with 100% n-hexane. The product was recrystallized from MeOH/H}_2O (20+1) to yield} \]
compound SI20 (54.0 mg, 0.198 mmol, 20%) as orange crystals. M.p. 92.5–95.0 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 6.77 (m, 2H), 6.77 (m, 2H), 3.44 (q, 4H, $^3J = 7.0$ Hz), 2.67 (s, 3H), 2.43 (s, 3H), 1.14 (t, 6H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 166.1, 153.4, 149.8, 142.4, 131.5, 124.3, 110.9, 44.0, 12.5 11.7, 11.3 ppm. HRMS calc. for C$_{15}$H$_{21}$N$_4$O [M+H]$^+$: 273.1715, found 273.1715.

4-(Diethylamino)-N-(3,5-dimethylisoxazol-4-yl)benzamide (SI21) and 1H-benzo[d][1,2,3]triazol-1-yl 4-(diethylamino)benzoate (SI22)

![Synthesis reaction scheme]

Synthesis according to the General procedure I. 4-(Diethylamino)benzoic acid 29 (431 mg, 2.23 mmol), 3,5-dimethylisoxazol-4-amine (0.250 g, 2.23 mmol), HBTU (1.27 g, 3.35 mmol, 1.5 equiv), DIPEA (0.583 mL, 3.35 mmol, 1.5 equiv), DMF (5 mL). Solvent for extraction: ethyl acetate. Recrystallization (MeOH/H$_2$O 10+1) after chromatography on silica gel gave compound SI21 (0.140 g, 0.487 mmol, 22%) as white needles. In addition, 1H-benzo[d][1,2,3]triazol-1-yl 4-(diethylamino)benzoate SI22, (0.200 g, 0.644 mmol, 29%) could be isolated as yellow needles.

SI21: M.p. 170.5–180.3 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 9.30 (s, 1H), 7.81 (m, 2H), 6.70 (m, 2H), 3.41 (q, 4H, $^3J = 7.0$ Hz), 2.27 (s, 3H), 2.10 (s, 3H), 1.12 (t, 6H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 165.4, 162.3, 157.9, 149.8, 129.4, 118.8, 114.8, 110.1, 43.7, 12.3 10.8, 9.5 ppm. HRMS calc. for C$_{16}$H$_{22}$N$_3$O$_2$ [M+H]$^+$: 288.1712, found 288.1714.

SI22: M.p. 140.0–141.4 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.15 (dt, 1H, $^3J = 8.4$ Hz, $^4J = 1.0$ Hz), 8.01 (m, 2H), 7.78 (dt, 1H, $^3J = 8.4$ Hz, $^4J = 1.0$ Hz), 7.65 (ddd, 1H, $^3J_{5,6}= 6.9$ Hz), 7.52 (ddd, 1H), 6.87 (m, 2H), 3.50 (q, 4H, $^3J = 7.0$ Hz), 1.17 (t, 6H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 167.4, 158.2, 151.0, 144.5, 130.9, 128.7, 127.8, 127.0, 126.3, 121.9, 112.9, 111.7, 43.7, 12.3 ppm. HRMS calc. for C$_{17}$H$_{19}$N$_4$O$_2$ [M+H]$^+$: 311.1503, found 311.1506.

1-(5-Methyl-3-phenylisoxazol-4-yl)-3-[4-(trifluoromethoxy)phenyl]urea (SI23)

![Synthesis reaction scheme]

Synthesis according to the General procedure IV. Deviating from the General procedure IV, the reaction mixture was stirred at room temperature for 3 d. Then n-hexane (2 mL) was added dropwise, the formed precipitate was filtered and recrystallized (MeOH/H$_2$O 10+1). 5-Methyl-3-phenylisoxazol-4-amine 28 (86.3 mg, 0.495 mmol), 4-trifluoromethoxyphenyl isocyanate (74.7 µL, 0.495 mmol).
mmol), toluene (2 mL). Recrystallization gave compound SI23 (0.110 g, 0.291 mmol, 59%) as white crystals. M.p. 161.2–162.4 °C. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 9.12 (bs, 1H), 7.93 (bs, 1H), 7.78–7.70 (m, 2H), 7.56–7.47 (m, 5H), 7.25 (m, 2H), 2.37 (s, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 166.2, 159.4, 153.7, 142.6, 139.1, 129.9, 128.9, 128.3, 127.3, 121.7, 120.2 (J = 266.5 Hz), 119.5, 113.2, 10.8 ppm. HRMS calc. for C$_{18}$H$_{15}$F$_3$N$_3$O$_3$ [M+H]$^+$: 378.1066 found 378.1063.

1-(5-Methyl-3-phenylisoxazol-4-yl)-3-[3-(trifluoromethyl)phenyl]urea (SI24)

Synthesis according to the General procedure IV. Deviating from the General procedure IV, the reaction mixture was stirred at room temperature for 4 d. 5-Methyl-3-phenylisoxazol-4-amine 28 (158 mg, 0.907 mmol), 3-(trifluoromethyl)phenyl isocyanate (0.127 mL, 0.907 mmol), toluene (2 mL). For recrystallization of the reaction mixture, toluene (3 mL) was added and ethyl acetate (1-2 mL) was added in small portions until the precipitate was soluble in the hot solution. This gave compound SI24 (271 mg, 0.750 mmol, 83%) as a white solid. M.p. 177.0–177.8 °C. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 9.22 (bs, 1H, NH), 7.99 (bs, 1H), 7.93 (bs, 1H), 7.79–7.71 (m, 2H), 7.65–7.59 (m, 1H), 7.55–7.43 (m, 4H), 7.31–7.25 (m, 1H), 2.38 (s, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 166.2, 159.3, 153.7, 140.6, 129.8, 129.7, 129.3 (q, J = 11.2 Hz), 128.7, 128.2, 127.1, 124.1 (q, J = 272.0 Hz), 121.9, 118.0 (q, J = 3.9 Hz), 114.3 (q, J = 4.0 Hz), 113.0, 10.7 ppm. HRMS calc. for C$_{18}$H$_{15}$F$_3$N$_3$O$_2$ [M+H]$^+$: 362.1116, found 362.1116.

1-Cyclohexyl-3-(5-methyl-3-phenylisoxazol-4-yl)urea (SI25)

Synthesis according to the General procedure IV. Deviating from the General procedure IV, toluene was removed with a rotary evaporator, and the crude product was recrystallized (EtOH/H$_2$O 10+1). 5-Methyl-3-phenylisoxazol-4-amine 28 (105 mg, 0.603 mmol), cyclohexyl isocyanate (77.0 µL, 0.603 mmol), toluene (2 mL). Recrystallization (EtOH/H$_2$O 10+1) gave compound SI25 (107 mg, 0.357 mmol, 59%) as white needles. M.p. 181.3–182.6 °C. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 7.73–7.66 (m, 2H), 7.53–7.44 (m, 3H), 7.36 (s, 1H), 6.16 (d, 1H, $^3$J = 8.1 Hz), 3.45–3.32 (m, 1H), 2.30 (s, 3H), 1.78–1.46 (m, 5H), 1.35–1.05 (m, 5H) ppm. $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 165.6, 159.3, 155.5, 129.6, 128.6, 128.5, 127.1, 113.9, 48.1, 32.9, 25.2, 24.4, 10.7 ppm. HRMS calc. for C$_{17}$H$_{22}$N$_3$O$_2$ [M+H]$^+$: 300.1712, found 300.1716.
1-(4-Benzoylphenyl)-3-(5-methyl-3-phenylisoxazol-4-yl)urea (SI26)

Synthesis according to the General procedure IV. 5-Methyl-3-phenylisoxazol-4-amine 28 (0.110 g, 0.631 mmol), 4-isocyanatobenzophenone (141 mg, 0.631 mmol), toluene (2 mL). Automated chromatography on silica gel gave compound SI26 (98.0 mg, 0.247 mmol, 39%) as a white solid. M.p. 187.1–192.9 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 9.36 (s, 1H), 8.01 (s, 1H), 7.78–7.48 (m, 14H), 2.39 (s, 3H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 194.3, 166.1, 159.3, 153.4, 144.2, 137.7, 132.0, 131.2, 130.0, 129.8, 129.2, 128.8, 128.4, 128.2, 127.2, 117.3, 113.0, 10.8 ppm. HRMS calc. for C\(_{13}\)H\(_{12}\)N\(_3\)O\(_3\) [M+H]\(^+\): 398.1505, found 398.1505.

N-(5-Methyl-3-phenylisoxazole-4-carbonyl)benzenesulfonylhydrazide (SI27)

Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid 6 (406 mg, 2.00 mmol), benzenesulfonylhydrazide (344 mg, 2.00 mmol), HBTU (986 mg, 2.60 mmol, 1.3 equiv), DIPEA (0.697 mL, 4.00 mmol, 2 equiv), DMF (5 mL). Solvent for extraction: ethyl acetate/diethyl ether (1+1). Recrystallization (EtOH) after chromatography on silica gel gave compound SI27 (233 mg, 0.652 mmol, 33%) as white crystals. M.p. 128.8–130.7 °C (decomp.). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 8.08–8.01 (m, 2H), 7.85–7.77 (m, 1H), 7.72–7.64 (m, 2H), 7.48–7.41 (m, 1H), 7.35–7.23 (m, 4H), 5.81 (s, 2H), 2.46 (s, 3H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 170.1, 163.9, 160.3, 137.7, 134.2, 130.0, 128.9, 128.7, 128.5, 127.7, 127.1, 111.0, 12.1 ppm. HRMS calc. for C\(_{17}\)H\(_{16}\)N\(_3\)O\(_4\)S [M+H]\(^+\): 358.0862, found 358.0861.

N\(^\prime\)-(4-Fluorophenyl)-5-methyl-3-phenylisoxazole-4-carboxydrazide (SI28)

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 2 d. 5-Methyl-3-phenylisoxazole-4-carboxylic acid, (203 mg, 1.00 mmol), (4-fluorophenyl)hydrazine hydrochloride (162 mg, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.523 mL, 3.00 mmol, 3 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate. Recrystallization (EtOH/H\(_2\)O 10+1) after chromatography on silica gel gave compound SI28 (97.3 mg, 0.313 mmol, 31%) as fine white needles. M.p. 195.7–196.4 °C (decomp.). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.18 (s, 1H), 7.96 (s, 1H), 7.72–7.64 (m, 2H), 7.57–7.45 (m, 3H), 7.00 (m, 2H), 6.79–6.69 (m, 2H), 2.61 (s, 3H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 169.7, 161.5, 160.4, 155.9 (d, \(J = 233.9\) Hz), 145.4, 130.0, 128.7, 128.0, 127.8, 115.2 (d, \(J = 22.4\) Hz), 113.5 (d, \(J = 7.7\) Hz), 111.2, 11.9 ppm. HRMS calc. for C\(_{17}\)H\(_{15}\)FN\(_3\)O\(_2\) [M+H]\(^+\): 312.1148, found 312.1154.
N-[2-(1,3-Dioxolan-2-yl)ethyl]-N-[4-(diethylamino)phenyl]-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide (SI29)

N-[4-(Diethylamino)phenyl]-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide 39g (75.0 mg, 0.190 mmol) was dissolved in absolute DMF (1 mL) under argon. A 60% suspension of sodium hydride in mineral oil (9.90 mg, 0.247 mmol, 1.3 equiv) was added, and the reaction mixture was stirred for 2 h at room temperature. 2-(2-Bromoethyl)-1,3-dioxolane (29.6 µL, 0.247 mmol, 1.3 equiv) was added, and the reaction mixture was stirred overnight at room temperature. A small amount of methanol and water was added. Diethyl ether was added and the organic phase was washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to give compound SI29 (59.5 mg, 0.120 mmol, 63%) as a brownish orange resin. 1H NMR (300 MHz, CDCl3): δ 8.29–8.23 (m, 2H), 7.88 (ddddd, 1H, 3J = 7.7 Hz, 4J = 1.4 Hz, 4J = 1.4 Hz), 7.56 (dd, 1H, 3J = 8.9 Hz), 6.32 (m, 2H), 6.17 (m, 2H), 4.93 (t, 1H, 3J = 4.6 Hz), 3.96–3.74 (m, 6H), 3.19 (q, 4H, 3J = 7.1 Hz), 2.45 (s, 3H), 1.94 (m, 2H), 1.06 (t, 6H) ppm. 13C NMR (75 MHz, CDCl3): δ 170.2, 163.0, 158.4, 148.4, 146.7, 133.7, 131.0, 129.7, 128.5, 127.9, 124.5, 122.9, 113.5, 111.1, 103.0, 65.1, 45.4, 44.5, 32.0, 12.6, 12.3 ppm. HRMS calc. for C26H31N4O6 [M+H]+: 495.2244, found 495.2244.
**N-[4-(Diethylamino)phenyl]-N-(2-methoxyethyl)-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide (SI30)**

N-[4-(Diethylamino)phenyl]-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide 39g (75.0 mg, 0.190 mmol) was dissolved in absolute DMF (1 mL) under argon. A 60% suspension of sodium hydride in mineral oil (9.90 mg, 0.247 mmol, 1.3 equiv) was added, and the reaction mixture was stirred for 2 h at room temperature. 1-Bromo-2-methoxyethane (23.2 µL, 0.247 mmol, 1.3 equiv) was added and the reaction mixture was stirred overnight at room temperature. A small amount of methanol and water was added. Then diethyl ether was added, and the organic phase was washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to give compound SI30 (53.3 mg, 0.118 mmol, 62%) as a brownish orange resin. ¹H NMR (300 MHz, CDCl₃): δ 8.31 (dd ≈ t, 1H, 4J = 1.8 Hz, 4J = 1.8 Hz), 8.26 (ddd, 1H, 3J = 8.2 Hz, 4J = 1.1 Hz), 7.56 (dd ≈ t, 1H), 6.42 (m, 2H), 6.19 (m, 2H), 3.95 (t, 2H, 3J = 5.6 Hz), 3.56 (t, 2H, 3J = 5.6 Hz), 3.33 (s, 3H), 3.22 (q, 4H, 3J = 7.1 Hz), 2.44 (s, 3H), 1.06 (t, 6H, 3J = 7.1 Hz) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 170.1, 163.5, 158.5, 148.5, 146.7, 133.9, 130.9, 129.7, 128.9, 127.9, 124.4, 113.5, 111.0, 69.2, 58.9, 49.5, 44.5, 12.6, 12.3 ppm. HRMS calc. for C₂₄H₂₉N₄O₅ [M+H]⁺: 453.2138, found 453.2139.

**6-Bromo-N-(5-methyl-3-phenyloxazol-4-yl)hexanamide (SI31)**

S32
5-Methyl-3-phenylisoxazol-4-amine 28 (211 mg, 1.00 mmol) and DIPEA (0.522 mL, 3.00 mmol) were dissolved in anhydrous THF (5 mL) and cooled to 0 °C. 6-Bromohexanoyl chloride (0.224 mL, 1.50 mmol) was added, and the reaction mixture was stirred overnight, while it was allowed to warm to rt. Diethyl ether was added, and the organic phase was washed with water, twice with a 2 M solution of sodium hydroxide in water, twice with 2 M hydrochloric acid solution and several times with water until the aqueous phase remained neutral. The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel using an increasing gradient of diethyl ether in n-hexane, starting with 0% of diethyl ether to yield compound SI31 (291 mg, 0.828 mmol, 83%) as a white solid. M.p. 79.4–82.1 °C. 1H NMR (300 MHz, DMSO-d6): δ 9.41 (s, 1H), 7.71–7.64 (m, 2H), 7.53–7.47 (m, 3H), 2.64 (t, 2H, J = 7.6 Hz), 3.52 (t, 2H, J = 6.7 Hz), 2.34–2.27 (m, 5H), 1.87–1.74 (m, 2H), 1.65–1.53 (m, 2H), 1.45–1.33 (m, 2H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 172.3, 165.8, 159.0, 129.9, 128.9, 128.2, 127.2, 112.8, 35.1, 35.0, 31.9, 27.2, 24.2, 10.8 ppm. HRMS calc. for C16H20BrN2O2 [M+H]+: 351.0708, found 351.0705.

4-Methoxy-N-(5-methyl-3-phenylisoxazol-4-yl)benzamide (SI32)

5-Methyl-3-phenylisoxazol-4-amine, 28 (105 mg, 0.500 mmol) was dissolved in anhydrous pyridine (2 mL) under argon and cooled to 0 °C. Anisoyl chloride (102 mg, 0.600 mmol) was added, and the reaction mixture was stirred overnight while it was allowed to warm to rt. DMAP (61.1 mg, 0.500 mmol) was added, and the reaction mixture was stirred overnight. HBTU (189 mg, 0.500 mmol) and DIPEA (0.261 mL, 1.50 mmol) were added, and the reaction mixture was stirred overnight. Diethyl ether was added, and the organic phase was washed with water, twice with a 2 M solution of sodium hydroxide in water, twice with 2 M hydrochloric acid and several times with water until the aqueous phase remained neutral. The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography on silica gel with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to yield compound SI32 (28 mg, 0.091 mmol, 18%) as a white solid. M.p. 150.4–155.4 °C. 1H NMR (300 MHz, DMSO-d6): δ 9.78 (s, 1H), 7.95 (m, 2H), 7.75–7.68 (m, 2H), 7.50–7.43 (m, 2H), 7.06 (m, 2H), 3.84 (s, 3H), 2.36 (s, 3H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 166.0, 165.6, 162.1, 159.3, 129.8, 129.5, 128.8, 128.3, 127.0, 125.4, 113.7 113.3, 55.4, 10.7 ppm. HRMS calc. for C18H20BrN2O3 [M+H]+: 309.1239, found 309.1237.
4-[(Dimethylamino)methyl]-N-(5-methyl-3-phenylisoxazol-4-yl)benzamide (SI33)

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction mixture was first stirred at room temperature for 4 d and then heated at 70 °C for 5 h. For the work-up ethyl acetate was added and the organic phase was washed twice with a 0.5 M solution of sodium hydroxide in water and once with water. 4-[(Dimethylamino)methyl]benzoic acid (52.2 mg, 0.291 mmol), 5-methyl-3-phenylisoxazol-4-amine (50.7 mg, 0.291 mmol), HBTU (144 mg, 0.378 mmol, 1.3 equiv), DIPEA (0.101 mL, 0.582 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: ethyl acetate. Automated chromatography on silica gel gave compound SI33 (37.0 mg, 0.110 mmol, 38%) as a brownish solid. M.p. 101.5–105.3 °C. 

1H NMR (300 MHz, DMSO-d6): δ 9.90 (s, 1H), 7.92 (m, 2H), 7.75–7.68 (m, 2H), 7.51–7.40 (m, 5H), 3.46 (s, 2H), 2.37 (s, 3H), 2.16 (s, 6H) ppm.

13C NMR (75 MHz, DMSO-d6): δ 166.1, 166.1, 159.3, 143.3, 131.9, 129.8, 128.8, 128.6, 128.3, 127.5, 127.0, 112.9, 62.9, 44.9, 10.7 ppm. HRMS calc. for C20H22N3O2 [M+H]+: 336.1712, found 336.1717.

N-(5-Methyl-3-phenylisoxazol-4-yl)-4-pentylbenzamide (SI34)

5-Methyl-3-phenylisoxazol-4-amine 28 (105 mg, 0.500 mmol) and DIPEA (0.261 mL, 1.50 mmol) were dissolved in anhydrous THF (3 mL) and cooled to 0 °C. 4-Pentylbenzoyl chloride (0.153 mL, 0.750 mmol) was added, the ice bath was removed after 30 min and the reaction mixture was stirred overnight at room temperature. Diethyl ether was added and the organic phase was washed with water, twice with a 2 M solution of sodium hydroxide ion water, twice with 2 M hydrochloric acid and several times with water until the aqueous phase remained neutral. The solvent was removed with a rotary evaporator, and the crude product was recrystallized (MeOH/H2O 10+1) to yield compound SI34 (128 mg, 0.367 mmol, 73%) as fine white crystals. M.p. 97.7–99.2 °C. 

1H NMR (300 MHz, DMSO-d6): δ 9.90 (s, 1H), 7.88 (m, 2H), 7.75–7.68 (m, 2H), 7.52–7.44 (m, 3H), 7.35 (m, 2H), 2.64 (t, 2H, J = 7.6 Hz), 2.36 (s, 3H), 1.60 (m), 1.37–1.21 (m, 4H), 0.86 (t, 3H, J = 6.9 Hz) ppm. 

13C NMR (75 MHz, DMSO-d6): δ 166.2, 166.2, 159.3, 146.9, 130.7, 129.9, 128.9, 128.5, 128.3, 127.7, 127.0, 113.0, 34.9, 30.8, 30.4, 21.9, 13.9, 10.8 ppm. HRMS calc. for C22H25N3O2 [M+H]+: 349.1916, found 349.1916.
**N-(5-Methyl-3-phenylisoxazol-4-yl)-4-pentylbenzothioamide (SI35)**

Synthesis according to the General procedure V. Deviating from the General procedure V, the solvent of the reaction mixture was removed with a rotary evaporator prior chromatography without purification by extraction. **N-(5-Methyl-3-phenylisoxazol-4-yl)-4-pentylbenzamide SI34** (45.0 mg, 0.129 mmol), Lawesson’s reagent (31.3 mg, 77.5 μmol, 0.6 equiv), toluene (1 mL). Reaction time: 7 h. Chromatography on silica gel gave compound SI35 (40.8 mg, 0.112 mmol, 87%) as a yellow solid. M.p. 136.7–137.7 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 11.31 (s, 1H), 7.85 (m, 2H), 7.72–7.64 (m, 2H), 7.53–7.45 (m, 3H), 7.31 (m, 2H), 2.64 (t, 2H, $^3$J = 7.6 Hz), 2.36 (s, 3H), 1.60 (m, 2H), 1.40–1.22 (m, 4H), 0.87 (t, 3H, $^3$J = 6.8 Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 200.7, 166.2, 158.9, 146.5, 137.6, 130.0, 128.9, 128.0, 127.5, 116.0, 34.8, 30.7, 30.2, 21.8, 13.8, 11.0 ppm. HRMS calc. for C$_{22}$H$_{25}$N$_2$OS [M+H]$^+$: 365.1688, found 365.1692.

**N-[4-[Ethyl(2-hydroxyethyl)amino]phenyl]-N,5-dimethyl-3-phenylisoxazole-4-carboxamide (SI36)**

$N$-[4-[Ethyl(2-hydroxyethyl)amino]phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide 4b (70.0 mg, 0.192 mmol) was dissolved in absolute DMF (2 mL) and cooled to 0 °C in an ice bath. To this solution a dispersion of sodium hydride in mineral oil (17.6 mg, 0.441 mmol) was added, and the reaction mixture was stirred for 1.5 h at 0 °C. Iodomethane (12.0 μL, 0.192 mmol) was added, and the reaction mixture was stirred for 2 h at 0 °C and overnight at room temperature. Another portion of a dispersion of sodium hydride in mineral oil (17.6 mg, 0.441 mmol) was added, and the reaction mixture was stirred for 2 h at room temperature. Iodomethane (12.0 μL, 0.192 mmol) was added and the reaction mixture was stirred overnight at room temperature. A small amount of water was added slowly, and the resulting mixture was diluted with ethyl acetate and washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel, using an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to give compound SI36 (54 mg, 0.142 mmol, 74%) as a slightly yellow resin. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.58–7.42 (m, 5H), 6.50 (m, 2H), 6.34 (m, 2H), 4.61 (t, 1H, $^3$J = 5.4 Hz), 3.51 (q, 2H, $^3$J = 5.8Hz), 3.32–3.17 (m, 7H), 2.33 (s, 3H), 1.00 (t, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 167.9, 162.4, 159.4, 146.2, 130.3, 129.9, 128.7, 128.3, 127.0, 126.6, 112.8, 110.9, 58.2, 52.0, 44.5, 44.5, 37.1, 11.7, 11.4 ppm. HRMS calc. for C$_{22}$H$_{26}$N$_2$O$_3$ [M+H]$^+$: 380.1974, found 380.1986.
**N-[4-(Benzyloxy)phenyl]-5-methyl-3-phenyliosaxazole-4-carbothioamide (SI37)**

Synthesis according to the General procedure V. **N-[4-(benzyloxy)phenyl]-5-methyl-3-phenyliosaxazole-4-carboxamide SI8** (130 mg, 0.338 mmol), Lawesson’s reagent (82.1 mg, 0.203 mmol, 0.6 equiv), toluene (2.5 mL). Reaction time: overnight. Recrystallization from ethanol after chromatography on silica gel gave compound **SI37** (112 mg, 0.280 mmol, 83%) as small yellow needles. M.p. 153.3–158.2 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 11.86 (s, 1H), 7.75–7.63 (m, 4H), 7.55–7.28 (m, 8H), 7.06 (m, 2H), 5.12 (s, 2H), 2.53 (s, 3H) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 186.3, 167.7, 158.8, 156.5, 136.9, 132.3, 130.0, 128.8, 128.5, 128.1, 127.9, 127.6, 127.5, 124.6, 114.7, 109.6, 69.4, 11.5 ppm. HRMS calc. for C\(_{24}\)H\(_{21}\)N\(_2\)O\(_2\)S [M+H]\(^+\): 401.1324, found 401.1326.

**N-[4-[Ethyl(isopropyl)amino]phenyl]-5-methyl-3-phenyliosaxazole-4-carbothioamide (SI38)**

Synthesis according to the General procedure V. 4-[Ethyl(isopropyl)amino]-N-(5-methyl-3-phenyliosaxol-4-yl)benzamide 4i (162 mg, 0.446 mmol), Lawesson’s reagent (108 mg, 0.267 mmol, 0.6 equiv), toluene (3 mL). Reaction time: overnight. Recrystallization (EtOAc/EtOH 3+2) after chromatography on silica gel gave compound **SI38** (92.0 mg, 0.242 mmol, 54%) as fine yellow needles. M.p. 221.8–223.4 °C (decomp.). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 11.68 (s, 1H), 7.74–7.65 (m, 2H), 7.60 (m, 2H), 7.53–7.42 (m, 3H), 6.72 (m, 2H), 4.05 (sept, 1H, \(^3J = 6.6\) Hz), 3.23 (q, 2H, \(^3J = 7.0\) Hz), 2.51 (s, 3H), 1.14 (d, 6H), 1.09 (t, 3H) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 184.0, 167.2, 158.6, 146.5, 129.8, 128.6, 128.1, 127.7, 127.4, 123.9, 111.5, 110.7, 47.5, 37.2, 19.8, 14.6, 13 ppm. HRMS calc. for C\(_{22}\)H\(_{26}\)N\(_3\)OS [M+H]\(^+\): 380.1797, found 380.1796.
\(N-(2,2\text{-Dimethyl-4-oxochroman-6-yl})-5\text{-methyl-3-phenylisoxazole-4-carboxamide} \text{(SI39)}\)

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 2 d. 5-Methyl-3-phenylisoxazole-4-carboxylic acid 6 (25.0 mg, 0.123 mmol), 6-amino-2,2-dimethylchroman-4-one (23.5 mg, 0.123 mmol), HBTU (60.6 mg, 0.160 mmol, 1.3 equiv), DIPEA (42.8 µL, 0.246 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: ether. Chromatography on silica gel gave compound SI39 (41.0 mg, 0.109 mmol, 89\%) as a slightly yellow solid. M.p. 167.0–168.4 °C. \(^{1}\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.41 (s, 1H), 8.07 (d, 1H, \(^{3}\)J = 2.7 Hz), 7.74–7.65 (m, 3H), 7.53–7.45 (m, 3H), 6.99 (d, \(^{3}\)J = 8.9 Hz), 2.79 (s, 2H), 2.58 (s, 3H), 1.39 (s, 6H) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 191.8, 169.8, 160.1, 159.7, 155.9, 131.7, 130.0, 128.8, 128.4, 128.0, 127.7, 119.4, 118.5, 116.3, 113.1, 79.3, 47.9, 25.9, 11.8 ppm. HRMS calc. for C\(_{22}\)H\(_{21}\)N\(_2\)O\(_4\) [M+H]\(^{+}\): 377.1501, found 377.1503.

\(6-[(5\text{-Methyl-3-phenylisoxazol-4-yl})\text{methylamino}]\text{-2-phenyl-4H-chromen-4-one} \text{(SI40)}\)

Synthesis according to the General procedure IX. Deviating from the General procedure IX, no sodium sulphate was used. Acetic acid (33.7 µL, 0.588 mmol), 5-methyl-3-phenylisoxazole-4-carbaldehyde (0.110 g, 0.588 mmol), 6-aminoflavone (139 mg, 0.588 mmol), THF (4 mL), a 1.0 M solution of sodium cyanoborohydride in THF (2.94 mL, 2.94 mmol, 5 equiv, added 1 h later). Reaction time: 4 d; quenched with a saturated solution of NaHCO\(_3\) in H\(_2\)O (5 mL) for 20 min. Solvents for extraction: ethyl acetate and a mixture of water and brine (3:1). Chromatography on silica gel gave compound SI40 (30.6 mg, 0.0749 mmol, 13\%) as a yellow solid. M.p. 185.0–186.4 °C. \(^{1}\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 8.10–8.03, 7.75–7.68 (each m, each 2H), 7.62–7.53 (m, 4H), 7.51–7.45 (m, 3H), 7.18 (dd, 1H, \(^{3}\)J = 2.9 Hz, \(^{3}\)J = 9.1 Hz), 7.05 (d, 1H, \(^{3}\)J = 2.9 Hz), 6.92 (s, 1H), 6.34 (t, 1H, \(^{3}\)J = 4.7 Hz), 4.14 (d, 2H, \(^{3}\)J = 4.7 Hz), 2.50 (s, 3H) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 177.0, 168.6, 162.0, 161.6, 148.4, 146.1, 131.5, 131.4, 129.7, 129.0, 128.9, 128.9, 127.8, 126.1, 124.1, 121.4, 119.1, 110.4, 105.9, 101.9, 36.2, 10.9 ppm. HRMS calc. for C\(_{26}\)H\(_{21}\)N\(_2\)O\(_3\) [M+H]\(^{+}\): 409.1552, found 409.1555.
**N₁,N¹-Diethyl-N₄-(pyridin-4-ylmethyl)benzene-1,4-diamine (SI41)**

![Chemical Structure](image)

A mixture of \( N,N \)-diethyl-p-phenylenediamine 17 (98.6 \( \mu \)L, 0.593 mmol, 1.5 equiv), 4-(bromomethyl)pyridine hydrobromide (0.100 g, 0.395 mmol) and cesium carbonate (129 mg, 0.395 mmol) in absolute DMF (3 mL) was stirred for 3 d at room temperature under argon. The reaction mixture was diluted with ethyl acetate and washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in \( n \)-hexane, starting with 0% of the ethyl acetate to give compound SI41 (34.4 mg, 0.135 mmol, 34%) as a brown solid. M.p. 157.6–158.9 °C. ¹H NMR (300 MHz, DMSO-\( d_6 \)): \( \delta \) 8.47 (m, 2H), 7.34 (m, 2H), 6.60–6.52 (bm, 2H), 6.50–6.43 (bm, 2H), 5.67 (t=bs, 1H), 4.22 (bd, 2H, \( ^3J = 5.0 \) Hz), 3.10 (q, 4H, \( ^3J = 7.0 \) Hz), 0.96 (t, 6H, \( ^3J = 7.0 \) Hz) ppm. ¹³C NMR (75 MHz, DMSO-\( d_6 \)): \( \delta \) 150.2, 149.3, 140.2, 139.9, 122.2, 116.3, 113.6, 46.4, 44.7, 12.3 ppm. HRMS calc. for \( C_{16}H_{22}N_3 \)[M+H]⁺: 256.1814, found 256.1815.

**\((E)-2,2',-[4-[[5-Methyl-3-phenylisoxazol-4-yl]imino]methyl]phenyl]azanediyl]bis(ethan-1-ol) (SI42)**

Synthesis according to the General procedure III. Deviating from the General procedure III, ethyl acetate was added to the reaction mixture to enhance solubility. Acetic acid was added after 8 h heating at 100 °C. After the addition of acetic acid, the reaction mixture was heated at 70 °C overnight. 4-[\( N,N \)-Bis(2-hydroxyethyl)amino]benzaldehyde (287 mg, 1.37 mmol), 5-methyl-3-phenylisoxazol-4-amine 28 (239 mg, 1.37 mmol), \( \text{Na}_2\text{SO}_4 \) (284 mg, 2.00 mmol), toluene (3 mL), ethyl acetate (1 mL). Chromatography on silica gel gave compound SI42 (0.310 g, 0.848 mmol, 62%) as a yellowish solid. M.p. 153.0–154.2 °C. ¹H NMR (300 MHz, DMSO-\( d_6 \)): \( \delta \) 8.37 (s, 1H), 7.95–7.87 (m, 2H), 7.68 (m, 2H), 7.53–7.43 (m, 3H), 6.80 (m, 2H), 4.78 (t, 2H, \( ^3J = 5.2 \) Hz, OH), 3.63–3.47 (m, 8H), 2.47 (s, 3H) ppm. ¹³C NMR (75 MHz, DMSO-\( d_6 \)): \( \delta \) 163.2, 156.6, 156.3, 150.9, 130.1, 129.5, 128.9, 128.6, 128.6, 127.5, 122.9, 111.1, 58.0, 53.1, 11.0 ppm. HRMS calc. for \( C_{21}H_{24}N_3O_3 \)[M+H]⁺: 366.1818, found 366.1817.
(E)-2,2’-[(4-[(5-Methyl-3-phenylisoxazol-4-yl)imino]methyl]phenyl]azanediyl]diethanol SI42
(0.200 g, 0.547 mmol) was dissolved under argon in a mixture of absolute THF (3.5 mL) and absolute MeOH (2 mL). Sodium cyanoborohydride (124 mg, 3.28 mmol, 6 equiv) was added and the reaction mixture was stirred for 2 d at room temperature. A saturated solution of sodium hydrogen carbonate in H2O (8 mL) was added and the solution was stirred for 20 min at room temperature. EtOAc was added and the organic phase was washed three times water. The solvent was removed with a rotary evaporator, and the residue was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of MeOH in EtOAc, starting with 0% of MeOH. The solvents of the fractions still containing both the reaction product and starting material were removed with a rotary evaporator. Treating the residue with a small amount of MeOH led to crystallization of the starting material overnight (85.9 mg, 0.235 mmol). The solvent of the mother liquor was removed with a rotary evaporator and the residue was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate gave compound SI43 (18.9 mg, 0.0514 mmol, 9%) as a yellow oil. 1H NMR (300 MHz, DMSO-d6): δ 7.92–7.84 (m, 2H), 7.55–7.44 (m, 3H), 7.93 (m, 2H), 6.56 (m, 2H), 4.68 (t, 2H, J = 5.4 Hz), 4.27 (t, 1H, J = 6.8 Hz), 3.69 (d, 1H), 3.55–3.46, 3.41–3.32 (each m, each 4H), 2.19 (s, 3H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 159.1, 157.4, 146.9, 129.4, 129.4, 128.9, 128.7, 127.1, 126.2, 123.2, 110.9, 58.1, 53.3, 51.4, 10.2 ppm. HRMS calc. for C21H26N3O3 [M+Na]+: 390.1794, found 390.1797.

(E)-5-(Diethylamino)-2-[[5-methyl-3-phenylisoxazol-4-yl]imino]methyl]phenol (SI44)

Synthesis according to the General procedure III. Deviating from the General procedure III, reaction mixture was heated at 70 °C overnight, 100 °C for 5 h before p-toluenesulfonic acid was added and then the reaction mixture was heated at 70 °C for 30 min. After cooling to rt, DIPEA (0.190 mL, 1.09 mmol) was added prior to the work-up procedure. 4-(Diethylamino)salicylaldehyde (211 mg, 1.09 mmol), 5-methyl-3-phenylisoxazol-4-amine 28 (0.190 g, 1.09 mmol), Na2SO4 (426 mg, 3.00 mmol), p-toluenesulfonic acid (51.9 mg, 0.273 mmol, 0.25 equiv), toluene (2.5 mL). Automated chromatography on silica gel gave compound SI44 (304 mg, 0.870 mmol, 80%) as yellow crystals.
(E)-N-[4-[1-(Dimethylamino)ethyl]benzylidene]-5-methyl-3-phenylisoxazol-4-amine (SI45)

Synthesis according to the General procedure III. Deviating from the General procedure III, the reaction mixture was first stirred at room temperature overnight and then heated at 70 °C for 2 h. 4-[1-(Dimethylamino)ethyl]benzaldehyde (50.0 mg, 0.282 mmol), 5-methyl-3-phenylisoxazol-4-amine 28 (49.1 mg, 0.282 mmol) Na2SO4 (80.1 mg, 0.564 mmol), AcOH (3.2 μL, 0.056 mmol, 0.2 equiv), toluene (2 mL). Chromatography on silica gel gave compound SI45 (72.0 mg, 0.216 mmol, 77%) as a colorless oil. 1H NMR (300 MHz, DMSO-d6): δ 8.62 (s, 1H), 7.93–7.83 (m, 4H), 7.55–7.43 (m, 5H), 3.34 (q, 1H, 3J = 6.7 Hz), 2.52 (s, 3H), 2.12 (s, 6H), 1.29 (d, 3H, Jd = 2.4 Hz), 6.91 (d, 1H, 3J = 6.9 Hz), 6.81 (m, 2H), 7.43 (m, 4H), 7.55 (dd, 1H, 3J = 8.9 Hz), 6.32 (dd, 1H, 4J = 2.4 Hz), 6.08 (d, 1H), 3.39 (q, 4H, 2J = 7.0 Hz), 2.53 (s, 3H), 1.11 (t, 6H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 165.5, 162.2, 157.7, 157.0, 151.6, 133.8, 129.7, 128.8, 128.4, 127.5, 126.1, 108.3, 103.8, 96.8, 43.9, 12.4, 11.2 ppm. HRMS calc. for C21H24N3O [M+H]+: 350.1869, found 350.1874.

(E)-N-[4-(Dimethylamino)benzylidene]-2-phenylimidazo[1,2-a]pyrimidin-3-amine (SI46)

Synthesis according to the General procedure III. Deviating from the General procedure III, the reaction mixture was first stirred at room temperature for 3 d, heated at 60 °C overnight. Then p-toluenesulfonic acid was added, and the reaction mixture was heated at 70 °C for 4 h. 4-(Dimethylamino)benzaldehyde (49.5 mg, 0.332 mmol, 1.5 equiv), 2-phenylimidazo[1,2-a]pyrimidin-3-ylamine (46.4 mg, 0.221 mmol), Na2SO4 (62.8 mg, 0.442 mmol), AcOH (2.5 μL, 0.044 mmol, 0.2 equiv), p-toluenesulfonic acid (4.2 mg, 0.022 mmol, 0.1 equiv), toluene (1 mL). Automated chromatography on silica gel gave compound SI46 (51.0 mg, 0.149 mmol, 68%) as yellow crystals. M.p. 199.1–200.4 °C (decomp.). 1H NMR (300 MHz, DMSO-d6): δ 8.86 (dd, 1H, 3J = 6.9 Hz, 4J = 2.0 Hz), 8.72 (s, 1H), 8.51 (dd, 1H, 3J = 4.1 Hz), 7.97 (m, 3H), 7.77 (m, 2H), 7.44 (m, 3H), 7.33 (m, 1H), 7.05 (dd, 1H), 6.81 (m, 2H), 3.01 (s, 6H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 161.1, 152.9, 149.6, 144.5, 134.2, 132.8, 131.8, 130.4, 128.5, 128.1, 127.6, 123.3, 111.6, 108.9, 39.7 ppm. HRMS calc. for C21H20N5 [M+H]+: 342.1719, found 342.1723.
Preparation of compounds in Scheme 3 and other related compounds

5-Methyl-4-[(4-nitrophenoxy)methyl]-3-phenylisoxazole (34b)

(5-Methyl-3-phenylisoxazol-4-yl)methanol 37 (189 mg, 1.00 mol), p-nitrophenol (167 mg, 1.20 mmol, 1.2 equiv) and triphenylphosphine (315 mg, 1.20 mmol, 1.2 equiv) were dissolved in anhydrous THF (4 mL) under argon and cooled to 0 °C in an ice bath. Diisopropyl azodicarboxylate (0.236 mL, 1.20 mmol, 1.2 equiv) was added, and the reaction mixture was stirred overnight, while the temperature was allowed to warm to rt. Diethyl ether was added, the organic phase was washed twice with water, twice with a 2 M solution of sodium hydroxide in water and several times with water until the aqueous phase remained neutral. The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing ethyl acetate starting with 100% n-hexane, followed by recrystallization (MeOH/ethyl acetate) to give compound 34b (0.100 g, 0.322 mol, 32%) as white crystals. M.p. 163.3–165.0 °C. 1H NMR (300 MHz, DMSO-d6): δ 8.22 (m, 2H), 7.70–7.63 (m, 2H), 7.52–7.46 (m, 3H), 7.22 (m, 2H), 5.16 (s, 2H), 2.55 (s, 3H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 170.1, 163.1, 162.0, 141.2, 129.9, 129.0, 128.4, 127.7, 125.9, 115.4, 108.8, 59.9, 10.8 ppm. HRMS calc. for C17H15N2O4 [M+H]+: 311.1032, found 311.1029.

Furan-3-ylmethyl 4-[(5-methyl-3-phenylisoaxazol-4-yl)methoxy]benzoate (35c)

Synthesis according to the General procedure VII. 4-[(5-Methyl-3-phenylisoxazol-4-yl)methoxy]benzoic acid 38 (22.6 mg, 0.0731 mmol), 3-hydroxymethylfuran (18.8 µL, 0.219 mmol, 3 equiv), HBTU (41.6 mg, 0.110 mmol, 1.5 equiv), DIPEA (25.5 µL, 0.146 mmol, 2 equiv), DMF (1 mL). Reaction time: 2 d. Solvent for extraction: ethyl acetate. Chromatography on silica gel gave compound 35c (16.7 mg, 0.0429 mmol, 59%) as a colorless oil. 1H NMR (300 MHz, CDCl3): δ 8.02 (m, 2H), 7.70–7.63 (m, 2H), 5.55 (m, 1H), 7.48–7.38 (m, 3H), 6.96 (m, 2H), 6.50 (dd, 1H, 4J = 0.9 Hz, 3J = 1.9 Hz), 5.22 (s, 2H), 4.91 (s, 2H), 2.52 (s, 3H) ppm. 13C NMR (75 MHz, CDCl3): δ 169.9, 166.1, 162.9, 162.1, 143.6, 141.7, 132.0, 130.0, 129.1, 129.0, 128.4, 123.6, 120.8, 114.6, 110.8, 109.3, 59.8, 58.3, 11.6 ppm. HRMS calc. for C23H26NO5 [M+H]+: 390.1341, found 390.1340.
2-Oxopropyl 4-[(5-methyl-3-phenylisoxazol-4-yl)methoxy]benzoate (35d)

Synthesis according to the General procedure VII. 4-[(5-Methyl-3-phenylisoxazol-4-yl)methoxy]benzoic acid 38 (23.2 mg, 0.0750 mmol), hydroxyacetone (15.4 µL, 0.225 mmol, 3 equiv), HBTU (42.7 mg, 0.113 mmol, 1.5 equiv), DIPEA (26.1 µL, 0.150 mmol, 2 equiv), DMF (1 mL). Reaction time: 2 d. Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 35d (18.9 mg, 0.0517 mmol, 69%) as an amorphous white solid. $^{1}$H NMR (300 MHz, CDCl$_3$): δ 8.07 (m, 2H), 7.71–7.63 (m, 2H), 7.48–7.38 (m, 3H), 6.98 (m, 2H), 4.92 (s, 2H), 4.85 (s, 2H), 2.52 (s, 3H), 2.23 (s, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): δ 202.0, 169.9, 165.5, 162.9, 162.4, 132.3, 130.0, 129.1, 129.0, 128.4, 122.6, 114.7, 109.2, 68.8, 59.9, 26.3, 11.6 ppm. HRMS calc. for C$_{23}$H$_{20}$NO$_5$ [M+H]$^+$: 366.1341, found 366.1342.

Isobutyl 4-[(5-methyl-3-phenylisoxazol-4-yl)methoxy]benzoate (35e)

Synthesis according to the General procedure VII. 4-[(5-Methyl-3-phenylisoxazol-4-yl)methoxy]benzoic acid 38 (25.6 mg, 0.0828 mmol), isobutanol (22.9 µL, 0.248 mmol, 3 equiv), HBTU (47.1 mg, 0.124 mmol, 1.5 equiv), DIPEA (28.8 µL, 0.166 mmol, 2 equiv), DMF (1 mL). Reaction time: 2 d. Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 35e (5.5 mg, 0.0151 mmol, 18%) as a colorless resin. $^{1}$H NMR (300 MHz, CDCl$_3$): δ 8.03 (m, 2H), 7.71–7.64 (m, 2H), 7.48–7.39 (m, 3H), 6.97 (m, 2H), 4.91 (s, 2H), 4.10 (d, 2H, $^3$J = 6.6 Hz), 2.52 (s, 3H), 2.08 (m, 1H), 1.03 (d, 3H, $^3$J = 6.7 Hz) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): δ 169.9, 166.3, 162.9, 162.0, 131.8, 130.0, 129.1, 129.0, 128.4, 124.1, 114.6, 109.3, 71.0, 59.8, 28.1, 19.4, 11.6 ppm. HRMS calc. for C$_{23}$H$_{20}$NO$_4$ [M+H]$^+$: 366.1705, found 366.1705.

N-(3-Hydroxypropyl)-N-methyl-4-[(5-methyl-3-phenylisoxazol-4-yl)methoxy]benzamide (36a)

Synthesis according to the General procedure I. 4-[(5-Methyl-3-phenylisoxazol-4-yl)methoxy]benzoic acid 38 (21.3 mg, 0.0689 mmol), 3-(methylamino)propan-1-ol (20.1 mg, 0.207 mmol, 3 equiv), HBTU (33.9 mg, 0.0896 mmol, 1.5 equiv), DIPEA (24.0 µL, 0.138 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate. Chromatography on silica gel gave compound 36a (20.3 mg, 0.0534 mmol, 77%) as a white solid. M.p. 63.6–68.3 °C. $^{1}$H NMR (300 MHz, CDCl$_3$): δ 7.73–7.66 (m, 2H), 7.53–7.46 (m, 3H), 7.35 (m, 2H), 7.03 (m, 2H), 5.02 (s, 2H), 4.41 (bs, 1H, OH), 3.51–3.31 (bm, 4H), 2.92 (s, 3H, N), 2.53 (s, 3H), 1.70 (bm, 2H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): δ 170.4, 162.5, 158.9, 130.4, 130.1, 129.4, 129.1, 128.3, 115.0, 109.8, 61.2, 59.6, 58.8, 31.1, 29.7, 11.3 ppm. HRMS calc. for C$_{22}$H$_{25}$N$_2$O$_4$ [M+H]$^+$: 381.1814, found 381.1814.
**N,N-Diethyl-4-[(5-methyl-3-phenyloxazol-4-yl)methoxy]benzamide (36b)**

Synthesis according to the General procedure I. 4-[(5-Methyl-3-phenyloxazol-4-yl)methoxy]benzoic acid 38 (22.6 mg, 0.0731 mmol), diethylamine (22.7 mg, 0.219 mmol, 3 equiv), HBTU (36.0 mg, 0.0950 mmol, 1.3 equiv), DIPEA (25.5 µL, 0.146 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate and a mixture of water with 30% brine. Chromatography on silica gel gave compound 36b (25.9 mg, 0.0711 mmol, 97%) as a colorless oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.73–7.66 (m, 2H), 7.47–7.39 (m, 3H), 7.36 (m, 2H), 6.94 (m, 2H), 4.87 (s, 2H), 3.42 (bs, 4H), 2.50 (s, 3H), 1.19 (bt, 6H, \(^3J = 7.1\) Hz) ppm. \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 171.1, 169.8, 162.9, 159.0, 130.7, 129.9, 129.1, 128.5, 128.0, 114.9, 109.5, 59.8, 44.0–38.5 (bs), 13.8, 11.5 ppm. HRMS calc. for C\(_{22}\)H\(_{25}\)N\(_2\)O\(_3\)[M+H\(^{+}\)]: 365.1965, found 365.1870.

**1-[4-[(3-Methyl-5-phenyloxazol-4-yl)methoxy]phenyl]propan-1-one (SI47)**

![SI47](image)

To a mixture of 3-methyl-5-phenyloxazol-4-yl)methanol (0.100 g, 0.529 mmol), 4'-hydroxypropiophenone (95.2 mg, 0.634 mmol, 1.2 equiv) and triphenylphosphine (166 mg, 0.634 mmol, 1.2 equiv) in anhydrous THF (3 mL) and cooled to 0 °C in an ice bath, diisopropyl azodicarboxylate (0.125 mL, 0.634 mmol, 1.2 equiv) was added. The reaction mixture was stirred overnight under argon, while the temperature was allowed to warm to rt. Diethyl ether was added, the organic phase was washed three times with water and the organic solvent was removed with a rotary evaporator. The crude product was purified by automated chromatography on silica gel, using a gradient of increasing ethyl acetate starting with 100% n-hexane. Recrystallization (MeOH/H\(_2\)O 10+1) gave compound SI47 (93.7 mg, 0.292 mmol, 55%) as a white solid. M.p. 142.1–147.2 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.97 (m, 2H), 7.72–7.65 (m, 2H), 7.51–7.45 (m, 3H), 7.00 (m, 2H), 5.01 (s, 2H), 2.96 (q, 2H, \(^3J = 7.3\) Hz), 2.39 (s, 3H), 1.23 (t, 3H, \(^3J = 7.3\) Hz) ppm. \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 199.5, 168.6, 162.0, 160.8, 131.0, 130.6, 130.5, 129.3, 127.6, 114.6, 109.5, 60.0, 31.7, 10.4, 8.6 ppm. HRMS calc. for C\(_{20}\)H\(_{20}\)NO\(_3\)[M+H\(^{+}\)]: 322.1443, found 322.1443.
5-Methyl-4-[(naphthalen-2-ylmethoxy)methyl]-3-phenylisoxazole (SI48)

(5-Methyl-3-phenylisoxazol-4-yl)methanol 37 (94.6 mg, 0.500 mmol) was dissolved in anhydrous THF (3 mL) under argon, cooled to 0 °C in an ice bath, and a 60% dispersion of sodium hydride in mineral oil (40.0 mg, 1.00 mmol, 2 equiv) was added. After one hour, 2-(bromomethyl)naphthalene (94.9 µL, 0.593 mmol, 1.1 equiv) was added. The ice bath was removed, and the reaction mixture was stirred overnight at room temperature. Water and dichloromethane were added, the phases were separated and the organic phase was washed twice with water. The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel using a gradient starting with 100% n-hexane and ending with 100% diethyl ether to give compound SI48 (121 mg, 0.367 mmol, 73%) as a colorless oil. ¹H NMR (300 MHz, DMSO-dma): δ 7.95–7.73 (m, 6H), 7.56–7.43 (m, 6H), 4.70 (s, 2H), 4.45 (s, 2H), 2.48 (s, 3H) ppm. ¹³C NMR (75 MHz, DMSO-dma): δ 169.5, 162.0, 135.5, 132.8, 132.5, 129.8, 128.9, 128.8, 127.9, 127.7, 127.6, 126.3, 126.2, 126.0, 110.4, 70.2, 60.2, 10.9 ppm. HRMS calc. for C₂₂H₂₀NO₂ [M+H]⁺: 330.1494, found 330.1494.

5-Methyl-3-phenyl-4-[[4-(trifluoromethoxy)benzyl]oxy]methyl]isoxazole (SI49)

(5-Methyl-3-phenylisoxazol-4-yl)methanol 37 (102 mg, 0.539 mmol) was dissolved in anhydrous DMF (3 mL) under argon, cooled to 0 °C in an ice bath, and a 60% dispersion of sodium hydride in mineral oil (23.7 mg, 0.593 mmol, 1.1 equiv) was added. After one hour, 4-(trifluoromethyl)benzyl bromide (94.9 µL, 0.593 mmol, 1.1 equiv) was added. The ice bath was removed, and the reaction mixture was stirred overnight at room temperature. Potassium tert-butoxide (36.3 mg, 0.323 mmol, 0.6 equiv) was added and stirring was continued overnight. Diethyl ether was added, the organic
phase was washed three times with water, and the organic solvents were removed with a rotary evaporator. The crude product was purified by automated chromatography on silica gel to give compound **SI49** (67.0 mg, 0.184 mmol, 34%) as a colorless oil. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 7.76–7.69 (m, 2H), 7.53–7.47 (m, 3H), 7.44 (m, 2H), 7.37–7.31 (m, 2H), 4.56 (s, 2H), 4.42 (s, 2H), 2.47 (s, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 169.5, 162.0, 147.7, 137.5, 129.8, 129.6, 128.9, 128.8, 127.8, 121.0, 110.3, 70.2, 60.2, 10.8 ppm. HRMS calc. for C$_{19}$H$_{18}$F$_3$NO$_3$ [M+H]$^+$: 364.1161, found 364.1160.

**Preparation of compounds in Scheme 4 and other related compounds**

$N$-[4-(Diethylamino)phenyl]-5-methyl-3-(4-nitrophenyl)isoxazole-4-carboxamide (39a)

![Chemical structure diagram]

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction mixture was diluted with ethyl acetate for the work-up and extracted once with a 2 M solution of sodium hydroxide in water and twice with 4 M hydrochloric acid. The combined hydrochloric acid phases were made alkaline with a 2 M solution of sodium hydroxide in water and extracted twice with ethyl acetate. The organic phase was washed twice with a mixture of water and brine (10:1). The starting material used for the synthesis of 39a was the once recrystallized product mixture from the nitration of 5-methyl-3-phenylisoxazole-4-carboxylic acid (41a:41g:41h), consisting of different regioisomers with the 3-nitrophenyl derivative as a major component. 41a:41g:41h, (248 mg, 1.00 mmol), $N,N$-diethyl-$p$-phenylenediamine hydrochloride 50 (236 mg, 1.18 mmol, 1.2 equiv), HBTU (759 mg, 2.00 mmol, 2 equiv), DIPEA (0.871 mL, 5.00 mmol, 5 equiv), DMF (5 mL). Recrystallization (twice from MeOH/H$_2$O 10+1) [without chromatography on silica gel] gave compound 39a (62.0 mg, 0.157 mmol, 16%) as fine orange needles. M.p. 179.8–181.0 °C. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 10.16 (s, 1H), 8.36 (m, 2H), 7.98 (m, 2H), 7.39 (m, 2H), 6.64 (m, 2H), 3.30 (q, 4H, $^3$J = 7.0 Hz), 2.61 (s, 3H), 1.06 (t, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 170.4, 158.9, 158.5, 148.3, 144.6, 134.4, 129.2, 127.0, 124.0, 121.1, 113.6, 111.7, 43.8, 12.4, 11.9 ppm. HRMS calc. for C$_{21}$H$_{22}$N$_4$O$_4$ [M+H]$^+$: 395.1719, found 395.1719.
5-Methyl-3-(4-nitrophenyl)isoxazole-4-carboxylic acid (41a):(41g):(41h), crude

\[
\begin{align*}
\text{5-Methyl-3-phenylisoxazole-4-carboxylic acid} \ 6 \ \text{was added in small portions to fuming nitric acid (12 mL), cooled to 0 °C in an ice bath. The reaction mixture was stirred at 0 °C for 1.5 h and quenched by addition of crushed ice. The precipitated product was obtained by filtration and after washing with water the wet solid was recrystallized from methanol to give compound 41a:41g:41h (2.11 g, 8.49 mmol, 85%) as yellowish white crystals. The product is a mixture of the 3- (major), 4- and 2-nitrophenyl (minor) derivatives.} \\
^{1}H \text{ NMR (300 MHz, DMSO-d6): } \delta \ 8.32 \ (d, \ J = 9.0 \text{ Hz}, 2\text{H}), \ 7.91 \ (d, \ J = 9.0 \text{ Hz}, 2\text{H}), \ 2.73 \ (s, 3\text{H}).
\end{align*}
\]

Note: The reaction procedure has not been optimized. The compound 41g can likely be obtained in much higher yield. 41h is only a minor side product. The synthesis of 41g is known (F. P. Doyle, J. C. Hanson, A. W. Long, J. H. C. Nayler, J. Chem. Soc. 1963, 5845-5854) and 41h is known (without experimental data): Z. Xin, H. Zhao, M. D. Sery, B. Liu, V. G. Schaefer, D. H. Falls, W. Kaszuska, C. A. Colins, H. L. Sham, G. Liu, Bioorg. Med. Chem. Lett. 2005, 15, 1201-1204.

5-Methyl-3-(3-nitrophenyl)isoxazole-4-carboxylic acid 41g and 5-methyl-3-(2-nitrophenyl)isoxazole-4-carboxylic acid (41h)

Note: The reaction procedure has not been optimized. The compound 41g can likely be obtained in much higher yield. 41h is only a minor side product. The synthesis of 41g is known (F. P. Doyle, J. C. Hanson, A. W. Long, J. H. C. Nayler, J. Chem. Soc. 1963, 5845-5854) and 41h is known (without experimental data): Z. Xin, H. Zhao, M. D. Sery, B. Liu, V. G. Schaefer, D. H. Falls, W. Kaszuska, C. A. Colins, H. L. Sham, G. Liu, Bioorg. Med. Chem. Lett. 2005, 15, 1201-1204.

5-Methyl-3-phenylisoxazole-4-carboxylic acid 6 (10.0 g, 49.2 mmol) was added in small portions during a period of 40 min to fuming nitric acid (60 mL), cooled to 0 °C in an ice bath. The reaction mixture was stirred at 0 °C for 4 h and quenched by addition of crushed ice (100 mL). Water (180 mL) was added slowly and the precipitated mixture of intermediates was obtained by filtration. The precipitate was washed with water and the wet solid was recrystallized from methanol to give an intermediate mixture of differently nitrated regioisomers (11.0 g, 44.2 mmol, 90%) as yellowish white crystals. This mixture of isomers was dissolved in DMSO (50 mL). Potassium carbonate (2.98 g, 53.0 mmol, 1.2 equiv) and iodomethane (5.50 mL, 88.4 mmol, 2 equiv) were added, and the reaction mixture was stirred for 5 d at room temperature. The reaction mixture was diluted with ethyl acetate
and washed three times with a mixture of water and brine (30%) and the organic solvent was removed with a rotary evaporator. The crude product was divided into five portions, which were separately purified by automated chromatography on silica gel, using a gradient of increasing acetone in n-hexane starting with 100% n-hexane. Hereby, the smaller second fraction was partially separated from the major first fraction. The combined second fractions were recrystallized from methanol/water (10+1) to give the intermediate methyl 5-methyl-3-(2-nitrophenyl)isoxazole-4-carboxylate (314 mg, 1.20 mmol, which was hydrolyzed by lithium hydroxide hydrate (64.8 mg, 1.54 mmol, 1.5 equiv) at room temperature overnight in a mixture of THF (1 mL), methanol (1 mL) and water (0.5 mL). This reaction mixture was diluted with water, washed once with diethyl ether, which in turn was re-extracted once with water. Ethyl acetate was added to the combined aqueous phases, which were acidified with 1 M hydrochloric acid. The phases were separated, and the organic phase was washed neutral with portions of water. The organic solvent was removed with a rotary evaporator, and the crude product was recrystallized from ethanol/water (10+1) to give compound 41h (0.250 g, 1.01 mmol, 2%).

The combined major fractions of the chromatography were recrystallized from n-hexane/benzene (2+1) and twice from ethanol/water (10 + 1) to give a mixture of the corresponding 3- and 4-nitro-substituted isoxazole methyl ester (3.48 g, 13.3 mmol) that contains methyl 5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxylate as the major component. This mixture of intermediates was hydrolyzed by lithium hydroxide hydrate (835 mg, 19.9 mmol, 1.5 equiv) at room temperature overnight in a mixture of THF (12 mL), methanol (12 mL) and water (6 mL). This reaction mixture was diluted with water and washed once with diethyl ether. Diethyl ether was added, and the aqueous phase was acidified with 1 M hydrochloric acid. The phases were separated and the organic phase was washed neutral with portions of water. The organic solvent was removed with a rotary evaporator, and the crude product was recrystallized twice from ethanol to give compound 41g (741 mg, 2.99 mmol, 6%).

41h 1H NMR (300 MHz, DMSO-d6): δ 8.25 (dd, 3J = 8.1, 1.4 Hz, 1H), 7.89 (dd, 3J = 7.5, 1.5 Hz, 1H), 7.84 (dd, 3J = 5.1, 1.7 Hz, 1H), 7.80 (dd, 3J = 7.6, 1.6 Hz, 1H), 7.66–7.51 (m, 1H), 2.72 (s, 3H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 174.9, 162.2, 160.7, 148.0, 133.9, 132.2, 131.3, 124.6, 124.0, 108.7, 12.8 ppm.

41g 1H NMR (300 MHz, DMSO-d6): δ 13.24 (br s, 1H), 8.48 (ddd, J = 2.3, 1.7, 0.5 Hz, 1H), 8.36 (ddd, J = 8.3, 2.4, 1.1 Hz, 1H), 8.10 (ddd, J = 7.7, 1.7, 1.1 Hz, 1H), 7.79 (ddd, J = 8.2, 7.7, 0.5 Hz, 1H), 2.73 (s, 3H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 176.1, 162.4, 160.5, 147.4, 135.7, 129.9, 129.7, 124.5, 124.0, 108.7, 13.1 ppm.
**N-[4-(Diethylamino)phenyl]-3-ethyl-5-methylisoxazole-4-carboxamide (39b)**

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 4 d at room temperature. 3-Ethyl-5-methylisoxazole-4-carboxylic acid 41b (0.100 g, 0.645 mmol), N,N-diethyl-p-phenylenediamine 17 (0.107 mL, 0.645 mmol), HBTU (318 mg, 0.839 mmol, 1.3 equiv), DIPEA (0.225 mL, 1.29 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 39b (127 mg, 0.421 mmol, 65%) as a greyish resin. M.p. 89.5–98.6 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 9.72 (s, 1H), 7.41 (m, 2H), 6.64 (m, 2H), 3.30 (q, 4H, \(\text{J} = 7.0 \text{ Hz}\)), 2.76 (q, 2H, \(\text{J} = 7.5 \text{ Hz}\)), 2.51 (s, 3H), 1.17 (t, 3H, \(\text{J} = 7.5 \text{ Hz}\)), 1.07 (t, 6H, \(\text{J} = 7.0 \text{ Hz}\)) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 168.6, 163.1, 159.3, 144.4, 127.3, 121.7, 113.2, 111.8, 43.7, 18.4, 12.3, 12.0, 11.9 ppm. HRMS calc. for C\(_{17}\)H\(_{24}\)N\(_3\)O\(_2\) [M+H]\(^+\): 302.1869, found 302.1870.

**N-[4-(Diethylamino)phenyl]-5-methyl-3-(pyridin-4-yl)isoxazole-4-carboxamide (39c)**

Synthesis according to the General procedure I. 5-Methyl-3-(4-pyridinyl)-4-isoxazolecarboxylic acid 41c (53.9 mg, 0.264 mmol), N,N-diethyl-p-phenylenediamine 17 (43.9 \(\mu\)L, 0.264 mmol), HBTU (0.130 g, 0.343 mmol, 1.3 equiv), DIPEA (92.0 \(\mu\)L, 0.604 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H\(_2\)O 10+1) without chromatography on silica gel gave compound 39c (43.0 mg, 0.123 mmol, 46%) as beige needles. M.p. 179.1–180.3 °C (decomp.). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.13 (s, 1H), 8.72 (m, 2H), 7.68 (m, 2H), 7.40 (m, 2H), 6.64 (m, 2H), 3.30 (q, 4H, \(\text{J} = 7.0 \text{ Hz}\)), 2.60 (s, 3H), 1.07 (t, 6H, \(\text{J} = 7.0 \text{ Hz}\)) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 170.3, 158.4, 158.4, 150.3, 144.6, 135.6, 127.0, 122.0, 121.6, 113.6, 111.7, 43.7, 12.3, 11.9 ppm. HRMS calc. for C\(_{20}\)H\(_{23}\)N\(_2\)O\(_2\) [M+H]\(^+\): 351.1821, found 351.1822.

**N-[4-(Diethylamino)phenyl]-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide (39g)**

Synthesis according to the General procedure I. 5-Methyl-3-(3-nitrophenyl)isoxazole-4-carboxylic acid 41g (0.400 g, 1.61 mmol), N,N-diethyl-p-phenylenediamine 17 (0.268 mL, 1.61 mmol), HBTU (795 mg, 2.10 mmol, 1.3 equiv), DIPEA (0.562 mL, 3.22 mmol, 2 equiv), DMF (5 mL). Solvent for extraction: diethyl ether. Recrystallization (EtOH/H\(_2\)O 19+1) after chromatography on silica gel gave compound 39g (538 mg, 1.36 mmol, 85%) as fine orange needles. M.p. 129.6–132.4 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.09 (s, 1H), 8.57 (dd\(\equiv\)t, 1H, \(\text{J} = 2.0 \text{ Hz}\)), 8.36 (ddd, 1H, \(\text{J} = 8.3 \text{ Hz}\)), 8.16 (dd\(\equiv\)ddt, 1H, \(\text{J} = 7.8 \text{ Hz}\)), 7.82 (dd\(\equiv\)t, 1H), 7.38 (m, 2H), 6.64 (m, 2H), 3.30 (q, 4H, \(\text{J} = 7.0 \text{ Hz}\)), 2.62 (s, 3H), 1.07 (t, 6H, \(\text{J} = 7.0 \text{ Hz}\)) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 170.3, 158.6, 158.6, 147.9, 144.7, 134.1, 130.5, 129.7, 126.8,
124.7, 122.3, 121.8, 113.4, 111.7, 43.7, 12.3, 11.9 ppm. HRMS calc. for C$_{21}$H$_{23}$N$_4$O$_4$ [M+H]$^+$: 395.1719, found 395.1722.

**N-[4-(Diethylamino)phenyl]-5-methyl-3-(2-nitrophenyl)isoxazole-4-carboxamide (39h)**

Synthesis according to the General procedure I. Deviating from the General procedure I the reaction time was 8 h at room temperature. 5-Methyl-3-(2-nitrophenyl)isoxazole-4-carboxylic acid 41h (75.0 mg, 0.302 mmol), N,N-diethyl-p-phenylenediamine 17 (50.2 μL, 0.302 mmol), HBTU (149 mg, 0.393 mmol, 1.3 equiv), DIPEA (0.105 mL, 0.604 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H$_2$O 10+1) after chromatography on silica gel gave compound 39h (101 mg, 0.256 mmol, 85%) as yellow crystals. M.p. 136.6–137.8 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 9.71 (s, 1H), 8.17 (dd, 1H, $^3J$ = 8.0 Hz, $^4J$ = 1.4 Hz), 7.87 (ddd $\approx$ ddt, 1H, $^3J$ = 7.5 Hz), 7.79 (ddd $\approx$ ddt, 1H, $^4J$ = 1.6 Hz), 7.67 (dd, 1H), 7.27 (m, 2H), 6.59 (m, 2H), 3.28 (q, 4H, $^3J$ = 7.0 Hz), 2.68 (s, 3H), 1.05 (t, 6H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 168.9, 159.8, 158.2, 148.1, 144.5, 133.7, 132.1, 131.2, 126.8, 124.5, 123.3, 122.1, 113.5, 111.6, 43.7, 12.4, 12.3 ppm. HRMS calc. for C$_{21}$H$_{23}$N$_4$O$_4$ [M+H]$^+$/428.0974, found 428.0974.

**3-(4-Bromophenyl)-N-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide (39i)**

Synthesis according to the General procedure I. 3-(4-Bromophenyl)-5-methylisoxazole-4-carboxylic acid 41i (503 mg, 1.78 mmol), N,N-diethyl-p-phenylenediamine 17 (0.296 mL, 1.78 mmol), HBTU (879 mg, 2.32 mmol, 1.3 equiv), DIPEA (0.621 mL, 3.56 mmol, 2 equiv), DMF (10 mL). Solvent for extraction: ethyl acetate. Recrystallization (EtOH/H$_2$O 10+1) after chromatography on silica gel gave compound 39i (501 mg, 1.17 mmol, 66%) as light blue crystals. M.p. 157.8–159.3 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.08 (s, 1H), 7.96 (m, 4H), 7.40 (m, 2H), 6.64 (m, 2H), 3.30 (q, 4H, $^3J$ = 7.0 Hz), 2.57 (s, 3H), 1.07 (t, 6H, $^4J$ = 7.0 Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 169.7, 159.3, 158.8, 144.5, 131.8, 129.7, 127.4, 127.1, 123.6, 121.6, 113.6, 111.7, 43.7, 12.3, 11.8 ppm. HRMS calc. for C$_{21}$H$_{23}$BrN$_3$O$_2$ [M+H]$^+$: 428.0974, found 428.0974.
N-[4-(Diethylamino)phenyl]-3-[4'-fluoro-[1,1'-biphenyl]-4-yl]-5-methylisoxazole-4-carboxamide (39j)

3-(4-Bromophenyl)-N-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide 39i (0.075 g, 0.175 mmol) was dissolved under argon in absolute toluene (2 mL). (4-Fluorophenyl)boronic acid (27.0 mg, 0.193 mmol, 1.1 equiv), ethanol (1 mL) and a 2.0 M solution of sodium carbonate in H₂O (1 mL) were added, and the mixture was degassed. Tetrakis(triphenylphosphine)palladium(0) (10.1 mg, 0.00875 mmol, 5 mol%) was added under argon, and the reaction mixture was heated at 80 °C under reflux conditions for 5 h and to 70 °C overnight. Ethyl acetate was added, and the organic phase was washed three times with a mixture of water and brine (3:1). The solvent was removed with a rotary evaporator, and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate gave compound 39j (53.1 mg, 0.120 mmol, 68%) as a white solid. M.p. 171.2–173.9 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.74 (m, 4H), 7.65–7.57 (m, 2H), 7.21–7.08 (m, 4H), 6.97 (bs, 1H), 6.58 (m, 2H), 3.30 (q, 4H, J = 7.0 Hz), 2.78 (s, 3H), 1.12 (t, 6H, J = 7.0 Hz) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 174.5, 164.7, 161.4, 159.7, 159.4, 145.7, 142.6, 136.2 (d, J = 3.6 Hz), 129.8, 129.0 (d, J = 8.1 Hz), 127.9, 127.1, 125.8, 122.3, 116.1 (d, J = 21.8 Hz), 112.3, 111.8, 44.7, 13.2, 12.6 ppm. HRMS calc. for C₂₇H₂₇FN₃O₂ [M+H]⁺: 444.2087, found 444.2094.

3-(2-Chlorophenyl)-N-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide (39k)

Synthesis according to the General procedure I. 3-(2-Chlorophenyl)-5-methylisoxazole-4-carboxylic acid 41k (75.0 mg, 0.316 mmol), N,N-diethyl-p-phenylenediamine 17 (52.5 µL, 0.316 mmol), HBTU (156 mg, 0.411 mmol, 1.3 equiv), DIPEA (0.110 mL, 0.632 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H₂O 10+1) after chromatography on silica gel gave compound 39k (90.0 mg, 0.234 mmol, 74%) as fine white needles. M.p. 111.5–113.9 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 9.66 (s, 1H), 7.60–7.43 (m, 4H), 7.29 (m, 2H), 6.60 (m, 2H), 3.28 (q, 4H, J = 7.0 Hz), 2.65 (s, 3H), 1.05 (t, 6H, J = 7.0 Hz) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 169.1, 159.8, 158.5, 144.4, 132.4, 131.7, 131.4, 129.5, 127.6, 127.2, 127.2, 121.7, 114.8, 111.7, 43.7, 12.3, 12.1 ppm. HRMS calc. for C₂₃H₂₃ClN₃O₂ [M+H]⁺: 384.1479, found 384.1475.
3-(4-Bromothiophen-2-yl)-N-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide (39i)

i. (E/Z)-5-Bromothiophene-3-carbaldehyde oxime (43l)

To a solution of 5-bromothiophene-3-carbaldehyde (1.00 g, 5.23 mmol) in EtOH (12 mL) hydroxylamine hydrochloride (0.400 g, 5.76 mmol, 1.1 equiv) and pyridine (0.466 mL, 5.75 mmol, 1.1 equiv) were added. After stirring at room temperature for 2.5 h, the reaction mixture was quenched with a mixture of a saturated aqueous solution of NH₄Cl (10 mL) and water (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed twice with water and once with a mixture of water and brine (2:1) until the solvent was removed and stirring was continued at room temperature for 1.5 h. The solvent was removed with a rotary evaporator, and the crude product mixture was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate. The chromatography gave 81.1 mg of a product mixture containing ethyl 3-(4-bromothiophen-2-yl)-5-methylisoxazole-4-carboxylate 45l, which was used without further purification in the next step.

ii. 3-(4-Bromothiophen-2-yl)-5-methylisoxazole-4-carboxylate (45l)

Diacetoxyiodobenzene (354 mg, 1.10 mmol, 1.1 equiv) was dissolved in a mixture of MeOH (4 mL) and water (400 µL) and stirred at 0 °C in an ice bath. Trifluoroacetic acid (15 µL) and (E/Z)-4-bromothiophene-2-carbaldehyde oxime 43l (206 mg, 1.00 mmol) were added, and after 2 min ethyl but-2-ynoate (82.8 µL, 1.10 mmol, 1.1 equiv) was added. The reaction mixture was stirred for 30 min at 0 °C, after which the ice-bath was removed and stirring was continued at room temperature for 1.5 h. The solvent was removed with a rotary evaporator, and the crude product mixture was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate. The chromatography gave 81.1 mg of a product mixture containing ethyl 3-(4-bromothiophen-2-yl)-5-methylisoxazole-4-carboxylate 45l, which was used without further purification in the next step.

iii. 3-(4-Bromothiophen-2-yl)-5-methylisoxazole-4-carboxylic acid (411)

3-(4-Bromothiophen-2-yl)-5-methylisoxazole-4-carboxylate 45l was dissolved in an equimixture of THF, MeOH and water (1.5 mL). Lithium hydroxide hydrate (16.1 mg, 0.385 mmol) was added and the reaction mixture was stirred overnight at room temperature. Ethyl acetate was added, and the organic phase was extracted twice with water. The combined aqueous phases were washed once with diethyl ether, acidified with a 1 M solution of HCl in H₂O and extracted with ethyl acetate. The organic phase was washed twice with water and once with a mixture of water and brine (2:1) until the aqueous phase remained neutral. Evaporation of the organic phase with a rotary evaporator and drying in an oil pump vacuum gave crude 3-(4-bromothiophen-2-yl)-5-methylisoxazole-4-carboxylic acid 411 (19.3 mg), which was used without purification.

iv. 3-(4-Bromothiophen-2-yl)-N-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide (39i)

Synthesis according to the General procedure I. Deviating from the General procedure I, HATU was used as a coupling reagent. 3-(4-Bromothiophen-2-yl)-5-methylisoxazole-4-carboxylic acid 411 (19.3 mg, crude), N,N-diethyl-p-phenylenediamine 17 (12.2 µL, 0.0737 mmol), HATU (33.1 mg, 0.0871 mmol) and DIPEA (23.3 µL, 0.134 mmol), DMF (0.5 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 39i (18.5 mg, 0.0426
mmol, 4%) as a yellow solid. M.p. 125.1–128.3 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.18 (s, 1H), 7.89 (d, 1H, \(J = 1.5\) Hz), 7.61 (d, 1H, \(J = 1.5\) Hz), 7.44 (m., 2H), 6.67 (m., 2H), 3.32 (q, 4H, \(J = 7.0\) Hz), 2.57 (s, 3H), 1.08 (t, 6H, \(J = 7.0\) Hz) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 170.1, 158.3, 154.0, 144.7, 130.9, 130.5, 126.8, 126.5, 121.7, 112.7, 111.7, 109.2, 43.7, 12.3, 12.0 ppm. HRMS calc. for C\(_{19}\)H\(_{21}\)BrN\(_3\)O\(_2\)S [M+H]\(^+\): 434.0538, found 434.0540.

**N-[4-(Diethylamino)phenyl]-5-methyl-3-(thiophen-3-yl)isoxazole-4-carboxamide (39m)**

*ii. Ethyl 5-methyl-3-(thiophen-3-yl)isoxazole-4-carboxylate (45m)*

A solution of (E/Z)-thiophencarbaldehyde oxime 43m (0.137 g, 1.08 mmol) in MeOH (6 mL) was added dropwise to a stirred solution of ethyl 2-butyloate (0.138 mL, 1.19 mmol 1.1 equiv) and (diacetoxyiodo)benzene (382 mg, 1.19 mmol, 1.1 equiv) in MeOH (10 mL) at 0 °C followed by three drops of trifluoroacetic acid. The solution was stirred for 1 h at 0 °C, allowed to warm to rt and stirred at room temperature for further 2 h. The solvents were evaporated in vacuo, and the crude product mixture (383 mg) was subjected to a purification by an automated flash silica chromatography (n-hexane/EtOAc, 5:1), which yielded compound 45m (81.0 mg, 0.341 mmol, 32%) as a clear oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.06 (dd, \(3^J = 3.0, 1.2\) Hz, 1H), 7.53 (dd, \(3^J = 5.1, 1.3\) Hz, 1H), 7.36 (dd, \(3^J = 5.1, 3.0\) Hz, 1H), 4.32 (q, \(3^J = 7.1\) Hz, 2H), 2.71 (s, 3H), 1.34 (t, \(3^J = 7.1\) Hz, 3H) ppm. \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 175.9, 162.2, 157.9, 128.3, 127.9, 125.3, 108.4, 61.0, 14.3, 13.9 ppm. This crude product was used in the next step without further purification.

*iii. 5-Methyl-3-(thiophen-3-yl)isoxazole-4-carboxylic acid (41m)*

Ethyl 5-methyl-3-(thiophen-3-yl)isoxazole-4-carboxylate 45m (64.0 mg, 0.270 mmol) was dissolved in an equimixture of MeOH/H\(_2\)O (8 mL), and NaOH (21.5 mg, 0.539 mmol, 2 equiv) was added. The reaction mixture was stirred at 60 °C for 22 h, and then most of the MeOH was removed by evaporation in vacuo. The aqueous layer was acidified with a 1 M solution of HCl in H\(_2\)O to pH 1, and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (20 mL), and the solvents were evaporated in vacuo to give compound 41m (45.0 mg, 0.215 mmol, 80%). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.09 (dd, \(3^J = 3.0, 1.2\) Hz, 1H), 7.56 (dd, \(3^J = 5.1, 1.3\) Hz, 2.12 Hz, 1H), 7.44 (m., 2H), 6.67 (m., 2H), 3.32 (q, 4H, \(J = 7.0\) Hz), 2.57 (s, 3H), 1.08 (t, 6H, \(J = 7.0\) Hz) ppm.
1H), 7.37 (dd, $J = 5.1$, 2.9 Hz, 1H), 2.77 (s, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.0, 167.4, 157.9, 128.4, 128.3, 128.1, 125.5, 107.5, 14.2 ppm.

iv. N-[4-(Diethylamino)phenyl]-5-methyl-3-(thiophen-3-yl)isoxazole-4-carboxamide (39m)

5-Methyl-3-(thiophen-3-yl)isoxazole-4-carboxylic acid 41m (18.0 mg, 0.0861 mmol) was dissolved in dry DMF (2 mL) under argon, and N,N-diethyl-p-phenylenediamine 17 (14.3 µL, 0.0861 mmol), HBTU (42.4 mg, 0.112 mmol, 1.3 equiv), and DIPEA (30.0 µL, 0.172 mmol, 2 equiv) were added to the solution. The reaction mixture was stirred for 16 h at room temperature. Diethyl ether (20 mL) was added, and the organic phase was washed with water (2 × 10 mL). The solvent was removed in vacuo, and the crude product mixture was subjected to a purification by an automated flash silica chromatography (n-hexane/EtOAc 1:0→0:1) to yield compound 39m (17 mg, 55%). M.p. 137.0 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.82 (dd, $J = 3.0$, 1.3 Hz, 1H), 7.52 (dd, $J = 5.0$, 3.0 Hz, 1H), 7.44 (dd, $J = 5.0$, 1.3 Hz, 1H), 7.20 (m, 2H), 6.62 (m, 2H), 3.32 (q, $J = 7.0$ Hz, 4H), 2.73 (s, 3H), 1.14 (t, $J = 7.0$ Hz, 6H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 173.7, 159.1, 155.6, 145.5, 128.4, 127.6, 127.4, 127.3, 125.7, 121.9, 112.2, 111.7, 44.5, 12.9, 12.5 ppm. HRMS calc. for C$_{10}$H$_{12}$N$_2$O$_2$S [M+H]+: 356.1433, found 356.1439.

N-[4-(Diethylamino)phenyl]-3-(furan-3-yl)-5-methylisoxazole-4-carboxamide (39n)

i. (E/Z)-Furan-3-carbaldehyde oxime (43n)

To a solution of furan-3-carbaldehyde 44n (423 mg, 4.40 mmol) in EtOH (9 mL), hydroxylamine hydrochloride (0.336 g, 4.84 mmol, 1.1 equiv) and pyridine (0.391 mL, 4.84 mmol, 1.1 equiv) were added. After stirring at room temperature for 1 h, the reaction mixture was quenched with a mixture of a saturated solution of NH$_4$Cl in H$_2$O (10 mL) and water (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried with Na$_2$SO$_4$, and the solvents were evaporated in vacuo to yield compound 43n (327 mg, 2.94 mmol, 67%) as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.36 (br, s, 1H), 8.29–8.16 (m, 1H, major), 8.08 (s, 1H, minor), 7.64 (t, $J = 1.1$ Hz, 1H, minor), 7.44 (t, $J = 1.7$ Hz, 1H, major), 7.42 (t, $J = 1.7$ Hz, 1H, minor), 7.35 (s, 1H, major), 6.71–6.68 (m, 1H, minor), 6.67 (dd, $J = 1.9$, 0.7 Hz, 1H, major). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 149.1 (pyridine), 147.2 (major), 144.3 (minor), 143.6 (minor), 142.8 (major), 142.5 (minor), 139.8 (major), 137.2 (pyridine), 124.2 (pyridine), 119.9 (C, minor), 116.3 (C, major), 110.9 (CH, major), 107.4 (CH, minor) ppm.

ii. Ethyl 3-(furan-3-yl)-5-methylisoxazole-4-carboxylate (45n)

A solution of (E/Z)-furan-3-carbaldehyde oxime 43n (111 mg, 1.00 mmol) in MeOH (6 mL) was added dropwise to a stirred solution of ethyl 2-butyanoate (0.128 mL, 1.10 mmol 1.1 equiv) and (diacetoxyiodo)benzene (354 mg, 1.10 mmol, 1.1 equiv) in MeOH (10 mL) at 0 °C, followed by three drops of trifluoroacetic acid. The resulting solution was stirred for 1 h at 0 °C and allowed to warm to rt and stirred at room temperature for further 2 h. The solvents were evaporated in vacuo, and the crude product mixture (260 mg) was subjected to a purification by an automated flash silica
chromatography (n-hexane/EtOAc 20:1), which yielded compound 45n (41.0 mg, 0.185 mmol, 19%). The product was used in the next step without further purification.

iii. 3-(Furan-3-yl)-5-methylisoxazole-4-carboxylic acid (41n)

To a solution of ethyl 5-methyl-3-(thiophen-3-yl)isoxazole-4-carboxylate 45n (27 mg, 0.12 mmol) in an equimixture of MeOH/H$_2$O (3.5 mL), NaOH (21 mg, 0.54 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 60 °C for 22 h and then most of the MeOH was removed in vacuo. The aqueous layer was acidified with a 1 M solution of HCl in H$_2$O to pH 1, and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (20 mL), and the solvents were evaporated in vacuo to give compound 41n (19.0 mg, 0.0983 mmol, 81%). The product was used in the next step without further purification.

iv. N-[4-(Diethylamino)phenyl]-3-(furan-3-yl)-5-methylisoxazole-4-carboxamide (39n)

To a solution of 3-(furan-3-yl)-5-methylisoxazole-4-carboxylic acid 41n (19.0 mg, 0.091 mmol) in dry DMF (2 mL), N,N-diethyl-p-phenylenediamine 17 (16.4 µL, 0.100 mmol, 2.0 equiv), HBTU (44.8 mg, 0.118 mmol, 1.3 equiv), and DIPEA (32 µL, 0.182 mmol, 2.0 equiv) were added under argon. The reaction mixture was stirred for 16 h at room temperature. Diethyl ether (20 mL) was added, and the organic phase was washed with water (2 × 10 mL). The solvent was removed in vacuo, and the crude product mixture was subjected to a purification by an automated flash silica chromatography (n-hexane/EtOAc 1:0→1:1) to yield compound 39n (18.0 mg, 0.0530 mmol, 59%). M.p. 136.6 °C. $^1$H NMR (300 MHz, DMSO-d$_6$): δ 10.04 (s, 1H), 8.15 (dd, $^3$J = 1.5, 0.8 Hz, 1H), 7.81 (m, 1H), 7.44 (m, $^4$J = 9.0 Hz, 2H), 6.85 (dd, $^3$J = 1.9, 0.8 Hz, 1H), 6.66 (m, 2H), 3.31 (q, $^3$J = 7.0 Hz, 4H), 2.56 (s, 3H), 1.07 (t, $^3$J = 7.0 Hz, 6H) ppm. $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ 169.1, 158.9, 153.5, 144.6, 144.2, 142.8, 127.1, 121.7, 114.0, 113.0, 111.8, 109.0, 43.7, 12.3, 11.9 ppm. HRMS calcd. for C$_{19}$H$_{21}$N$_3$O$_3$ [M+H]$^+$: 340.1661, found 340.1664.

N-[4-(Diethylamino)phenyl]-5,5'-dimethyl-[3,3'-bisoxazole]-4-carboxamide (39o)

i. (E/Z)-5-Methylisoxazole-3-carbaldehyde oxime (43o)

To a solution of 5-methylisoxazole-3-carbaldehyde 44o (0.200 g, 1.80 mmol) in MeOH (8 mL), hydroxylamine hydrochloride (138 mg, 1.98 mmol, 1.1 equiv) and sodium acetate (0.207 g, 2.52 mmol, 1.4 equiv) were added. After stirring at room temperature for 1 h, the reaction mixture was quenched with a mixture of a saturated solution of NH$_4$Cl in H$_2$O (10 mL) and water (5 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried with anhydrous Na$_2$SO$_4$, and the solvents were evaporated in vacuo to yield crude compound 43o (225 mg) as a white solid. $^1$H NMR (300 MHz, DMSO-d$_6$): δ 12.16 (s, 1H, minor), 11.94 (s, 1H, major), 8.13 (s, 1H, major), 7.61 (s, 1H, minor), 6.80 (d, $J = 1.0$ Hz, 1H, minor), 6.44 (d, $J = 0.7$ Hz,
1H, major), 2.45 (d, J = 0.9 Hz, 3H, minor), 2.43 (d, J = 0.9 Hz, 3H, major). 13C NMR (75 MHz, DMSO-d6) δ 169.9, 158.5, 154.5, 139.2, 135.5, 103.9, 98.7, 14.1, 11.7 ppm.

ii. Ethyl 5,5'-dimethyl-[3,3'-biisoxazole]-4-carboxylate (45o)

To a stirred solution of (E/Z)-5-methylisoxazole-3-carbaldehyde oxime 43o (126 mg, 1.00 mmol), ethyl 2-butyanoate (0.140 mL, 1.20 mmol, 1.2 equiv) and PhI (40.8 mg, 0.200 mmol, 0.20 equiv) in H2O (6 mL) was added Oxone® (922 mg, 3.00 mmol, 3.0 equiv) in small portions. The resulting solution was stirred at room temperature for 18 h, and the aqueous phase was extracted with dichloromethane (3 × 4 mL). The combined organic phases were dried with anhydrous Na2SO4, and the solvents were evaporated in vacuo. The crude product mixture was subjected to a purification by an automated flash silica chromatography (n-hexane/EtOAc, 10:1) to yield compound 45o (17 mg, 7.0%). 1H NMR (300 MHz, CDCl3): δ 6.40 (q, J = 0.9 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 2.73 (s, 3H), 2.50 (d, J = 0.9 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H) ppm. 13C NMR (75 MHz, CDCl3): δ 175.9, 169.8, 161.3, 153.6, 153.5, 109.3, 103.0, 61.2, 14.2, 13.4, 12.3 ppm.

iii. 5,5'-Dimethyl-[3,3'-biisoxazole]-4-carboxylic acid (41o)

To a solution of ethyl 5,5'-dimethyl-[3,3'-biisoxazole]-4-carboxylate 45o (16.8 mg, 0.075 mmol) in an equimixture of MeOH/H2O (2.2 mL), NaOH (6.0 mg, 0.15 mmol, 2.0 equiv) was added. The reaction mixture was stirred at room temperature for 28 h and then most of the MeOH was removed in vacuo. The aqueous layer was acidified with a 1 M solution of HCl in H2O to pH 1, and then extracted with dichloromethane (3 × 10 mL). The organic phase was dried with Na2SO4 and the solvents were evaporated in vacuo to give compound 41o (14.2 mg, 91%) as a white solid. 1H NMR (300 MHz, CDCl3): δ 6.67 (d, J = 0.9 Hz, 1H), 2.85 (s, 4H), 2.58 (d, J = 0.9 Hz, 4H) ppm. 13C NMR (75 MHz, CDCl3): δ 180.4, 171.7, 160.7, 154.4, 149.8, 108.4, 101.1, 14.0, 12.4 ppm.

iv. N-[4-(Diethylamino)phenyl]-5,5'-dimethyl-[3,3'-biisoxazole]-4-carboxamide (39o)

To a solution of 5,5'-dimethyl-[3,3'-biisoxazole]-4-carboxylic acid 41o (14.2 mg, 0.0683 mmol) in dry DMF (0.5 mL), N,N-diethyl-p-phenylenediamine 17 (11.8 µL, 0.0751 mmol, 1.1 equiv), HBTU (33.6 mg, 0.0887 mmol, 1.3 equiv), and DIPEA (23.8 µL, 137 mmol, 2.0 equiv) were added under argon. The reaction mixture was stirred at room temperature for 18 h. Diethyl ether (20 mL) was added, and the organic phase was washed with water (2 × 10 mL). The solvent was removed in vacuo, and the crude product mixture was subjected to a purification by an automated flash silica chromatography (n-hexane/EtOAc 1:0→0:1) to yield compound 39o (0.0196 g, 0.0553 mmol, 81%). M.p. 117.5-119.2 °C. 1H NMR (300 MHz, CDCl3): δ 10.87 (s, 1H), 7.53 (d, J = 9.1 Hz, 1H), 6.69 (d, J = 9.1 Hz, 2H), 6.62 (d, J = 1.1 Hz, 1H), 3.34 (q, J = 7.0 Hz, 4H), 2.88 (s, 3H), 2.55 (d, J = 0.9 Hz, 3H), 1.15 (t, J = 7.0 Hz, 6H) ppm. 13C NMR (75 MHz, CDCl3): δ 177.9, 170.7, 158.4, 155.6, 149.6, 145.4, 127.3, 122.4, 112.7, 111.5, 101.9, 44.8, 14.10, 12.7, 12.3 ppm. HRMS calc. for C19H23N6O3 [M+H]+: 355.1770, found 355.1771.
N-[4-(Diethylamino)phenyl]-5-methyl-3-(5-methylthiophen-2-yl)isoxazole-4-carboxamide (39p)

i. (E/Z)-2-Methylthiophene-2-carbaldehyde oxime (43p)

To a solution of 5-methylthiophene-2-carbaldehyde 44p (0.500 g, 3.96 mmol) in EtOH (10 mL), hydroxylamine hydrochloride (0.302 g, 4.36 mmol, 1.1 equiv) and pyridine (0.353 mL, 4.36 mmol, 1.1 equiv) were added. After stirring at room temperature for 4 h, the reaction mixture was quenched with a mixture of a saturated solution of NH₄Cl in H₂O (10 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried with anhydrous Na₂SO₄, and the solvents were evaporated in vacuo to yield compound 43p (542 mg, 97%) as a light orange solid.

1H NMR (300 MHz, Acetone-d₆): δ 11.14 (br, s, 1H, minor), 10.34 (br, s, 1H, major), 8.44 (d, J = 0.5 Hz, 1H, minor), 8.00 (d, J = 0.5 Hz, 1H, major), 7.97 (d, J = 0.6 Hz, 1H, major), 7.38 (d, J = 0.5 Hz, 1H, minor), 2.43 (s, 3H, minor), 2.41 (s, 3H, major) ppm.

13C NMR (75 MHz, Acetone-d₆): δ 162.8, 161.5, 143.4, 141.5, 140.0, 138.5, 138.3, 136.2, 13.6, 13.4 ppm.

ii. Ethyl 5-methyl-3-(5-methylthiophen-2-yl)isoxazole-4-carboxylate (45p)

To a stirred solution of (E/Z)-2-methylthiophene-2-carbaldehyde oxime 43p (0.100 g, 0.708 mmol), KCl (52.8 mg, 0.708 mmol) and Oxone® (326 mg, 1.1 mmol, 1.5 equiv) in H₂O (5 mL), ethyl 2-butyroate (0.206 mL, 1.77 mmol, 2.50 equiv) was added. The solution was stirred at room temperature for 5 h, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried with anhydrous Na₂SO₄, and the solvents were evaporated in vacuo. The crude product mixture was subjected to a purification by an automated flash silica chromatography (n-hexane/EtOAc, 95:5) yielded compound 45p (75.5 mg, 42%).

1H NMR (300 MHz, CDCl₃): δ 7.71 (d, 3J = 3.6 Hz, 1H), 6.78 (dq, 3J = 3.7, 1.0 Hz, 1H), 4.35 (q, 3J = 7.1 Hz, 2H), 2.69 (s, 3H), 2.52 (d, 4J = 1.1 Hz, 3H), 1.37 (t, 3J = 7.1 Hz, 3H).

iii. 5-Methyl-3-(5-methylthiophen-2-yl)isoxazole-4-carboxylic acid (41p)

To a solution of ethyl 5-methyl-3-(5-methylthiophen-2-yl)isoxazole-4-carboxylate 45p (94.0 mg, 0.374 mmol) in an equimixture of MeOH/H₂O (16 mL), NaOH (42.0 mg, 1.05 mmol, 2.8 equiv) was added. The reaction mixture was stirred at 60 °C for 20 h and then most of the MeOH was removed in vacuo. The aqueous layer was acidified with a 1 M solution of HCl in H₂O to pH 1, and then extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with brine (20 mL), and the solvents were evaporated in vacuo to give compound 41p (52.0 mg, 0.249 mmol, 66%).

1H (NMR 300 MHz, DMSO-d₆): δ 13.30 (s, 1H), 7.78 (d, 3J = 3.7 Hz, 1H), 6.89 (dq, 3J = 3.7, 0.9 Hz, 1H), 2.66 (s, 3H), 2.49 (d, 4J = 0.9 Hz, 3H).
To a solution of 5-methyl-3-(5-methylthiophen-2-yl)isoxazole-4-carboxylic acid 41p (0.040 g, 0.179 mmol) in dry DMF (2 mL), N,N-diethyl-p-phenylenediamine 17 (32.7 µL, 0.20 mmol, 1.1 equiv), HBTU (88.3 mg, 0.233 mmol, 1.3 equiv), and DIPEA (62.4 µL, 0.358 mmol, 2.0 equiv) were added under argon. The reaction mixture was stirred at room temperature for 18 h. Diethyl ether (20 mL) was added, and the organic phase was washed with water (2 × 10 mL). The solvent was removed in vacuo, and the crude product mixture was subjected to a purification by an automated flash silica chromatography (n-hexane/EtOAc 1:0→0:1). Recrystallization (MeOH/H2O 10:1) after the chromatographic purification gave compound 39p (47.6 mg, 0.129 mmol, 72%). M.p. 161.5–162.2 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.16 (s, 1H), 7.44 (m, 2H), 7.42 (d, 3J = 3.6 Hz, 1H), 6.86 (dd, 3,4J = 3.7, 1.1 Hz, 1H), 6.66 (m, 2H), 3.31 (q, 3J = 6.9 Hz, 4H), 2.52 (s, 3H), 2.47 (d, 4J = 1.1 Hz, 3H), 1.07 (t, 3J = 7.0 Hz, 6H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 169.2, 158.8, 154.9, 144.6, 142.5, 129.2, 127.1, 126.4, 126.3, 121.6, 112.8, 111.8, 43.8, 14.9, 12.4, 11.8 ppm. HRMS calc. for C20H24N3O2S [M+H]+: 370.1589, found 370.1588.

**N-[4-(Dimethylamino)phenyl]-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide (40)**

Synthesis according to the General procedure I. 5-Methyl-3-(3-nitrophenyl)isoxazole-4-carboxylic acid 41g (58.0 mg, 0.234 mmol), N,N-dimethyl-p-phenylenediamine 42 (31.8 mg, 0.234 mmol), HBTU (115 mg, 0.304 mmol, 1.3 equiv), DIPEA (81.5 µL, 0.468 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/2-propanol/ethyl acetate/H2O 30+20+10+1) after chromatography on silica gel gave compound 40 (67.0 mg, 0.183 mmol, 78%) as fine slightly orange needles. M.p. 202.2–203.9 °C (decomp.). 1H NMR (300 MHz, DMSO-d6): δ 10.14 (s, 1H), 8.56 (dd≈t, 1H, 4J = 2.0 Hz, 4J = 2.0 Hz), 8.37 (ddd, 1H, 3J = 8.3 Hz, 4J = 1.0 Hz), 8.16 (ddd≈ddt, 1H, 3J = 7.8 Hz), 7.82 (dd≈t, 1H), 7.42 (m, 2H), 6.71 (m, 2H), 2.86 (s, 6H), 2.62 (s, 3H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 170.4, 158.7, 158.6, 147.9, 147.7, 134.1, 130.5, 129.7, 127.8, 124.7, 122.4, 121.4, 113.4, 112.4, 40.3, 11.9 ppm. HRMS calc. for C19H19N4O4 [M+H]+: 367.1406, found 367.1409.
3-Ethyl-5-methyl-N-(4-oxo-2-phenyl-4H-chromen-6-yl)isoxazole-4-carboxamide (SI50)

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 4 d at room temperature. 3-Ethyl-5-methylisoxazole-4-carboxylic acid (50.0 mg, 0.322 mmol), 6-aminoflavone (76.5 mg, 0.322 mmol), HBTU (159 mg, 0.419 mmol, 1.3 equiv), DIPEA (0.112 mL, 0.644 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: ethyl acetate and water containing 30% brine. Chromatography on silica gel gave compound SI50 (78.9 mg, 0.211 mmol, 65%) as a yellowish solid. M.p. 197.9–198.7 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.40 (s, 1H), 8.42 (d, 1H, \(^4J = 2.7\) Hz), 8.15–8.09 (m, 2H), 8.06 (dd, 1H, \(^3J = 9.1\) Hz), 7.82 (d, 1H), 7.66–7.56 (m, 3H), 7.03 (s, 1H), 2.81 (q, 2H, \(^3J = 7.5\) Hz), 2.58 (s, 3H), 1.20 (t, 3H, \(^3J = 7.5\) Hz) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 176.8, 169.6, 163.2, 162.4, 160.3, 152, 136.1, 131.7, 131.1, 129.1, 126.4, 126.3, 123.5, 119.1, 114.2, 112.7, 106.5, 18.4, 12.1, 11.9 ppm. HRMS calc. for C\(_{159}\)H\(_{97}\)N\(_{15}\)O\(_{4}\) [M+H]: 375.1345, found 375.1351.

3-(2-Chlorophenyl)-5-methyl-N-(4-oxo-2-phenyl-4H-chromen-6-yl)isoxazole-4-carboxamide (SI51)

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 3 d at room temperature. 3-(2-Chlorophenyl)-5-methylisoxazole-4-carboxylic acid 41k (47.9 mg, 0.202 mmol), 6-aminoflavone 5g (47.8 mg, 0.202 mmol), HBTU (99.7 mg, 0.263 mmol, 1.3 equiv), DIPEA (70.4 µL, 0.404 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (2:1). Chromatography on silica gel gave compound SS51 (32.8 mg, 0.0718 mmol, 36%) as a yellow solid. M.p. 244.2–244.4 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.44 (s, 1H), 8.29 (d, 1H, \(^4J = 2.7\) Hz), 8.13–8.07 (m, 2H), 7.94 (dd, 1H, \(^3J = 9.1\) Hz, \(^4J = 2.7\) Hz), 7.78 (d, 1H, \(^3J = 9.1\) Hz), 7.65–7.46 (m, 7H), 7.02 (s, 1H), 2.71 (s, 3H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 176.8, 169.9, 162.4, 159.9, 159.6, 152.0, 136.0, 132.3, 131.8, 131.6, 131.1, 129.6, 129.1, 127.4, 127.3, 126.4, 126.3, 123.4, 119.1, 114.2, 106.5, 12.3 ppm. HRMS calc. for C\(_{26}\)H\(_{18}\)ClN\(_{2}\)O\(_{4}\) [M+H]: 457.0955, found 457.0956.

\(N\)-(4-Isopropyl-3-methylphenyl)-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide (SI52)

Synthesis according to the General procedure I. 5-Methyl-3-(3-nitrophenyl)isoxazole-4-carboxylic acid 41g (66.8 mg, 0.269 mmol), 4-isopropyl-3-methylaniline hydrochloride (50.0 mg, 0.269 mmol), HBTU (133 mg, 0.350 mmol, 1.3 equiv), DIPEA (0.141 mL, 0.807 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Recrystallization (EtOH/H\(_2\)O 10+1) without chromatography on silica gel gave compound SI52 (83.2 mg, 0.219 mmol, 82%) as fine white needles. M.p. 181.3–
182.4 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.30 (s, 1H), 8.55 (dd=bs, 1H), 8.36 (ddd, 1H, $^3J = 8.3$ Hz, $^4J = 2.4$ Hz, $^5J = 1.0$ Hz), 8.15 (dd=bd, 1H, $^3J = 7.8$ Hz), 7.81 (dd=dt, 1H), 7.45–7.34 (m, 2H), 7.19 (d, 1H), 3.06 (sept, 1H, $^3J = 6.8$ Hz), 2.62 (s, 3H), 2.27 (s, 3H), 1.16 (d, 6H, $^3J = 6.8$ Hz) ppm.

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 170.7, 159.2, 158.6, 147.9, 142.5, 135.6, 144.9, 134.1, 130.6, 129.6, 124.8, 124.7, 122.3, 121.6, 118.0, 113.3, 28.3, 23.0, 18.9, 12.0 ppm. HRMS calc. for C$_{21}$H$_{22}$N$_3$O$_4$ [M+H]$^+$: 380.1610, found 380.1614.

3-(2,6-Dichlorophenyl)-N-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carbothioamide (SI53)

Synthesis according to the General procedure V. 3-(2,6-Dichlorophenyl)-N-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide 39e (0.100 g, 0.239 mmol), Lawesson's reagent (58.0 mg, 0.143 mmol, 0.6 equiv), toluene (2 mL). Reaction time: 6 h. Recrystallization (EtOH) after chromatography on silica gel gave compound SI53 (76.0 mg, 0.175 mmol, 73%) as yellow crystals. M.p. 155.7–158.9 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 11.49 (s, 1H), 7.62–7.45 (m, 5H), 6.65 (m, 2H), 3.33 (q, 4H, $^3J = 7.0$ Hz), 2.62 (s, 3H), 1.08 (t, 6H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 182.7, 164.4, 158.2, 145.8, 134.8, 131.7, 128.2, 128.1, 127.6, 124.4, 110.7, 109.5, 43.7, 12.3, 12.0 ppm. HRMS calc. for C$_{21}$H$_{22}$Cl$_2$N$_3$OS [M+H]$^+$: 434.0861, found 434.0862.

Preparation of compounds in Table 1 and other related compounds

$N,N$-Diethyl-$p$-phenylenediamine hydrochloride (50)

$N,N$-Diethyl-$p$-phenylenediamine 17 (4.77 mL, 29.0 mmol) was dissolved in diethyl ether (13 mL). A 4 M solution of hydrochloric acid in 1,4-dioxane (7 mL) was added. The mixture was stirred for 2 h at room temperature. The solvent was removed with a rotary evaporator. The residue was treated with methanol and the solvent was removed with a rotary evaporator to give a solid material, which was recrystallized from 2-propanol, filtered and washed with ethyl acetate to give compound 50 (3.00 g, 14.9 mmol, 51%) as brownish white crystals, which was used without further purification or characterization.
**N-[4-(Diethylamino)phenyl]-5-phenyloxazole-4-carboxamide (47a)**

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction mixture was diluted with ethyl acetate for the work-up and extracted once with a 2 M solution of sodium hydroxide in water and twice with 4 M hydrochloric acid. The combined hydrochloric acid phases were made alkaline with a 2 M solution of sodium hydroxide in water and extracted twice with ethyl acetate. The combined organic phases were washed twice with a mixture of water and brine (10:1). 5-Phenyl-1,3-oxazole-4-carboxylic acid (50.0 mg, 0.264 mmol), N,N-diethyl-p-phenylenediamine hydrochloride 50 (62.4 mg, 0.311 mmol, 1.2 equiv), HBTU (0.300 g, 0.792 mmol, 3 equiv), DIPEA (0.230 mL, 1.32 mmol, 5 equiv), DMF (2.5 mL). Recrystallization (twice with MeOH/H\(_2\)O 10+1) [without chromatography on silica gel] gave compound 47a (56.0 mg, 0.167 mmol, 63%) as greenish plates. M.p. 85.1 – 88.4 °C. \(^1\)H NMR (300 MHz, DMSO-d\(_6\)): \(\delta\) 9.86 (s, 1H), 8.64 (s, 1H, 8.21–8.15 (m, 2H), 7.60–7.45 (m, 5H), 6.64 (m, 2H), 3.31 (q, 4H, \(J = 7.0\) Hz), 1.08 (t, 6H, \(J = 7.0\) Hz) ppm. \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)): \(\delta\) 158.6, 151.1, 150.1, 144.4, 129.8, 129.3, 128.4, 127.7, 126.9, 122.2, 111.6, 43.7, 12.4 ppm. HRMS calc. for C\(_{20}\)H\(_{22}\)N\(_3\)O\(_2\)[M+H]\(^+\): 336.1712, found 336.1711.

**N-[4-(Diethylamino)phenyl]-5-methyl-2-phenyl-2H-1,2,3-triazole-4-carboxamide (47b)**

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction mixture was diluted with diethyl ether for the work-up and washed with water, a 2 M solution of sodium hydroxide in water and twice with water. 5-Methyl-2-phenyl-2H-1,2,3-triazole-4-carboxylic acid 46b (102 mg, 0.500 mmol), N,N-diethyl-p-phenylenediamine hydrochloride 50 (118 mg, 0.588 mmol, 1.2 equiv), HBTU (284 mg, 0.750 mmol, 1.5 equiv), DIPEA (0.348 mL, 2.00 mmol, 4 equiv), DMF (3 mL). Recrystallization (MeOH/H\(_2\)O 10+1) after chromatography on silica gel gave compound 47b (137 mg, 0.392 mmol, 78%) as fine greenish crystals. M.p. 112.2–114.1 °C. \(^1\)H NMR (300 MHz, DMSO-d\(_6\)): \(\delta\) 10.06 (s, 1H), 8.15–8.08 (m, 2H), 7.65–7.43 (m, 5H), 6.70–6.62 (m, 2H), 3.32 (q, 4H, \(J = 7.0\) Hz), 2.57 (s, 3H) ppm. \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)): \(\delta\) 158.1, 146.8, 144.5, 140.8, 138.8, 129.7, 128.2, 126.8, 122.3, 118.7, 111.6, 43.7, 12.4, 11.1 ppm. HRMS calc. for C\(_{20}\)H\(_{24}\)N\(_5\)O [M+H]\(^+\): 350.1981, found 350.1980.
N-[4-(Diethylamino)phenyl]-5-phenylisoxazole-4-carboxamide (47d)

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction mixture was diluted with diethyl ether for the work-up and washed twice with water, twice with a 2 M solution of sodium hydroxide in water and twice with water. 5-Phenylisoxazole-4-carboxylic acid 46d (189 mg, 1.00 mmol), N,N-diethyl-p-phenylenediamine hydrochloride 50 (283 mg, 1.41 mmol, 1.4 equiv), HBTU (569 mg, 1.50 mmol, 1.5 equiv), DIPEA (0.697 mL, 4.00 mmol, 4 equiv), DMF (5 mL). Automated chromatography on silica gel gave compound 47d (136 mg, 0.405 mmol, 41%) as a brown-yellow resin. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.06 (s, 1H), 9.04 (s, 1H), 8.02–7.95 (m, 2H), 7.58–7.52 (m, 3H), 7.44 (m, 2H), 6.66 (m, 2H), 3.31 (q, 4H, $^3$$J$ = 7.0 Hz), 1.08 (t, 6H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 167.4, 158.2, 151.0, 144.5, 130.9, 128.7, 127.8, 127.0, 126.3, 121.9, 112.9, 111.7, 43.7, 12.3 ppm. HRMS calc. for C$_{20}$H$_{22}$N$_3$O$_2$ [M+H]$^+$: 336.1712, found 336.1711.

N-[4-(Diethylamino)phenyl]-1-methyl-5-phenyl-1H-pyrazole-4-carboxamide (47e)

Synthesis according to the General procedure I. 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid 46e (101 mg, 0.500 mmol), N,N-diethyl-p-phenylenediamine 17 (83.1 µL, 0.500 mmol), HBTU (247 mg, 0.650 mmol, 1.3 equiv), DIPEA (0.174 mL, 1.00 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Automated chromatography on silica gel gave compound 47e (92.1 mg, 0.264 mmol, 53%) as a white solid. M.p. 151.0–153.4 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 9.32 (s, 1H), 8.07 (s, 1H), 7.53–7.42 (m, 5H), 7.33 (m, 2H), 6.58 (m, 2H), 3.68 (s, 3H), 3.27 (q, 4H, $^3$$J$ = 7.0 Hz), 1.04 (t, 6H, $^3$$J$ = 7.1 Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 160.1, 144.0, 143.4, 137.8, 130.4, 129.2, 128.7, 128.0, 127.8, 121.8, 116.4, 111.8, 43.7, 37.0, 12.3 ppm. HRMS calc. for C$_{21}$H$_{23}$N$_4$O [M+H]$^+$: 349.2028, found 349.2026.

N-[4-(Diethylamino)phenyl]-1-methyl-3-(5-methylisoxazol-3-yl)-1H-pyrazole-4-carboxamide (47f)

Synthesis according to the General procedure I. 1-Methyl-3-(5-methylisoxazol-3-yl)-1H-pyrazole-4-carboxylic acid 46f (5.0 mg, 0.024 mmol), N,N-diethyl-p-phenylenediamine 17 (6.0 µL, 0.036 mmol, 1.5 equiv), HBTU (12 mg, 0.031 mmol, 1.3 equiv), DIPEA (8.4 µL, 0.048 mmol, 2 equiv), DMF (0.5 mL). Solvent for extraction: diethyl ether. Eluent for purification: MeOH/DCM 1:9. Chromatography on silica gel gave compound 47f (6.4 mg, 0.18 mmol, 75%) as a white solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 11.25 (s, 1H), 8.17 (s, 1H), 7.60 (m, 2H), 6.69 (m, 2H), 6.55 (d, $^4$$J$ = 0.9 Hz, 1H), 3.96 (s, 3H), 3.33 (q, $^3$$J$ = 7.0 Hz, 4H), 2.51 (d, $^4$$J$ = 0.9 Hz, 3H), 1.15 (t, $^3$$J$ = 7.0 Hz, 1H).
6H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 169.6, 159.3, 158.5, 145.0, 137.4, 137.1, 128.2, 122.1, 119.4, 112.9, 101.4, 44.8, 39.7, 12.7, 12.3 ppm. HRMS calc. for C\(_{10}\)H\(_{24}\)N\(_5\)O\(_2\) [M+H]\(^+\): 354.1930, found 354.1930.

**N-[4-(Diethylamino)phenyl]-5-methyl-2-(5-methylisoxazol-3-yl)furan-3-carboxamide (47h)**

Synthesis according to the General procedure I. 5-Methyl-2-(5-methylisoxazol-3-yl)furan-3-carboxylic acid 46h (5.0 mg, 0.024 mmol), \(N,N\)-diethyl-\(p\)-phenylenediamine 17 (6.0 \(\mu\)L, 0.036 mmol, 1.5 equiv), HBTU (12 mg, 0.031 mmol, 1.3 equiv), DIPEA (8.2 \(\mu\)L, 0.048 mmol, 2 equiv), DMF (0.5 mL). Solvent for extraction: diethyl ether. Eluent for purification: \(n\)-heptane/EtOAc 4:1. Chromatography on silica gel gave compound 47h (6.4 mg, 0.181 mmol, 75%) as a white solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 11.25 (s, 1H), 8.17 (s, 1H), 7.60 (m, 2H), 6.69 (m, 2H), 6.55 (d, \(^4J = 0.9\) Hz, 1H), 3.96 (s, 3H), 3.33 (q, \(^3J = 7.0\) Hz, 4H), 2.51 (d, \(^4J = 0.9\) Hz, 3H), 1.15 (t, \(^3J = 7.0\) Hz, 6H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 169.6, 159.3, 158.5, 145.0, 137.4, 137.1, 128.2, 122.1, 119.4, 112.9, 101.4, 44.8, 39.7, 12.7, 12.3 ppm. HRMS calc. for C\(_{20}\)H\(_{24}\)N\(_3\)O\(_3\) [M+H]\(^+\): 354.1818, found 354.1818.

**N-[4-(Diethylamino)phenyl]-2-[2-(thiophen-2-yl)ethyl]furan-3-carboxamide (47i)**

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 3 d. 2-[2-(Thiophen-2-yl)ethyl]furan-3-carboxylic acid 46i (25.0 mg, 0.112 mmol), \(N,N\)-diethyl-\(p\)-phenylenediamine 17 (18.7 \(\mu\)L, 0.112 mmol), HBTU (60.1 mg, 0.159 mmol, 1.3 equiv), DIPEA (39.0 \(\mu\)L, 0.224 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 47i (38.4 mg, 0.104 mmol, 93%) as a greyish resin. M.p. 89.9–91.5 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.34–7.28 (m, 3H), 7.10 (dd, 1H, \(J = 1.2\) Hz, \(J = 5.1\) Hz), 7.07 (bs, 1H), 6.90 (dd, 1H, \(J = 3.4\) Hz), 6.79 (m, 1H), 6.65 (m, 2H), 6.52 (bs, 1H), 3.42–3.22 (m, 8H), 1.15 (t, 6H, \(J = 7.0\) Hz) ppm. \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 161.8, 158.7, 145.6, 143.6, 141.0, 127.0, 126.4, 124.9, 123.6, 122.9, 117.2, 112.6, 108.7, 44.7, 29.9, 28.3, 12.7 ppm. HRMS calc. for C\(_{21}\)H\(_{25}\)N\(_2\)O\(_2\)S [M+H]\(^+\): 369.1637, found 369.1639.
N-[4-(Diethylamino)phenyl]-3-phenylcinnoline-4-carboxamide (47j)

Synthesis according to the General procedure I. 3-Phenylcinnoline-4-carboxylic acid 46j (53.6 mg, 0.214 mmol), N,N-diethyl-p-phenylenediamine 17 (35.6 µL, 0.214 mmol), HBTU (106 mg, 0.278 mmol, 1.3 equiv), DIPEA (74.5 µL, 0.428 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Recrystallization (EtOH/water 10+1) after chromatography on silica gel gave compound 47j (30.6 mg, 0.0772 mmol, 36%) as yellow needles. M.p. 246.3–249.9 ºC (decomp). 1H NMR (300 MHz, DMSO-d6): δ 10.40 (s, 1H), 8.62 (m, 1H), 8.07–7.93 (m, 5H), 7.59–7.47 (m, 3H), 7.32 (m, 2H), 6.63 (m, 2H), 3.30 (q, 4H, 3J = 7.0 Hz), 1.07 (t, 6H, 6J = 7.0 Hz) ppm. 13C NMR (75 MHz, DMSO-d6): δ 161.8, 150.3, 135.7, 129.6, 129.4, 129.3, 128.3, 70.2, 59.1, 55.5, 52.4 ppm. HRMS calc. for C25H23N4O [M+H]+: 397.2028, found 397.2033.

1-(2-Methoxyethyl)-4-phenyl-1H-1,2,3-triazole-5-carboxylic acid (46k)

i. Methyl 1-(2-methoxyethyl)-4-phenyl-1H-1,2,3-triazole-5-carboxylate (SI54)

Synthesis according to the General procedure VIII, method B. Methyl phenylpropionate (0.160 g, 1.00 mmol), 1-bromo-2-methoxynaphth (94.0 µL, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol), Solvent volume (2.5 mL). reaction conditions: first overnight at room temperature and then 70 min, 140 ºC. Chromatography on silica gel gave compound SI54 (121 mg, 0.463 mmol, 46%) as a colorless oil. 1H NMR (300 MHz, CDCl3): δ 7.89–7.81 (m, 2H), 7.48–7.38 (m, 3H), 4.68 (t, 2H, 3J = 5.7 Hz), 3.97 (t, 2H, 3J = 5.7 Hz), 3.92 (s, 3H), 3.36 (s, 3H) ppm. 13C NMR (75 MHz, CDCl3): δ 161.8, 150.3, 135.7, 129.6, 129.4, 129.3, 128.3, 70.2, 59.1, 55.5, 52.4 ppm. HRMS calc. for C13H16N3O [M+H]+: 262.1192, found 262.1190.

ii. 1-(2-Methoxyethyl)-4-phenyl-1H-1,2,3-triazole-5-carboxylic acid (46k)

A mixture of methyl 1-(2-methoxyethyl)-4-phenyl-1H-1,2,3-triazole-5-carboxylate SI54 (99.7 mg, 0.382 mmol) and lithium hydroxide monohydrate (24.0 mg, 0.572 mmol, 1.5 equiv) in an equimixture of THF, methanol and water (1.50 mL) was stirred for 2 d at room temperature. The reaction mixture was diluted with ethyl acetate and transferred to a separatory funnel. Water was added, and the mixture was acidified with 1 M hydrochloric acid. The phases were separated, the organic phase was washed neutral with three portions of water and the solvent was removed with a rotary evaporator to give compound 46k (83.3 mg, 0.337 mmol, 88%) as a brownish solid. The product was used as such
in next step without further purification. M.p. 114.0–114.3 °C. HRMS calc. for C_{12}H_{14}N_{3}O_{3} [M+H]^+: 248.1035, found 248.1037.

**N-[4-(Diethylamino)phenyl]-1-(2-methoxyethyl)-4-phenyl-1H-1,2,3-triazole-5-carboxamide (47k)**

Synthesis according to the General procedure I. 1-(2-Methoxyethyl)-4-phenyl-1H-1,2,3-triazole-5-carboxylic acid 46k (40.5 mg, 0.164 mmol), N,N-diethyl-p-phenylenediamine 17 (27.2 μL, 0.164 mmol), HBTU (80.9 mg, 0.213 mmol, 1.3 equiv), DIPEA (57.1 μL, 0.328 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether and a mixture of water with 20% brine. Chromatography on silica gel gave compound 47k (52.4 mg, 0.133 mmol, 81%) as a brownish oil. ¹H NMR (300 MHz, DMSO-d₆): δ 10.14 (s, 1H), 7.90–7.85 (m, 2H), 7.54–7.37 (m, 5H), 6.64 (m, 2H), 4.69 (t, 2H, J = 5.3 Hz), 3.93 (t, 2H, J = 5.3 Hz), 3.31 (q, 4H, J = 7.0 Hz), 3.28 (s, 3H), 1.07 (t, 6H, J = 7.0 Hz) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 158.7, 145.7, 144.4, 139.5, 129.6, 128.6, 128.3, 128.0, 127.0, 111.7, 69.5, 57.9, 54.5, 43.7, 12.3 ppm. HRMS calc. for C_{22}H_{28}N_{5}O_{2} [M+H]^+: 394.2243, found 394.2246.

**N-[4-(Diethylamino)phenyl]-5-methyl-2-(5-methylisoxazol-3-yl)thiophene-3-carboxamide (47l)**

Synthesis according to the General procedure I. 5-Methyl-2-(5-methylisoxazol-3-yl)thiophene-3-carboxylic acid 46l (5.0 mg, 0.022 mmol), N,N-diethyl-p-phenylenediamine 17 (5.6 μL, 0.034 mmol, 1.5 equiv), HBTU (11 mg, 0.029 mmol, 1.3 equiv), DIPEA (7.8 μL, 0.045 mmol, 2 equiv), DMF (0.5 mL). Solvent for extraction: diethyl ether. Eluent for purification: n-hexane/EtOAc, 4:1. Chromatography on silica gel gave compound 47l (5.3 mg, 0.14 mmol, 64%) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 9.81 (s, 1H), 7.51 (d, 3J = 8.9 Hz, 2H), 7.34 (m, 1H), 6.68 (d, 3J = 9.0 Hz, 2H), 6.27 (d, 4J = 0.9 Hz, 1H), 3.33 (q, 3J = 7.1 Hz, 4H), 2.50 (d, 4J = 1.1 Hz, 3H), 2.46 (d, 4J = 0.9 Hz, 3H), 1.15 (t, 3J = 7.0 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃): δ 170.22, 160.67, 157.45, 145.26, 141.03, 137.30, 130.01, 127.43, 126.45, 122.17, 112.61, 102.90, 44.74, 15.29, 12.69, 12.38. HRMS calc. for C_{20}H_{24}N_{3}O_{3} [M+H]^+: 370.1587, found 370.1588.

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N-[4-(Diethylamino)phenyl]-1-methyl-4-(5-methylisoxazol-3-yl)-1H-pyrrole-3-carboxamide (47m)

Synthesis according to the General procedure I. 1-Methyl-4-(5-methylisoxazol-3-yl)-1H-pyrrole-3-carboxylic acid 46m (5.0 mg, 0.024 mmol), N,N-diethyl-p-phenylenediamine 17 (8.1 µL, 0.049 mmol, 2.0 equiv), HATU (14 mg, 0.036 mmol, 1.5 equiv), DIPEA (8.5 µL, 0.049 mmol, 2 equiv), DMF (0.5 mL). Solvent for extraction: diethyl ether. Eluent for purification: MeOH/DCM, 1:9. Chromatography on silica gel gave compound 47m (7.1 mg, 0.020 mmol, 84%) as a brown solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 11.19 (s, 1H), 7.61 (d, \(J = 8.6\) Hz, 2H), 7.55 (d, \(J = 2.7\) Hz, 1H), 6.93 (d, \(J = 2.7\) Hz, 1H), 6.70 (d, \(J = 8.5\) Hz, 2H), 6.12 (d, \(J = 1.0\) Hz, 1H), 3.71 (s, 3H), 3.32 (q, \(J = 7.0\) Hz, 2H). HRMS calc. for C\(_{36}\)H\(_{37}\)N\(_3\)O\(_3\): 500.2522, found 500.2523. C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 168.79, 161.32, 158.46, 144.61, 130.46, 128.83, 124.55, 121.87, 119.29, 113.00, 109.64, 100.68, 44.72, 36.77, 12.55, 12.09 ppm. HRMS calc. for C\(_{20}\)H\(_{24}\)N\(_3\)O\(_3\) [M+H]^+: 353.1983, found 353.1981.

N-[4-(Diethylamino)phenyl]-4-phenyl-1,2,3-thiadiazole-5-carboxamide (47n)

Synthesis according to the General procedure I. 4-Phenyl-1,2,3-thiadiazole-5-carboxylic acid 46n (50.0 mg, 0.242 mmol), N,N-diethyl-p-phenylenediamine 17 (40.3 µL, 0.242 mmol), HBTU (119 mg, 0.315 mmol, 1.3 equiv), DIPEA (84.3 µL, 0.484 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Automated chromatography on silica gel gave compound 47n (40.9 mg, 0.116 mmol, 48%) as a brown resin. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.62 (s, 1H), 7.96–7.89 (m, 2H), 7.60–7.46 (m, 3H), 7.39 (m, 2H), 6.65 (m, 2H), 3.31 (q, 4H, \(J = 7.0\) Hz), 1.07 (t, 6H, \(J = 7.0\) Hz) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 158.6, 156.7, 145.0, 144.9, 130.1, 129.5, 129.0, 128.0, 126.5, 121.6, 111.6, 43.7, 12.3 ppm. HRMS calc. for C\(_{19}\)H\(_{21}\)N\(_4\)OS [M+H]^+: 353.1436, found 353.1434.

Methyl 1-methyl-4-phenyl-1H-1,2,3-triazole-5-carboxylate (46o) and methyl 1-methyl-5-phenyl-1H-1,2,3-triazole-4-carboxylate (46p)

Synthesis according to the General procedure VIII, method B. Methyl phenylpropiolate (0.160 g, 1.00 mmol), iodomethane (62.3 µL, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol). Solvent volume: 2.5 mL. Reaction conditions: first overnight at room temperature, then 160 min 130 °C. Chromatography on silica gel gave compound 46o (35.0 mg, 0.161 mmol, 16%) as a white solid and 46p (37.1 mg, 0.171 mmol, 17%) as a colorless resin. Both compounds were slightly impure and used in the next step without further purification. Compound 46o: M.p. 139–145 °C (decomp.). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.76–7.68 (m, 2H), 7.50–7.38 (m, 3H), 4.35 (s, 3H), 3.87 (s, 3H) ppm. \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 161.7, 150.6, 129.5, 129.1, 128.2, 52.5, 38.5 ppm.
HRMS calc. for C_{11}H_{12}N_{3}O_{2} \text{[M+H]}^+: 218.0930, found 218.0936. Compound 46p: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.57–7.48 (m, 3H), 7.46–7.34 (m, 2H), 3.95 (s, 3H), 3.86 (s, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 161.6, 148.2, 141.6, 136.6, 130.4, 129.8, 129.0, 128.9, 125.9, 52.1, 35.6 ppm. HRMS calc. for C_{11}H_{12}N_{3}O_{2} \text{[M+H]}^+: 218.0930, found 218.0930.

N-[4-(Diethylamino)phenyl]-1-methyl-4-phenyl-1H-1,2,3-triazole-5-carboxamide (47o)

Synthesis according to the General procedure VI. Methyl 1-methyl-4-phenyl-1H-1,2,3-triazole-5-carboxylate 46o (33.8 mg, 0.156 mmol), LiOH·H$_2$O (9.80 mg, 0.233 mmol, 1.5 equiv). solvent volume: 300 $\mu$L each. N,N-diethyl-p-phenylenediamine 17 (25.9 $\mu$L, 0.156 mmol), HBTU (76.9 mg, 0.203 mmol, 1.3 equiv), DIPEA (54.3 $\mu$L, 0.312 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Recrystallization (EtOH) after chromatography on silica gel gave compound 47o (12.4 mg, 0.0355 mmol, 23%) as a white solid. M.p. 167.5–171.1 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.54 (s, 1H), 7.80–7.75 (m, 2H), 7.50–7.34 (m, 5H), 6.67 (m, 2H), 4.11 (s, 3H), 3.32 (q, 4H, $^3$J = 7.0 Hz), 1.08 (t, 6H, $^3$J = 7.0 Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 156.7, 144.9, 143.4, 130.4, 130.1, 128.7, 128.2, 126.4, 126.2, 121.6, 111.7, 43.7, 35.6, 12.3 ppm. HRMS calc. for C$_{20}$H$_{24}$N$_5$O [M+H]$^+$: 350.1981, found 350.1981.

N-[4-(Diethylamino)phenyl]-1-methyl-5-phenyl-1H-1,2,3-triazole-4-carboxamide (47p)

Synthesis according to the General procedure VI. Methyl 1-methyl-5-phenyl-1H-1,2,3-triazole-4-carboxylate 46p (36.5 mg, 0.168 mmol), LiOH·H$_2$O (10.6 mg, 0.252 mmol, 1.5 equiv). Solvent volume: 0.30 mL each. N,N-diethyl-p-phenylenediamine 17 (27.9 $\mu$L, 0.168 mmol), HBTU (82.8 mg, 0.218 mmol, 1.3 equiv), DIPEA (58.5 $\mu$L, 0.336 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 47p (22.7 mg, 0.0650 mmol, 39%) as a brownish resin. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.00 (s, 1H), 7.60–7.48 (m, 7H), 6.60 (m, 2H), 3.95 (s, 3H), 3.29 (q, 4H, $^3$J = 7.0 Hz), 1.06 (t, 6H, $^3$J = 7.0 Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 157.8, 144.2, 139.0, 138.5, 130.0, 129.4, 128.1, 127.2, 126.0, 121.9, 111.7, 43.7, 35.4, 12.3 ppm. HRMS calc. for C$_{20}$H$_{24}$N$_5$O [M+H]$^+$: 350.1981, found 350.1982.
Synthesis according to the General procedure I. 1-Methyl-5-phenoxy-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid 46q

N,N-diethyl-p-phenylenediamine 17 (14.5 μL, 0.0873 mmol), HBTU (43.0 mg, 0.113 mmol, 1.3 equiv), DIPEA (30.4 μL, 0.175 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 47q (34.1 mg, 0.0789 mmol, 90%) as a white solid. M.p. 152.8–154.2 °C (decomp.).

1H NMR (300 MHz, CDCl3): δ 7.54 (s, 1H), 7.44–7.36 (m, 2H), 7.23–7.14 (m, 3H), 7.01 (m, 2H), 6.56 (m, 2H), 3.71 (s, 3H), 3.29 (q, 4H, J = 7.0 Hz), 1.10 (t, 6H, J = 7.0 Hz) ppm. 13C NMR (75 MHz, CDCl3): δ 156.7, 155.7, 149.1, 144.4, 127.0, 124.3, 122.0, 111.7, 43.7, 12.4 ppm. HRMS calc. for C22H24F3N4O2 [M+H]+: 433.1851, found 433.1860.

5-Cyclopropyl-N-[4-(diethylamino)phenyl]isoxazole-4-carboxamide 47r

Synthesis according to the General procedure I. 5-Cyclopropylisoxazole-4-carboxylic acid 46r (153 mg, 1.00 mmol), N,N-diethyl-p-phenylenediamine 17 (0.166 mL, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave an oil that was crystallized on cooling its solution in MeOH/H2O (20+1) in a refrigerator to yield compound 47r (41.0 mg, 0.137 mmol, 14%) as slightly pink needles. M.p. 132.1–140.0 °C (decomp.). 1H NMR (300 MHz, DMSO-d6): δ 9.68 (s, 1H), 9.00 (s, 1H), 7.43 (m, 2H), 6.66 (m, 2H), 3.31 (q, 4H, J = 7.0 Hz), 2.99–2.89 (m, 1H), 1.24–1.05 (m, 10H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 175.7, 158.5, 149.1, 144.4, 126.9, 122.3, 111.8, 111.7, 43.7, 12.3, 9.5, 8.1 ppm. HRMS calc. for C17H22N3O2 [M+H]+: 300.1712, found 300.1716.

N-[4-(Diethylamino)phenyl]isothiazole-4-carboxamide 47s

Synthesis according to the General procedure I. 4-Isothiazolecarboxylic acid (258 mg, 2.00 mmol), N,N-diethyl-p-phenylenediamine 17 (0.333 mL, 2.00 mmol), HBTU (986 mg, (2.60 mmol, 1.3 equiv), DIPEA (0.697 mL, 4.00 mmol, 2 equiv), DMF (5 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H2O 10+1) without chromatography on silica gel gave compound 47s (449 mg, 1.29 mmol, 64%) as brown crystals. M.p. 112.7–115.0 °C. 1H NMR (300 MHz, DMSO-d6): δ 9.95 (s, 1H), 9.23 (d, 1H, J = 2.0 Hz), 8.40 (d, 1H, J = 2.0 Hz), 7.59 (m, 2H), 6.64 (m, 2H), 3.31 (q, 4H, J = 7.0 Hz), 1.07 (t, 6H, J = 7.0 Hz) ppm. 13C NMR (75 MHz, DMSO-d6): δ 159.3, 154.7, 151.1, 144.4, 127.0, 124.3, 122.0, 111.7, 43.7, 12.4 ppm. HRMS calc. for C14H18N5O2 [M+H]+: 276.1171, found 276.1183.
**N-[4-(Diethylamino)phenyl]-5-methyl-4-phenylthiophene-3-carboxamide (47t)**

Synthesis according to the General procedure I. 5-Methyl-4-phenylthiophene-3-carboxylic acid, 46t, (0.100 g, 0.458 mmol), N,N-diethyl-p-phenylenediamine 17 (76.2 μL, 0.458 mmol), HBTU (226 mg, 0.595 mmol, 1.3 equiv), DIPEA (0.160 mL, 0.916 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H2O 10+1) without chromatography on silica gel gave compound 47t (99.0 mg, 0.272 mmol, 59%) as brown crystals. M.p. 118.8–119.6 °C. 1H NMR (300 MHz, DMSO-δ6): δ9.65 (s, 1H), 7.73 (s, 1H), 7.42–7.24 (m, 7H), 6.57 (m, 2H), 3.26 (q, 4H, 2J = 7.0 Hz), 2.32 (s, 3H), 1.04 (t, 6H) ppm. 13C NMR (75 MHz, DMSO-δ6): δ162.2, 144.1, 139.1, 137.4, 135.4, 135.4, 135.3, 129.3, 127.9, 127.8, 126.8, 123.6, 121.4, 111.8, 43.7, 13.6, 12.3 ppm. HRMS calc. for C22H25N2OS [M+H]+: 365.1688, found 365.1692.

**N-[4-(Diethylamino)phenyl]-5-nitrothiophene-3-carboxamide (47u)**

Synthesis according to the General procedure I. 5-Nitrothiophene-3-carboxylic acid 46u (23.2 mg, 0.134 mmol), N,N-diethyl-p-phenylenediamine 17 (22.3 μL, 0.134 mmol), HBTU (66.1 mg, 0.174 mmol, 1.3 equiv), DIPEA (46.7 μL, 0.268 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 47u (35.3 mg, 0.111 mmol, 82%) as an orange solid. M.p. 197.9–200.1 °C. 1H NMR (300 MHz, DMSO-δ6): δ10.01 (s, 1H), 8.64 (d, 1H, J = 1.9 Hz), 8.61 (d, 1H, J = 1.9 Hz), 7.49 (m, 2H), 6.66 (m, 2H), 3.31 (q, 4H, 2J = 7.0 Hz), 1.08 (t, 6H, J = 7.0 Hz) ppm. 13C NMR (75 MHz, DMSO-δ6): δ158.2, 151.1, 144.5, 136.8, 136.8, 128.0, 126.8, 122.2, 111.6, 43.7, 12.4 ppm. HRMS calc. for C15H18N2O5S [M+H]+: 320.1069, found 320.1071.

**N-[4-(Diethylamino)phenyl]thieno[2,3-d][1,2,3]thiadiazole-6-carboxamide (47v)**

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 3 d. Thieno[2,3-d][1,2,3]thiadiazole-6-carboxylic acid 46v (25.0 mg, 0.134 mmol), N,N-diethyl-p-phenylenediamine 17 (22.3 μL, 0.134 mmol), HBTU (66.1 mg, 0.174 mmol, 1.3 equiv), DIPEA (46.7 μL, 0.268 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 47v (34.9 mg, 0.105 mmol, 78%) as a beige solid. M.p. 188.4–194.8 °C (decomp.). 1H NMR (300 MHz, DMSO-δ6): δ10.35 (s, 1H), 9.12 (s, 1H), 7.51 (m, 2H), 6.68 (m, 2H), 3.32 (q, 4H, 2J = 7.1 Hz), 1.09 (t, 6H, 2J = 7.1 Hz) ppm. 13C NMR (75 MHz, DMSO-δ6): δ161.8, 157.6, 146.7, 144.6, 137.60, 126.9, 126.6, 122.2, 111.6, 43.7, 12.3 ppm. HRMS calc. for C15H17N3O5S2 [M+H]+: 332.0766, found 332.4437.
**N-[4-(Diethylamino)phenyl]-3,5-bis(methylthio)isothiazole-4-carboxamide (47w)**

Synthesis according to the General procedure I. 3,5-Bis(methylthio)isothiazole-4-carboxylic acid 46w (24.8 mg, 0.112 mmol), N,N-diethyl-p-phenylenediamine 17 (18.6 µL, 0.112 mmol), HBTU (55.2 mg, 0.146 mmol, 1.3 equiv), DIPEA (39.0, µL 0.224 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 47w (26.2 mg, 0.713 mmol, 64%) as a white solid. M.p. 138.9–142.2 °C. 1H NMR (300 MHz, DMSO-d6): δ 9.88 (s, 1H), 7.42 (m, 2H), 6.65 (m, 2H), 3.31 (q, 4H, \( ^3J = 7.0 \) Hz), 2.63, 2.59 (each s, each 3H), 1.07 (t, 6H, \( ^3J = 7.0 \) Hz) ppm. 13C NMR (75 MHz, DMSO-d6): δ 165.4, 162.6, 159.0, 144.5, 128.9, 127.2, 121.3, 111.8, 43.7, 17.3, 13.5, 12.3 ppm. HRMS calc. for C_{16}H_{22}N_3O_3 [M+H]^+: 368.0925, found 368.0930.

**N-[4-(Diethylamino)phenyl]-5-(furan-2-yl)oxazole-4-carboxamide (47x)**

Synthesis according to the General procedure I. 5-(Furan-2-yl)oxazole-4-carboxylic acid 46x (35.1 mg, 0.196 mmol), N,N-diethyl-p-phenylenediamine 17 (32.6 µL, 0.196 mmol), HBTU (96.6 mg, 0.255 mmol, 1.3 equiv), DIPEA (68.3 µL, 0.392 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: a mixture of ethyl acetate and diethyl ether (2:1) and water. Chromatography on silica gel gave compound 47x (57.1 mg, 0.175 mmol, 90%) as a white solid. M.p. 88.2–90.5 °C. 1H NMR (300 MHz, DMSO-d6): δ 9.79 (s, 1H), 8.61 (s, 1H), 7.94 (dd, 1H, \( ^4J = 0.8 \) Hz, \( ^3J = 1.8 \) Hz), 7.72 (dd, 1H, \( ^3J = 3.5 \) Hz, \( ^4J = 0.8 \) Hz), 7.57 (m, 2H), 6.73 (dd, 1H, \( ^3J = 3.5 \) Hz, \( ^4J = 1.8 \) Hz), 6.64 (m, 2H), 3.31 (q, 4H, \( ^3J = 7.0 \) Hz), 1.08 (t, 6H, \( ^3J = 7.0 \) Hz) ppm. 13C NMR (75 MHz, DMSO-d6): δ 158.0, 149.8, 145.0, 144.4, 143.5, 141.8, 127.9, 126.8, 122.2, 114.5, 112.3, 111.6, 43.7, 12.4 ppm. HRMS calc. for C_{18}H_{20}N_3O_3 [M+H]^+: 326.1505, found 326.1514.

**5-(4-Bromophenyl)-N-[4-(diethylamino)phenyl]-2-(trifluoromethyl)furan-3-carboxamide (47y)**

Synthesis according to the General procedure I. 5-(4-Bromophenyl)-2-(trifluoromethyl)furan-3-carboxylic acid 46 (33.7 mg, 0.101 mmol), N,N-diethyl-p-phenylenediamine 17 (16.7 µL, 0.101 mmol), HBTU (47.8 mg, 0.131 mmol, 1.3 equiv), DIPEA (35.2 µL, 0.202 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether and water/brine (2:1). Chromatography on silica gel gave compound 47y (41.4 mg, 0.0860 mmol, 85%) as a yellow solid. M.p. 132.2–135.2 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.15 (s, 1H), 7.75 (m, 4H), 7.61 (q=sd, 1H, \( ^3J = 1.0 \) Hz), 7.46 (m, 2H), 6.66 (m, 2H), 3.31 (q, 4H, \( ^3J = 7.0 \) Hz), 1.08 (t, 6H, \( ^3J = 7.0 \) Hz) ppm. 13C NMR (75 MHz, DMSO-d6): δ 157.5, 153.3, 144.6, 137.5 (q, \( ^3J = 41.8 \) Hz), 132.2, 127.2, 127.0 (q, \( ^3J = 2.5 \) Hz), 126.8, 126.2, 122.7,
121.7, 118.8 (q, \( J = 268.2 \) Hz), 111.7, 107.5, 43.7, 12.3 ppm. HRMS calc. for C\(_{22}\)H\(_{21}\)BrF\(_3\)N\(_2\)O\(_2\) [M+H]: 481.0739, found 481.0740.

**N-[4-(Diethylamino)phenyl]-1-(4-fluorophenyl)-2-(methylthio)-1H-imidazole-5-carboxamide (47z)**

Synthesis according to the General procedure I. 1-(4-Fluorophenyl)-2-(methylthio)-1H-imidazole-5-carboxylic acid (91.0 mg, 0.361 mmol), \( N,N \)-diethyl-\( p \)- phenylenediamine 17 (60.0 \( \mu \)L, 1 equiv), HBTU (178 mg, 0.469 mmol, 1.3 equiv), DIPEA (0.126 mL, 0.722 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H\(_2\)O 10+1) without chromatography on silica gel gave compound 47z (133 mg, 0.333 mmol, 92%) as white needles. M.p. 197.0–198.7 °C. \( ^1 \)H NMR (300 MHz, DMSO-\( d_6 \)): \( \delta \) 9.73 (s, 1H), 7.86 (s, 1H), 7.40–7.27 (m, 6H), 6.58 (m, 2H), 3.27 (q, 4H, \( ^3 \)\( J = 7.0 \) Hz), 2.54 (s, 3H, S), 1.04 (t, 6H) ppm. \( ^{13} \)C NMR (75 MHz, DMSO-\( d_6 \)): \( \delta \) 161.8 (d, \( ^3 \)\( J = 245.8 \) Hz), 156.3, 148.5, 144.1, 132.2, 129.6, 129.5 (d, \( ^3 \)\( J = 9.2 \) Hz), 127.2, 121.9, 115.7 (d, \( ^3 \)\( J = 22.8 \) Hz), 111.7, 43.7, 14.3, 12.3 ppm. HRMS calc. for C\(_{21}\)H\(_{24}\)FN\(_4\)OS [M+H]: 399.1655, found 399.1657.

**N-[4-(Diethylamino)phenyl]imidazo[1,2-a]pyrimidine-3-carboxamide (47aa)**

Synthesis according to the General procedure I. Imidazo[1,2-\( a \)]pyrimidine-3-carboxylic acid 46aa (79.1 mg, 0.485 mmol), \( N,N \)-diethyl-\( p \)- phenylenediamine 17 (86.6 \( \mu \)L, 0.485 mmol), HBTU (239 mg, 0.631 mmol, 1.3 equiv), DIPEA (0.169 mL, 0.970 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: ethyl acetate. Recrystallization (MeOH/H\(_2\)O 10+1) without chromatography on silica gel gave compound 47aa (98.0 mg, 0.317 mmol, 65%) as fine beige crystals. M.p. 238.5–241.3 °C (decomp.). \( ^1 \)H NMR (300 MHz, DMSO-\( d_6 \)): \( \delta \) 10.02 (s, 1H), 9.77 (dd, 1H, \( ^3 \)\( J = 6.9 \) Hz, \( ^4 \)\( J = 2.0 \) Hz), 8.72 (dd, 1H, \( ^3 \)\( J = 4.2 \) Hz), 8.65 (s, 1H), 7.50 (m, 2H), 7.28 (dd, 1H), 7.68 (m, 2H), 3.32 (q, 4H, \( ^3 \)\( J = 7.0 \) Hz), 1.09 (t, 6H, \( ^3 \)\( J = 7.0 \) Hz) ppm. \( ^{13} \)C NMR (75 MHz, DMSO-\( d_6 \)): \( \delta \) 157.6, 151.9, 149.6, 144.4, 137.8, 135.9, 126.8, 122.3, 116.9, 111.7, 110.2, 43.7, 12.4 ppm. HRMS calc. for C\(_{17}\)H\(_{20}\)N\(_5\)O [M+H]: 310.1668, found 310.1675.
N-[4-(Diethylamino)phenyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide (47ab)

Synthesis according to the General procedure I. 2-Methylimidazo[1,2-a]pyridine-3-carboxylic acid 46ab (0.100 g, 0.568 mmol), N,N-diethyl-p-phenylenediamine 17 (94.4 µL, 0.568 mmol), HBTU (0.280 g, 0.738 mmol, 1.3 equiv), DIPEA (0.198 mL, 1.14 mmol, 2 equiv), DMF (5 mL). Solvent for extraction: ethyl acetate. Automated chromatography on silica gel gave compound 47ab (73.0 mg, 0.226 mmol, 40%) as greyish crystals. M.p. 176.3–177.3 °C (decomp.). 1H NMR (300 MHz, DMSO-d6): δ 9.53 (s, 1H), 8.91 (dddt, 1H, J = 6.9 Hz, 4J = 1.2 Hz, 4J = 1.2 Hz), 7.58 (dddt, 1H, 2J = 9.0 Hz), 7.48 (m, 2H), 7.38 (dddt, 1H), 7.02 (dddt, 1H), 7.68 (m, 2H), 3.32 (q, 4H, J = 7.0 Hz), 2.62 (s, 3H), 1.09 (t, 6H) ppm. 13C NMR (75 MHz, DMSO-d6): 158.7, 145.1, 144.9, 144.4, 127.3, 126.9, 126.4, 122.0, 116.1, 112.8, 111.9, 43.7, 15.4, 12.3 ppm. HRMS calc. for C19H23N4O [M+H]+: 323.1872, found 323.1876.

N-[4-(Diethylamino)phenyl]-2-(trifluoromethyl)isonicotinamide (47ac)

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 3 d at room temperature. 2-(Trifluoromethyl)isonicotinic acid 46ac (0.100 g, 0.523 mmol) N,N-diethyl-p-phenylenediamine 17 (87.0 µL, 0.523 mmol), HBTU (258 mg, 0.680 mmol, 1.3 equiv), DIPEA (0.182 mL, 1.05 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 47ac (163 mg, 0.483 mmol, 92%) as an orange resin. M.p. 107.4–108.9 °C (decomp.). 1H NMR (300 MHz, CDCl3): δ 10.37 (s, 1H), 8.96 (d, 1H, J = 5.0 Hz), 8.34 (bd, 1H), 8.18 (dd, 1H, J = 1.2 Hz), 7.54 (m, 2H), 6.68 (m, 2H), 3.32 (q, 4H, J = 7.0 Hz), 1.09 (t, 6H, J = 7.0 Hz) ppm. 13C NMR (75 MHz, CDCl3): δ 161.3, 150.9, 147.0 (q, J = 34.0 Hz), 144.8, 144.2, 126.7, 125.1, 122.3, 121.5 (q, J = 274.2 Hz), 118.2 (q, J = 2.8 Hz), 111.5, 43.7, 12.3 ppm. HRMS calc. for C17H19F3N3O [M+H]+: 338.1480, found 338.1482.

(E)-N-[4-(Diethylamino)phenyl]-5-[(4-(diethylamino)phenyl)imino]methyl]-3-phenylisoxazole-4-carboxamide (48)

5-Methyl-3-phenylisoxazole-4-carboxylic acid (2.03 g, 10.0 mmol) was dissolved in carbon tetrachloride (40 mL) under argon. N-Bromosuccinimide (1.78 g, 10.0 mmol) and benzylo peroxyxide (242 mg, 1.00 mmol) were added, and the reaction mixture was heated under reflux conditions for 8.5 h at 60 °C, stirred at room temperature overnight and heated for 6 h at 60 °C. The solution was filtered after cooling to rt, washed once with water and the aqueous phase was extracted once with DCM. The combined organic phases were extracted with a 2 M solution of sodium hydroxide in H2O. The aqueous phase was acidified with 1 M hydrochloric acid and extracted with ethyl acetate. The organic
phase was washed neutral with water (twice). The solvent was removed with a rotary evaporator and the crude product was subjected to automated chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate, but it was not able to separate the mixture of intermediates. The resulting crude product mixture (380 mg) was dissolved in absolute DMF (5 mL). N,N-Diethyl-p-phenylenediamine hydrochloride 50 (442 mg, 1.87 mmol), HBTU (1.42 g, 3.74 mmol) and DIPEA (1.63 mL, 9.35 mmol) were added to the solution, and the reaction mixture was stirred for 2 d at room temperature. The reaction mixture was diluted with ethyl acetate, and washed with a mixture of water and brine (50%). The phases were separated and the aqueous phase was extracted once with ethyl acetate. The combined organic phases were washed once with a small amount of water and the solvent was removed with a rotary evaporator. The crude product was subjected to automated chromatography. Recrystallization (MeOH/H2O 10+1) after automated chromatography on silica gel, using an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate, gave compound 48 (129 mg, 0.253 mmol, 3%) as fine orange needles. M.p. 175.3–177.0 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.63 (s, 1H), 8.70 (s, 1H), 7.80–7.74 (m, 2H), 7.59–7.49 (m, 3H), 7.43, 7.38 (each m, each 2H), 6.71, 6.65 (each m, each 2H), 3.39, 3.31 (each q, each 4H, each 2H). HRMS calc. for C31H33N3O2 [M+2H]2+: 255.6474, found 255.6479.

Methyl (E)-5-[[4-(diethylamino)phenyl]imino]methyl]-3-phenylisoxazole-4-carboxylate (51)

i. Methyl 5-(bromomethyl)-3-phenylisoxazole-4-carboxylate (53)

Methyl 5-methyl-3-phenylisoxazole-4-carboxylate (2.17 g, 10.0 mmol) was dissolved in carbon tetrachloride (40 mL) under argon. N-Bromosuccinimide (1.78 g, 10.0 mmol) and benzoylperoxide (242 mg, 1.00 mmol, 0.1 equiv) were added, and the reaction mixture was heated under reflux conditions for 6 h to 60 °C and stirred at room temperature for 4 d. The solution was dissolved to ethyl acetate and extracted three times with H2O. The solvent was removed with a rotary evaporator, and the crude product was subjected to automated chromatography. The chromatography on silica gel, with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate gave compound 53, which was used in a next step without further purification.

ii. Methyl (E)-5-[[4-(diethylamino)phenyl]imino]methyl]-3-phenylisoxazole-4-carboxylate (51)

Crude mixture of methyl 5-(bromomethyl)-3-phenylisoxazole-4-carboxylate 53 (135 mg, purity ~50%) was dissolved in methanol (2 mL) and N,N-diethyl-p-phenylenediamine 17 (0.0758 mL, 0.456 mmol) was added to the solution. The reaction mixture was irradiated in a microwave (30 min, 120 °C). Diethyl ether was added, and organic phase was washed twice with a 0.5 M solution of NaOH in H2O and two times with H2O and brine. Recrystallization (EtOH/H2O) without chromatography gave compound 51 (61 mg, 0.16 mmol, 2%) as red needles. M.p. 109.7–111.0 °C. 1H NMR (300 MHz, DMSO-d6): δ 8.91
(s, 1H), 7.71–7.65 (m, 2H), 7.59–7.49 (m, 3H), 7.45 (m, 2H), 6.76 (m, 2H), 3.80 (s, 3H), 3.42 (q, 4H, \(^3J = 7.0\) Hz), 1.13 (t, 6H) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 169.0, 162.2, 161.2, 148.5, 137.8, 136.4, 130.2, 129.1, 128.3, 127.5, 124.5, 111.5, 110.6, 52.3, 44.0, 12.5 ppm. HRMS calc. for C\(_{22}\)H\(_{24}\)N\(_3\)O\(_3\) [M+H]+: 378.1818, found 378.1823.

Methyl 1-allyl-4-phenyl-1\(H\)-1,2,3-triazole-5-carboxylate (SI55)

Synthesis according to the General procedure VIII, Method A. Methyl phenylpropionate (0.160 g, 1.00 mmol), allyl bromide (86.5 \(\mu\)L, 1.00 mmol), TBAB (322 mg, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol), solvent volume: 1.5 mL each. Reaction conditions: 150 °C for 70 min. Solvent for extraction: once with ethyl acetate and once with toluene. Chromatography on silica gel gave compound SI55 (21.2 mg, 0.0871 mmol, 9%) as a brownish oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.76–7.69 (m, 2H), 7.48–7.39 (m, 3H), 6.07 (m, 1H), 5.38–5.21 (m, 4H), 3.85 (s, 3H) ppm. \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 159.8, 150.5, 131.8, 130.4, 129.4, 129.1, 128.2, 124.0, 119.4, 53.3, 52.5 ppm. HRMS calc. for C\(_{13}\)H\(_{14}\)N\(_3\) [M+H]+: 244.1086, found 244.1092.

1-Allyl-N-[4-(diethylamino)phenyl]-4-phenyl-1\(H\)-1,2,3-triazole-5-carboxamide (SI56)

Synthesis according to the General procedure VI. Deviating from the General procedure VI, both reaction times were 2 d at room temperature. Methyl 1-allyl-5-phenyl-1\(H\)-1,2,3-triazole-4-carboxylate SI55 (19.8 mg, 0.0814 mmol), LiOH-H\(_2\)O (5.10 mg, 0.122 mmol, 1.5 equiv), solvent volume: 200 \(\mu\)L each. N,N-Diethyl-\(p\)-phenylenediamine (13.5 \(\mu\)L, 0.0814 mmol), HBTU (40.1 mg, 0.106 mmol, 1.3 equiv), DIPEA (28.4 \(\mu\)L, 0.163 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate. Chromatography on silica gel gave compound SI56 (21.9 mg, 0.0583 mmol, 72%) as a colorless oil. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.52 (s, 1H), 7.80–7.75 (m, 2H), 7.50–7.34 (m, 5H), 6.66 (m, 2H), 6.04 (m, 1H), 5.29–5.09 (m, 2H), 3.32 (q, 4H, \(^3J = 7.0\) Hz), 1.08 (t, 6H, \(^3J = 7.0\) Hz) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 156.7, 144.9, 143.5, 131.8, 130.1, 130.0, 128.8, 128.3, 126.3, 126.3, 121.7, 119.0, 111.6, 51.2, 43.7, 12.3 ppm. HRMS calc. for C\(_{22}\)H\(_{26}\)N\(_3\)O\(_2\) [M+H]+: 376.2137, found 376.2136.

Methyl 1-[2-(1,3-dioxolan-2-yl)ethyl]-4-phenyl-1\(H\)-1,2,3-triazole-5-carboxylate (SI57)

Synthesis according to the General procedure VIII, Method A. Methyl phenylpropionate (0.160 g, 1.00 mmol), 2-(2-bromoethyl)-1,3-dioxolane (0.120 mL, 1.00 mmol), TBAB (322 mg, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol), solvent volume: 1.5 mL each. reaction conditions: stirring overnight at room temperature and 70 min in the microwave.
reactor at 150 °C. Solvent for extraction: twice with toluene and once with ethyl acetate. Chromatography on silica gel gave compound SI57 (33.5 mg, 0.110 mmol, 11%) as a brownish oil. 

\[ ^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta 7.89–7.80 (m, 2H), 7.49–7.37 (m, 3H), 5.03 (t, 1H, \^J = 4.3 Hz), 4.61 (m, 2H), 4.03–3.81 (m, 7H), 2.44 (m, 2H) \text{ ppm.} \]

\[ ^{13}\text{C NMR (75 MHz, CDCl}_3\text{): } \delta 161.9, 150.1, 135.5, 129.8, 129.6, 129.3, 128.3, 101.8, 65.3, 52.4, 51.0, 33.6 \text{ ppm.} \]

HRMS calc. for C\textsubscript{15}H\textsubscript{18}NO\textsubscript{3} [M+H]^+: 294.1243, found 294.1246.

1-[2-(1,3-Dioxolan-2-yl)ethyl]-N-[4-(diethylamino)phenyl]-4-phenyl-1\textit{H}-1,2,3-triazole-5-carboxylate (SI58)

Synthesis according to the General procedure VI. Deviating from the General procedure VI, the reaction time of the hydrolysis was 2 d at room temperature. Methyl 1-[2-(1,3-dioxolan-2-yl)ethyl]-4-phenyl-1\textit{H}-1,2,3-triazole-5-carboxylate SI57 (37.8 mg, 0.125 mmol), LiOH:HO\textsubscript{2} (7.80 mg, 0.187 mmol, 1.5 equiv), solvent volume: 200 \textmu L each. N,N-Diethyl-p-phenylenediamine 17 (20.8 \textmu L, 0.125 mmol), HBTU (61.6 mg, 0.163 mmol, 1.3 equiv), DIPEA (43.5 \textmu L, 0.250 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate. Chromatography on silica gel gave compound SI58 (34.7 mg, 0.0797 mmol, 64%) as a brown oil. 

\[ ^1\text{H NMR (300 MHz, DMSO-d}_6\text{): } \delta 10.08 (s, 1H), 7.92–7.86 (m, 2H), 7.51 (m, 2H), 7.49–7.37 (m, 3H), 6.65 (m, 2H), 4.99 (t, 1H, \^J = 4.5 Hz), 4.61 (d, \^J = 7.3 Hz, \^J = 7.3 Hz), 3.99–3.76 (m, 4H), 3.31 (q, 4H, \^J = 7.0 Hz), 2.33 (m, 2H), 1.08 (t, 6H, \^J = 7.0 Hz) \text{ ppm.} \]

\[ ^{13}\text{C NMR (75 MHz, DMSO-d}_6\text{): } \delta 158.7, 145.7, 144.4, 139.4, 129.6, 128.6, 128.2, 128.0, 127.0, 122.0, 111.7, 101.0, 64.4, 50.2, 43.7, 33.1, 12.3 \text{ ppm. HRMS calc. for C}_{24}H_{30}N_{5}O_{3} [M+H]^+: 436.2349, found 436.2351.} \]

1-Benzyl-N-[4-(diethylamino)phenyl]-4-phenyl-1\textit{H}-1,2,3-triazole-5-carboxamide (SI60)

\textit{i. Methyl 1-benzyl-4-phenyl-1\textit{H}-1,2,3-triazole-5-carboxylate (SI59)}

Synthesis according to the General procedure VIII, method A. Methyl phenylpropionate (80.1 mg, 0.500 mmol), benzyl bromide (59.5 \mu L, 0.500 mmol), TBAB (161 mg, 0.500 mmol), sodium azide (32.5 mg, 0.500 mmol). solvent volume: 1 mL each. Reaction conditions: 20 min, 130 °C and 70 min, 150 °C. Solvent for extraction: twice with toluene. Chromatography on silica gel gave compound SI59 (34.1 mg, 0.116 mmol, 23%) as a colorless resin. HRMS calc. for C\textsubscript{17}H\textsubscript{16}N\textsubscript{3}O\textsubscript{2} [M+H]^+: 294.1243, found 294.1246.
ii. 1-Benzyl-N-[4-(diethylamino)phenyl]-4-phenyl-1H-1,2,3-triazole-5-carboxamide (SI60)

Synthesis according to the General procedure VI. Deviating from the General procedure VI, the reaction time of the amide coupling was 2 d at room temperature. Methyl 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-carboxylate SI59 (20.3 mg, 0.0692 mmol), LiOH·H₂O (4.40 mg, 0.104 mmol, 1.5 equiv), Solvent volume: 200 μL each. N,N-Diethyl-p-phenylenediamine 17 (11.5 μL, 0.0692 mmol), HBTU (34.1 mg, 0.0900 mmol, 1.3 equiv), DIPEA (24.1 μL, 0.138 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound SI60 (19.3 mg, 0.0454 mmol, 66%) as yellow needles. M.p. 173.9–175.5 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 10.52 (s, 1H), 7.78–7.74 (m, 2H), 7.49–7.27 (m, 10H), 6.64 (m, 2H, 5.69 (s, 2H), 3.31 (q, 4H, ³J = 7.0 Hz), 1.08 (t, 6H, ³J = 7.0 Hz) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 156.7, 144.9, 143.6, 135.1, 130.0, 129.9, 128.7, 128.6, 128.3, 128.1, 127.9, 126.3, 126.2, 121.8, 111.6, 52.2, 43.7, 12.3 ppm. HRMS calc. for C₁₆H₁₈N₅O [M+H]+: 426.2294, found 426.2299.

Methyl 4-phenyl-1-[(tetrahydrofuran-2-yl)methyl]-1H-1,2,3-triazole-5-carboxylate (SI61)

Synthesis according to the General procedure VIII, method B. Methyl phenylpropiolate (0.160 g, 1.00 mmol), 2-(chloromethyl)tetrahydrofuran (0.109 mL, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol). Solvent volume: 2 mL. Reaction conditions: first 60 min, 80 °C, then 50 min, 140 °C. Chromatography on silica gel gave compound SI61 (49.6 mg, 0.173 mmol, 17%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 7.89–7.81 (m, 2H), 7.48–7.38 (m, 3H), 4.65–4.46 (m, 3H), 3.96–3.76 (m, 5H), 2.14–1.72 (m, 4H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 161.8, 150.3, 135.7, 129.6, 129.4, 129.3, 128.3, 77.1, 68.7, 59.6, 52.4, 29.3, 25.6 ppm. HRMS calc. for C₁₅H₁₈N₃O [M+H]+: 288.1348, found 288.1350.

N-[4-(Diethylamino)phenyl]-4-phenyl-1-[(tetrahydrofuran-2-yl)methyl]-1H-1,2,3-triazole-5-carboxamide (SI62)

Synthesis according to the General procedure VI. Methyl 4-phenyl-1-[(tetrahydrofuran-2-yl)methyl]-1H-1,2,3-triazole-5-carboxylate SI61 (34.7 mg, 0.121 mmol), LiOH·H₂O (7.60 mg, 0.181 mmol, 1.5 equiv). Solvent volume: 0.200 mL each. N,N-Diethyl-p-phenylenediamine 17 (20.1 μL, 0.121 mmol), HBTU (59.7 mg, 0.157 mmol, 1.3 equiv), DIPEA (42.2 μL, 0.242 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound SI62 (34.1 mg, 0.0813 mmol, 67%) as a brownish oil. ¹H NMR (300 MHz, DMSO-d₆): δ 10.10 (s, 1H), 7.90–7.85 (m, 2H), 7.51 (m, 2H), 7.49–7.37 (m, 3H), 6.65 (m, 2H, 6.43–4.40 (m, 3H), 3.79 (m, 1H), 3.67 (m, 1H), 3.31 (q, 4H, ³J = 7.0 Hz), 1.21–1.69 (m, 4H), 1.08 (t, 6H, ³J = 7.0
Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 158.7, 145.7, 144.4, 139.5, 129.6, 128.6, 128.3, 128.0, 127.0, 122.0, 111.7, 76.5, 67.4, 58.5, 43.7, 28.4, 24.9, 12.3 ppm. HRMS calc. for $C_{24}H_{30}N_5O_2$ [M+H]$^+$: 420.2400, found 420.2397.

**Methyl 4-phenyl-1-propyl-1H-1,2,3-triazole-5-carboxylate (SI63)**

Synthesis according to the General procedure VIII, method B. Methyl phenylpropionate (0.160 g, 1.00 mmol), propyl bromide (90.8 μL, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol), solvent volume: 2.5 mL. Reaction conditions: first 60 min, 70 °C, then 70 min, 140 °C. Chromatography on silica gel gave compound SI63 (118 mg, 0.481 mmol, 48%) as a brownish oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.89–7.81 (m, 2H), 7.49–7.38 (m, 3H), 4.47 (t, 2H, $^3J$ = 7.1 Hz), 3.93 (s, 3H), 2.07 (tq=sext, 2H, $^3J$ = 7.1 Hz, $^3J$ = 7.4 Hz), 0.99 (t, 3H, $^3J$ = 7.4 Hz) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 161.9, 150.1, 135.3, 129.7, 129.3, 128.3, 57.6, 52.4, 23.3, 11.2 ppm. HRMS calc. for $C_{13}H_{18}N_5O_2$ [M+H]$^+$: 246.1243, found 246.1247.

**4-Propyl-1-propyl-1H-1,2,3-triazole-5-carboxylic acid (SI64)**

A mixture of methyl 4-phenyl-1-propyl-1H-1,2,3-triazole-5-carboxylate SI63 (83.4 mg, 0.340 mmol) and lithium hydroxide monohydrate (21.4 mg, 0.510 mmol, 1.5 equiv) in an equimixture of THF, methanol and water (0.90 mL) was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and transferred to a separatory funnel. Water was added and the mixture was acidified with 1 M hydrochloric acid. The phases were separated, the organic phase was washed neutral with three portions of water, and the organic solvent was removed with a rotary evaporator to give compound SI64 (79.0 mg, 0.342 mmol, quant.) as a slightly white solid. M.p. 102.9–106.4 °C. $^1$H NMR (300 MHz, Acetone-$d_6$): $\delta$ 11.47 (br s, 1H), 7.96–7.88 (m, 2H), 7.49–7.37 (m, 3H), 4.49 (t, 2H, $^3J$ = 7.0 Hz), 2.05 (m, 2H), 0.98 (t, 3H, $^3J$ = 7.4 Hz) ppm.

**N-[4-(Diethylamino)phenyl]-4-phenyl-1-propyl-1H-1,2,3-triazole-5-carboxamide (SI65)**

Synthesis according to the General procedure I. 4-Phenyl-1-propyl-1H-1,2,3-triazole-5-carboxylic acid SI64 (28.0 mg, 0.121 mmol), N,N-diethyl-p-phenylenediamine 17 (20.1 μL, 0.121 mmol), HBTU (59.7 mg, 0.157 mmol, 1.3 equiv), DIPEA (42.2 μL, 0.242 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound SI65 (31.7 mg, 0.0840 mmol, 69%) as a brownish resin. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.09 (s, 1H), 7.91–7.85 (m, 2H), 7.51 (m, 2H), 7.49–7.36 (m, 3H), 6.64 (m, 2H), 4.49 (t, 2H, $^3J$ = 7.0 Hz), 3.31 (q, 4H, $^3J$ = 7.0 Hz), 2.00 (tq=sext, $^3J$ = 7.0 Hz, $^3J$ = 7.5 Hz, 2H), 1.08 (t, 6H, $^3J$ = 7.0 Hz), 0.95 (t, 3H, $^3J$ = 7.0 Hz).
7.5 Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 158.8, 145.6, 144.4, 139.3, 129.7, 128.6, 128.3, 128.0, 127.0, 122.0, 111.7, 56.3, 43.7, 22.5, 12.3, 10.9 ppm. HRMS calc. for C$_{22}$H$_{28}$N$_3$O [M+H]$^+$: 378.2294, found 378.2293.

**N-[4-(Diethylamino)phenyl]-1-isobutyl-4-phenyl-1H-1,2,3-triazole-5-carboxamide (SI68)**

*i. Methyl 1-isobutyl-4-phenyl-1H-1,2,3-triazole-5-carboxylate (SI66)*

Synthesis according to the of the General procedure VIII, method B. Methyl phenylpropionate (0.160 g, 1.00 mmol), 1-bromo-2-methylpropane (0.109 mL, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol). solvent volume: 2.5 mL. reaction conditions: first 60 min, 70 °C, then 70 min, 140 °C. Chromatography on silica gel gave compound SI66 (174 mg, 0.671 mmol, 67%) as colorless oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.90–7.81 (m, 2H), 7.49–7.38 (m, 3H), 4.32 (d, 2H, $^3J = 7.3$ Hz), 3.93 (s, 3H), 2.45 (m, 2H), 0.98 (d, 6H, $^3J = 6.7$ Hz) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 161.9, 150.1, 135.3, 129.7, 129.3, 129.3, 128.3, 63.0, 52.4, 29.6, 20.0 ppm. HRMS calc. for C$_{14}$H$_{18}$N$_3$O [M+H]$^+$: 260.1399, found 260.1402.

*ii. 1-Isobutyl-4-phenyl-1H-1,2,3-triazole-5-carboxylic acid (SI67)*

![Diagram](image)

A mixture of methyl 1-isobutyl-4-phenyl-1H-1,2,3-triazole-5-carboxylate SI66 (135 mg, 0.521 mmol) and lithium hydroxide monohydrate (32.8 mg, 0.781 mmol, 1.5 equiv) in an equimixture of THF, methanol and water (1.20 mL) was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and transferred to a separatory funnel. Water was added, and the mixture was acidified with 1 M hydrochloric acid. The phases were separated, the organic phase was washed neutral with three portions of water, and the solvent was removed with a rotary evaporator to give compound SI67 (123 mg, 0.501 mmol, 96%) as a white solid that was used in the next step without further purification. M.p. 88.4–94.8 °C.

*iii. N-[4-(Diethylamino)phenyl]-1-isobutyl-4-phenyl-1H-1,2,3-triazole-5-carboxamide (SI68):* Synthesis according to the General procedure I. 1-Isobutyl-4-phenyl-1H-1,2,3-triazole-5-carboxylic acid SI67 (36.8 mg, 0.150 mmol), N,N-diethyl-p-phenylenediamine 17 (24.9 µL, 1.50 mmol), HBTU (74.0 mg, 0.195 mmol, 1.3 equiv), DIPEA (52.3 µL, 0.300 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: ethyl acetate. Chromatography on silica gel gave compound SI68 (49.7 mg, 0.127 mmol, 85%) as a yellowish oil. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.06 (s, 1H), 7.91–7.86 (m, 2H), 7.50 (m, 2H), 7.49–7.37 (m, 3H), 6.65 (m, 2H), 4.35 (d, 2H, $^3J = 6.9$ Hz),
3.31 (q, 4H, \( \delta J = 7.0 \) Hz), 2.35 (m, 1H), 1.08 (t, 6H, \( \delta J = 6.8 \) Hz) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\( d_6 \)): \( \delta \) 158.8, 145.5, 144.4, 139.3, 129.7, 128.6, 128.3, 128.0, 127.0, 122.0, 111.7, 61.6, 43.7, 28.9, 19.5, 12.3 ppm. HRMS calc. for C\(_{23}\)H\(_{30}\)N\(_5\)O [M+H]+: 392.2450, found 392.2454.

1-[4-(Diethylamino)phenyl]-2-(5-phenyl-1H-tetrazol-1-yl)ethanone (SI69)

A mixture of 5-phenyl-1H-tetrazole (189 mg, 1.30 mmol) and a 60% suspension of sodium hydride in mineral oil (62.2 mg, 1.56 mmol, 1.2 equiv) in absolute DMF (2.5 mL) was stirred for 1.5 h at room temperature under argon. 2-Bromo-1-[4-(diethylamino)phenyl]ethanone (0.350 g, 1.30 mmol) was added, and the reaction mixture was stirred for 2 d at room temperature. The reaction mixture was diluted with ethyl acetate, washed three times with water and the organic solvent was removed with a rotary evaporator. The crude product was purified by automated chromatography on silica gel, using a gradient of increasing ethyl acetate starting with 100% n-hexane to give compound SI69 (183 mg, 0.547 mmol, 42%) as an orange resin. \(^1\)H NMR (300 MHz, DMSO-\( d_6 \)): \( \delta \) 8.21–8.13 (m, 2H), 7.86 (m, 2H), 7.51–7.42 (m, 3H), 6.67 (m, 2H), 6.01 (s, 3H), 3.45 (q, 4H, \( \delta J = 7.1 \) Hz), 1.24 (t, 6H, \( \delta J = 7.1 \) Hz) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\( d_6 \)): \( \delta \) 186.1, 165.6, 152.3, 131.0, 130.4, 128.9, 127.7, 127.2, 121.2, 110.7, 57.7, 44.8, 12.6 ppm. HRMS calc. for C\(_{19}\)H\(_{22}\)N\(_5\)O [M+H]+: 336.1824, found 336.1823.

N-(4-Methoxyphenyl)-5-phenylisoxazole-4-carboxamide (SI70)

Synthesis according to the General procedure I. 5-Phenylisoxazole-4-carboxylic acid 46d (189 mg, 1.00 mmol), 4-methoxyaniline (123 mg, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H\(_2\)O 19+1) gave compound SI70 (125 mg, 0.425 mmol, 42%) as white needles. M.p. 129.7–133.0 °C. \(^1\)H NMR (300 MHz, DMSO-\( d_6 \)): \( \delta \) 10.30 (s, 1H), 9.09 (s, 1H), 8.01–7.94 (m, 2H), 7.63–7.51 (m, 5H), 6.93 (m, 2H), 3.74 (s, 3H) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\( d_6 \)): \( \delta \) 167.9, 158.7, 155.8, 151.1, 131.6, 131.2, 128.9, 127.9, 126.3, 126.3, 121.7, 113.9, 112.7, 55.2 ppm. HRMS calc. for C\(_{17}\)H\(_{15}\)N\(_2\)O\(_3\) [M+H]+: 295.1083, found 295.1077.
**N-[4-[(Dimethylamino)methyl]phenyl]-5-phenylisoxazole-4-carboxamide (SI71)**

Synthesis according to the General procedure I. 3-Methyl-5-phenylisoxazole-4-carboxylic acid (61.4 mg, 0.302 mmol), 4-[(dimethylamino)methyl]aniline hydrochloride (56.4 mg, 0.302 mmol), HBTU (149 mg, 0.393 mmol, 1.3 equiv), DIPEA (0.158 mL, 0.906 mmol, 3 equiv), DMF (1.5 mL). Solvent for extraction: ethyl acetate and washing with an equimixture of water and brine, 4 times. Recrystallization after chromatography on silica gel gave compound SI71 (73.3 mg, 0.219 mmol, 72%) as white needles. M.p. 128.3–130.0 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.50 (s, 1H), 7.85–7.77 (m, 2H), 7.59 (m, 2H), 7.58–7.51 (m, 3H), 7.26 (m, 2H), 3.35 (s, 2H), 2.36 (s, 3H), 2.14 (s, 6H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 166.6, 159.9, 158.9, 137.2, 134.8, 130.9, 129.1, 126.6, 126.4, 119.5, 113.5, 62.9, 44.8, 10.2 ppm. HRMS calc. for C_{20}H_{22}N_{3}O_{2} [M+H]^+: 336.1712, found 336.1717.

**N-(4-Isopropyl-3-methylphenyl)-3-methyl-5-phenylisoxazole-4-carboxamide (SI72)**

Synthesis according to the General procedure I. 3-Methyl-5-phenylisoxazole-4-carboxylic acid (40.0 mg, 0.197 mmol), 4-isopropyl-3-methylaniline hydrochloride (36.6 mg, 0.197 mmol), HBTU (97.1 mg, 0.256 mmol, 1.3 equiv), DIPEA (0.103 mL, 0.591 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether/ethyl acetate (1:1). Recrystallization (EtOH/H_{2}O 10+) without chromatographic purification gave compound SI72 (55.1 mg, 0.165 mmol, 84%) as fine white needles. M.p. 165.1–166.6 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.38 (s, 1H), 7.85–7.76 (m, 2H), 7.59–7.50 (m, 3H), 7.46–7.38 (m, 2H), 7.20 (bd, 1H, \(^1J = 8.9\) Hz), 3.07 (sep, 1H, \(^3J = 6.8\) Hz), 2.35 (s, 3H), 2.28 (s, 3H), 1.17 (d, 6H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 165.8, 159.8, 158.9, 142.3, 135.8, 134.9, 130.8, 129.1, 126.5, 126.4, 124.9, 121.3, 117.8, 113.5, 28.3, 23.1, 10.1 ppm. HRMS calc. for C_{21}H_{23}N_{2}O_{2} [M+H]^+: 335.1760, found 335.1765.

**N-[4-(Diethylamino)phenyl]-3’,4,5-trimethyl-[3,5’-biisoxazole]-4’-carboxamide (SI73)**

Synthesis according to the General procedure I. 3’,4,5-trimethyl-[3,5’-biisoxazole]-4’-carboxylic acid (0.020 g, 0.090 mmol), N,N-diethyl-p-phenylenediamine 17 (22 µL, 0.140 mmol, 1.5 equiv), HBTU (80.9 mg, 0.213 mmol, 1.3 equiv), DIPEA (31 µL, 0.180 mmol, 2.0 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Eluent for purification: n-heptane/EtOAc 4:1. Chromatography on silica gel gave compound SI73 (35.5 mg, 0.0104 mmol, 88%). 1H NMR (400 MHz, CDCl3): δ 10.62 (s, 1H), 7.50 (m, 2H), 6.67 (m, 2H), 3.34 (q, \(^3J = 7.1\) Hz, 4H), 2.66 (s, 3H), 2.47 (d, \(^4J = 0.8\) Hz, 3H), 2.22 (d, \(^4J = 0.7\) Hz, 6H), 1.14 (t, \(^3J = 7.0\) Hz, 6H). 13C NMR (101 MHz, CDCl3): δ 167.6, 162.6, 157.9, 157.0, 153.0, 145.2, 126.9, 122.2, 115.3, 112.4, 111.1, 44.6, 12.5, 12.2, 10.7, 7.8 ppm. HRMS calc. for C_{20}H_{25}N_{4}O_{3} [M+H]^+: 369.1927, found 369.1929.

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N-[4-(Diethylamino)phenyl]-3’-methyl-5-[2-(pyridin-2-yloxy)ethyl]-[3,5’-biisoxazole]-4’-carboxamide (SI74)

Synthesis according to the General procedure I. 3’-Methyl-5-[2-(pyridin-2-yloxy)ethyl]-[3,5’-biisoxazole]-4’-carboxylic acid hydrochloride (0.010 g, 0.0280 mmol), N,N-diethyl-p-phenylenediamine 17 (7.1 µL, 0.043 mmol, 1.5 equiv), HBTU (14 mg, 0.037 mmol, 1.3 equiv), DIPEA (0.010 mL, 0.057 mmol, 2.0 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Eluent for purification: n-heptane/EtOAc 4:1. Chromatography on silica gel gave compound SI74 (8.3 mg, 0.0180 mmol, 63%). 1H NMR (400 MHz, CDCl3): δ 10.59 (s, 1H), 8.15 (ddd, J = 5.1, 2.0, 0.8 Hz, 1H), 7.59 (ddd, J = 8.4, 7.1, 2.0 Hz, 1H), 7.53 (m, 1H), 6.90 (ddd, J = 7.1, 5.1, 1.0 Hz, 1H), 6.78–6.74 (m, 2H), 6.68 (m, 2H), 4.71 (t, J = 6.2 Hz, 2H), 3.39 (q, J = 7.0 Hz, 4H), 2.94 (qd, J = 7.6, 0.9 Hz, 2H), 1.43 (t, J = 7.6 Hz, 3H), 2.70 (s, 3H), 1.18 (t, J = 7.0 Hz, 6H). 13C NMR (101 MHz, CDCl3): δ 172.4, 163.2, 162.9, 157.7, 155.7, 153.5, 146.8, 145.3, 138.9, 126.8, 122.3, 117.3, 114.6, 112.4, 111.2, 102.1, 62.0, 44.6, 27.0, 12.5, 12.4 ppm. HRMS calc. for C25H28N5O4[M+H]+: 462.2141, found 462.2140.

N-[4-(Diethylamino)phenyl]-5-ethyl-3’-methyl-[3,5’-biisoxazole]-4’-carboxamide (SI75)

Synthesis according to the General procedure I. 5-Ethyl-3’-methyl-[3,5’-biisoxazole]-4’-carboxylic acid (5.0 mg, 0.023 mmol), N,N-diethyl-p-phenylenediamine 17 (5.6 µL, 0.034 mmol, 1.5 equiv), HBTU (11 mg, 0.029 mmol, 1.3 equiv), DIPEA (7.8 µL, 0.045 mmol, 2.0 equiv), DMF (0.5 mL). Solvent for extraction: diethyl ether. Eluent for purification: n-heptane/EtOAc 5:1. Chromatography on silica gel gave compound SI75 (6.9 mg, 0.0187 mmol, 81%) as a yellow solid. 1H NMR (400 MHz, CDCl3): δ 10.67 (s, 1H), 7.56 (m, 2H), 6.71 (m, 2H), 6.64 (s, 1H), 3.37 (q, J = 7.0 Hz, 4H), 2.94 (qd, J = 7.6, 0.9 Hz, 2H), 1.43 (t, J = 7.6 Hz, 3H), 2.70 (s, 3H), 1.18 (t, J = 7.0 Hz, 6H). 13C NMR (101 MHz, CDCl3): δ 176.61, 163.19, 157.79, 155.92, 153.41, 145.30, 126.89, 122.30, 114.54, 112.41, 100.43, 44.59, 20.21, 12.53, 12.40, 11.55 ppm. HRMS calc. for C25H28N4O3[M+H]+: 369.1927, found 369.1928.
**N-[4-(Diethylamino)phenyl]-5-(furan-2-yl)-3'-methyl-[3,5'-biisoxazole]-4'-carboxamide (SI76)**

Synthesis according to the General procedure I. 5-(Furan-2-yl)-3'-methyl-[3,5'-biisoxazole]-4'-carboxylic acid (5.20 mg, 0.020 mmol), N,N-diethyl-p-phenylenediamine 17 (5.00 µL, 0.030 mmol, 1.5 equiv), HBTU (10.0 mg, 0.0260 mmol, 1.3 equiv), DIPEA (7.00 µL, 0.040 mmol, 2.0 equiv), DMF (0.5 mL). Solvent for extraction: diethyl ether. Eluent for purification: n-heptane/EtOAc 4:1. Chromatography on silica gel gave compound SI76 (5.10 mg, 0.0125 mmol, 63%).

**1H NMR (400 MHz, CDCl₃):** δ 10.51 (s, 1H), 7.64 (dd, J = 1.8, 0.7 Hz, 1H), 7.55 (m, 2H), 7.07 (dd, J = 3.5 Hz, 0.8 Hz, 1H), 7.02 (s, 1H), 6.70 (m, 2H), 6.62 (dd, J = 3.5, 1.8 Hz, 1H), 3.35 (q, 3J = 7.1 Hz, 4H), 2.69 (s, 3H), 1.16 (t, 3J = 7.1 Hz, 6H) ppm.

**13C NMR (101 MHz, CDCl₃):** δ 163.3, 162.9, 157.6, 155.3, 153.7, 145.4, 141.8, 126.8, 122.3, 114.9, 112.4, 112.3, 98.6, 44.6, 12.5, 12.4 ppm. HRMS calc. for C₂₅H₂₈N₅O₄ [M+H]+: 407.1719, found 407.1718.

**N,3',5'-Trimethyl-N-(4-oxo-2-phenyl-4H-chromen-6-yl)-[3,5'-biisoxazole]-4'-carboxamide (SI77)**

3',5-Dimethyl-N-(4-oxo-2-phenyl-4H-chromen-6-yl)-[3,5'-biisoxazole]-4'-carboxamide 73 (34.1 mg, 0.0798 mmol) was dissolved under argon in absolute DMF (1.5 mL). A 60% dispersion of sodium hydride in mineral oil (4.8 mg, 0.120 mmol, 1.5 equiv) was added and the reaction mixture was stirred for 1 h at room temperature. Iodomethane (9.90 µL, 0.160 mmol, 2 equiv) was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed three times with a mixture of water and brine (3:1). The solvent was removed with a rotary evaporator and the residue was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate gave compound SI77 (20.8 mg, 0.0471 mmol, 59%) as fine white needles. M.p. 224.6–226.4 °C (decomp.).

**1H NMR (300 MHz, DMSO-d₆):** δ 8.13–8.05 (m, 2H), 7.75–7.45 (m, 6H), 7.03 (s, 1H), 6.47 (bs, 1H), 3.43 (bs, 3H), 2.46 (s, 3H), 2.34 (s, 3H) ppm.

**13C NMR (75 MHz, DMSO-d₆):** δ 176.2, 171.9, 162.7, 160.6, 159.0, 156.0, 153.9, 151.0, 139.5, 132.5, 131.9, 130.9, 129.1, 126.4, 123.2, 121.6, 119.3, 114.9, 106.6, 100.6, 11.7, 9.9 ppm. HRMS calc. for C₂₅H₂ₙN₃O₄ [M+H]+: 442.1403, found 442.1405.
N¹-[3-(4-Fluorophenyl)-1H-pyrazol-4-yl]methyl]-N⁴,N⁴-dimethylbenzene-1,4-diamine (SI78)

(E)-N¹-[3-(4-Fluorophenyl)-1H-pyrazol-4-yl]methylene]-N⁴,N⁴-dimethylbenzene-1,4-diamine 75 (50.0 mg, 0.162 mmol) was dissolved in absolute methanol (0.50 mL). Sodium cyanoborohydride (10.2 mg, 0.162 mmol) was added, and the reaction mixture was stirred overnight at room temperature. A few drops of water were added and after 15 min the reaction mixture was diluted with ethyl acetate and washed three times with water. The solvent was removed with a rotary evaporator and the product mixture was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to give compound SI78 (24.0 mg, 0.773 mmol, 48%) as a brownish oil. ¹H NMR (300 MHz, Acetone-d₆): δ 12.04 (bs, 1H), 7.87–7.79 (m, 2H), 7.71 (s, 1H), 7.22–7.11 (m, 2H), 6.73–6.64 (m, 4H), 4.41 (bs, 1H), 4.22 (s, 2H), 2.77 (s, 6H) ppm. ¹³C NMR (75 MHz, Acetone-d₆): δ 163.1 (d, J = 244.7 Hz), 146.5 (br), 145.0, 142.2, 133.7 (br), 130.7 (br), 130.2 (d, J = 8.1 Hz), 117.1, 116.3, 116.1 (d, J = 21.5 Hz), 115.0, 42.3, 40.4 ppm. HRMS calc. for C₁₈H₂₀FN₄ [M+H]⁺: 311.1672, found 311.1680.

N¹-[3-(3,5-Difluorophenyl)-1H-pyrazol-4-yl]methyl]-N⁴,N⁴-diethylbenzene-1,4-diamine (SI79)

Synthesis according to the General procedure IX. Anhydrous sodium sulphate (215 mg, 1.51 mmol) was flame dried in an evacuated Schlenck flask. Absolute THF (2.5 mL), 3-(3,5-difluorophenyl)-1H-pyrazole-4-carbaldehyde (105 mg, 0.504 mmol), N,N-diethyl-p-phenylenediamine 17 (83.8 µL, 0.504 mmol) and acetic acid (28.9 µL, 0.504 mmol) were added. The reaction mixture was stirred at room temperature for 4 h and a 1.0 M solution of sodium cyanoborohydride in THF was added (2.02 mL, 2.02 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 4 d and quenched with a saturated solution of sodium hydrogen carbonate in H₂O. After 20 min ethyl acetate and water were added, the phases were separated and the organic phase was washed twice with a mixture of water and brine (1:1). The solvent was removed with a rotary evaporator. The crude product was purified twice by automated preparative chromatography. The chromatographies on silica gel were performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to yield compound SI79 (83.5 mg, 0.234 mmol, 46%) as a brownish oil. ¹H NMR (300 MHz, acetone-d₆): δ 12.10 (bs, 1H), 7.80
(bs, 1H), 7.56–7.47 (m, 2H), 6.95 (tt, 1H, $J = 2.4$ Hz, $J = 9.2$ Hz), 6.70 (m, 4H), 4.26 (bs, 2H), 3.20 (q, 4H, $J = 7.0$ Hz), 1.05 (t, 6H, $J = 7.0$ Hz) ppm. $^{13}$C NMR (75 MHz, acetone-$d_6$): $\delta$ 164.0 (dd, $J = 13.4$ Hz, $J = 245.1$ Hz), 146.7 (br), 142.0, 142.0, 142.0, 138.4, 132.8, 117.9, 117.7 (br), 115.4, 110.8 (m), 103.0 (t, $J = 25.9$ Hz), 46.3, 40.5, 13.0 ppm. HRMS calc. for C$_{20}$H$_{23}$F$_2$N$_4$ [M+H]$^+$: 357.1891, found 357.1891.

$N^1,N^1$-Diethyl-$N^4$-[(3-(4-fluorophenyl)-1H-pyrazol-4-yl)methyl]benzene-1,4-diamine (SI80) and $N^1,N^1$-diethyl-$N^4$-[(3-(4-fluorophenyl)-1H-pyrazol-4-yl)methyl]-$N^3$-isopropylbenzene-1,4-diamine (SI81)

Synthesis according to the General procedure IX. Deviating from the General procedure IX, no sodium sulphate was used. Acetic acid (50.0 \( \mu \)L, 0.873 mmol), 3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (166 mg, 0.873 mmol), N,N-diethyl-p-phenylenediamine 17 (0.145 mL, 0.873 mmol), THF (4 mL), a 1.0 M solution of sodium cyanoborohydride in THF (4.37 mL, 4.37 mmol, 5 equiv, added 1 h later). Reaction time: 4 d; quenched with a saturated solution of NaHCO$_3$ in H$_2$O (5 mL) for 20 min. Solvents for extraction: ethyl acetate and a mixture of water and brine (3:1). Chromatography on silica gel gave compound SI80 (84.7 mg, 0.250 mmol, 29%) as a slightly violet solid and compound SI81 (70.8 mg, 0.209 mmol, 24%) as a violet oil. Compound SI80: $^1$H NMR (300 MHz, acetone-$d_6$): $\delta$ 12.07 (bs, 1H), 7.84 (m, 2H), 7.72 (bs, 1H), 7.18 (m, 2H), 6.68 (m, 4H), 4.38 (bs, 1H), 4.22 (s, 2H), 3.19 (q, 4H, $J = 7.0$ Hz), 1.05 (t, 6H, $J = 7.0$ Hz) ppm. $^{13}$C NMR (75 MHz, Acetone-$d_6$): $\delta$ 163.2 (d, $J = 244.7$ Hz), 148.3, 142.3, 141.9, 130.2 (d, $J = 8.0$ Hz), 130.0, 128.2, 117.9, 117.1, 116.1 (d, $J = 21.5$ Hz), 115.2, 46.4, 40.5, 13.0 ppm. HRMS calc. for C$_{20}$H$_{24}$FN$_4$ [M+H]$^+$: 339.1985, found 339.1985. Compound SI81: $^1$H NMR (300 MHz, Acetone-$d_6$): $\delta$ 11.90 (bs, 1H), 7.92 (m, 2H), 7.46 (s, 1H), 7.19 (m, 2H), 6.84, 6.61 (each m, each 2H), 4.23 (s, 2H), 3.68 (sep, 1H, $J = 6.6$ Hz), 3.25 (q, 4H, $J = 7.0$ Hz), 1.10 (d, 6H, $J = 6.6$ Hz), 1.07 (t, 6H, $J = 7.0$ Hz) ppm. $^{13}$C NMR (75 MHz, Acetone-$d_6$): $\delta$ 163.1 (d, $J = 244.2$ Hz), 144.0, 139.9, 134.0, 130.5 (d, $J = 8.1$ Hz), 130.4, 128.5, 123.5, 118.1, 115.8 (d, $J = 21.4$ Hz), 114.6, 52.2, 45.4, 44.0, 20.1, 13.0 ppm. HRMS calc. for C$_{23}$H$_{30}$FN$_4$ [M+H]$^+$: 381.2455, found 381.2457.
(E)-N-[[3-(4-Fluorophenyl)-1H-pyrazol-4-yl]methylene]-4-morpholinoaniline (SI82)

Synthesis according to the General procedure III. Deviating from the General procedure III, the reaction mixture was first stirred at room temperature overnight, then heated at 70 °C for 5 h and stirred at room temperature overnight. p-Toluenesulfonic acid and one additional equivalent of Na₂SO₄ were added, and the reaction mixture was heated at 90 °C for 4 h and at 70 °C overnight. 3-(4-Fluorophenyl)-1H-pyrazole-4-carboxaldehyde (95.1 mg, 0.500 mmol), 4-morpholinoaniline (89.1 mg, 0.500 mmol), Na₂SO₄ (142 mg + 71.0 mg, 1.00 mmol + 0.500 mmol), AcOH (5.7 µL, 0.10 mmol, 0.2 equiv), p-toluenesulfonic acid (9.5 mg, 0.050 mmol, 0.1 equiv), toluene (2 mL). Chromatography on silica gel gave compound **SI82** (62.0 mg, 0.177 mmol, 35%) as a brown solid.

1H NMR (300 MHz, CDCl₃): δ 8.41 (s, 1H), 8.27 (s, 1H), 7.56 (m, 2H), 7.19–7.08 (m, 4H), 6.89 (m, 2H), 3.85 (m, 4H), 3.14 (m, 4H) ppm.

13C NMR (75 MHz, CDCl₃): δ 163.5 (d, J = 249.4 Hz), 150.5, 150.1, 144.2, 130.7 (d, J = 8.2 Hz), 122.0, 118.5, 118.2, 116.6, 116.4, 116.3 (d, J = 21.6 Hz), 67.1, 49.7 ppm. HRMS calc. for C₂₀H₂₀FN₄O [M+H]^+: 351.1621, found 351.1622.

N¹,N¹-Diethyl-N⁴-[[3-(thiophen-2-yl)-1H-pyrazol-4-yl]methyl]benzene-1,4-diamine (SI83)

Synthesis according to the General procedure IX. Deviating from the General procedure IX, the product was purified by two subsequent automated chromatography runs. Anhydrous sodium sulphate (120 mg), acetic acid (8.6 µL, 0.15 mmol, 0.5 equiv), 3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde (53.7 mg, 0.301 mmol), N,N-diethyl-p-phenylenediamine 17 (50.1 µL, 0.301 mmol), THF (2 mL), a 1.0 M solution of sodium cyanoborohydride in THF (1.20 mL, 1.20 mmol, 4 equiv, added 1 h later). Reaction time: 2 d; quenched with a saturated solution of NaHCO₃ in H₂O (5 mL). Chromatography on silica gel gave compound **SI83** (41.9 mg, 0.128 mmol, 43%) as a greenish resin.

1H NMR (300 MHz, DMSO-d₆): δ 12.73 (bs, 1H), 7.72, 7.44, 7.32, 7.08 (each br s, each 1H), 6.60 (m, 4H), 5.10 (t, 1H, ^3J = 5.3 Hz), 4.41 (d, 2H, ^3J = 5.1 Hz), 3.12 (q, 4H, ^3J = 7.0 Hz), 0.99 (t, 6H, ^3J = 7.0 Hz) ppm. 13C NMR (75 MHz, DMSO-d₆): δ 143.4, 141.0, 139.9, 136.6, 129.5, 127.7, 124.5, 124.1, 116.5, 115.5, 113.7, 44.9, 30.6, 12.4 ppm. HRMS calc. for C₁₈H₂₅N₄S [M+H]^+: 327.1643, found 327.1645.
A mixture of 3-phenyl-1H-pyrazol-4-yl)methanamine (54.2 mg, 0.313 mmol), 4-(diethylamino)benzaldehyde (77.6 mg, 0.438 mmol, 1.4 equiv) and sodium sulfate (133 mg, 0.939 mmol, 3 equiv) in anhydrous THF (3 mL) was stirred for 2 d at room temperature under argon. Sodium cyanoborohydride (49.2 mg, 0.783 mmol, 2.5 equiv) was added, and the reaction mixture was stirred for 3 d at room temperature. Sodium borohydride (11.8 mg, 0.313 mmol) was added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed three times with a mixture of water and brine (2:1). The solvent was removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of a mixture of ethyl acetate and 1% TEA in n-hexane, starting with 100% of n-hexane to give compound SI84 (54.9 mg, 0.164 mmol, 52%) as white needles. M.p. 95.2–96.4 °C. 

1H NMR (300 MHz, DMSO-d6): δ 12.67 (bs, 1H), 7.78–7.66 (m, 2H), 7.62 (bs, 1H), 7.44–7.26 (m, 3H), 7.11 (m, 2H), 6.60 (m, 2H), 3.61 (s, 2H), 3.60 (s, 2H), 3.30 (q, 4H, 3J = 7.0 Hz), 1.06 (t, 6H, 3J = 7.0 Hz) ppm.

13C NMR (75 MHz, DMSO-d6): δ 146.3, 129.1, 128.3, 127.1, 127.0, 116.6, 111.5, 52.3, 43.6, 42.5, 12.4 ppm. HRMS calc. for C21H27N4 [M+H]+: 335.2236, found 335.2245.

N1(3-Cyclohexyl-1H-pyrazol-4-yl)methyl]-N4,N4-diethylbenzene-1,4-diamine (SI85)

N1[(3-phenyl-1H-pyrazol-4-yl)methyl]amino)methyl]aniline (SI84)

A mixture of 3-phenyl-1H-pyrazol-4-yl)methanamine (54.2 mg, 0.313 mmol), 4-(diethylamino)benzaldehyde (77.6 mg, 0.438 mmol, 1.4 equiv) and sodium sulfate (133 mg, 0.939 mmol, 3 equiv) in anhydrous THF (3 mL) was stirred for 2 d at room temperature under argon. Sodium cyanoborohydride (49.2 mg, 0.783 mmol, 2.5 equiv) was added, and the reaction mixture was stirred for 3 d at room temperature. Sodium borohydride (11.8 mg, 0.313 mmol) was added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed three times with a mixture of water and brine (2:1). The solvent was removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of a mixture of ethyl acetate and 1% TEA in n-hexane, starting with 100% of n-hexane to give compound SI84 (54.9 mg, 0.164 mmol, 52%) as white needles. M.p. 95.2–96.4 °C. 

1H NMR (300 MHz, DMSO-d6): δ 12.67 (bs, 1H), 7.78–7.66 (m, 2H), 7.62 (bs, 1H), 7.44–7.26 (m, 3H), 7.11 (m, 2H), 6.60 (m, 2H), 3.61 (s, 2H), 3.60 (s, 2H), 3.30 (q, 4H, 3J = 7.0 Hz), 1.06 (t, 6H, 3J = 7.0 Hz) ppm.

13C NMR (75 MHz, DMSO-d6): δ 146.3, 129.1, 128.3, 127.1, 127.0, 116.6, 111.5, 52.3, 43.6, 42.5, 12.4 ppm. HRMS calc. for C21H27N4 [M+H]+: 335.2236, found 335.2245.

N1(3-Cyclohexyl-1H-pyrazol-4-yl)methyl]-N4,N4-diethylbenzene-1,4-diamine (SI85)

Synthesis according to the General procedure IX. Anhydrous sodium sulphate (120 mg), acetic acid (8.6 µL, 0.15 mmol, 0.5 equiv), 3-cyclohexyl-1H-pyrazole-4-carbaldehyde (53.8 mg, 0.302 mmol), N,N-diethyl-p-phenylenediamine 17 (50.2 µL, 0.302 mmol), THF (3 mL), a 1.0 M solution of sodium cyanoborohydride in THF (1.21 mL, 1.21 mmol, 4 equiv, added 1 h later). Reaction time: 2 d; quenched with a saturated solution of NaHCO3 in H2O (5 mL). Chromatography on silica gel gave compound SI85 (31.6 mg, 0.0872 mmol, 29%) as a brown resin. 

1H NMR (300 MHz, Acetone-d6): δ 11.44 (bs, 1H), 7.43 (s, 1H), 6.72–6.10 (m, 4H), 4.08 (s, 1H), 3.17 (q, 4H, 3J = 7.0 Hz), 2.80 (tt, 1H, J = 3.5 Hz, J = 11.9 Hz), 1.93–1.17 (m, 10H), 1.03 (t, 6H, 3J = 7.0 Hz) ppm.

13C NMR (75 MHz, Acetone-d6): δ 142.8, 141.61, 135.2, 118.3, 115.8, 115.0, 46.5, 39.8, 36.3, 33.6, 27.4, 26.9, 13.0 ppm. HRMS calc. for C20H31N4 [M+H]+: 327.2549, found 327.2549.
3-Cyclohexyl-N-[4-(diethylamino)phenyl]-1H-pyrazole-4-carboxamide (SI86)

Synthesis according to the General procedure I. 3-Cyclohexyl-1H-pyrazole-4-carboxylic acid (0.100 g, 0.515 mmol), N,N-diethyl-p-phenylenediamine 17 (85.6 µL, 0.515 mmol), HBTU (254 mg, 0.670 mmol, 1.3 equiv), DIPEA (0.179 mL, 1.03 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (1:1). Chromatography on silica gel gave compound SI86 (102 mg, 0.300 mmol, 58%) as a white solid. M.p. 153.9–155.4 °C. 1H NMR (300 MHz, Acetone-d6): δ 12.03 (bs, 1H), 8.74 (s, 1H), 8.02 (s, 1H), 7.52 (m, 2H), 6.68 (m, 2H), 3.54 (tt, 1H, J = 3.4 Hz, J = 12.0 Hz), 3.35 (q, 4H, 3J = 7.0 Hz), 2.03–1.94 (m, 2H), 1.86–1.20 (m, 8H), 1.12 (t, 6H, 3J = 7.0 Hz) ppm. 13C NMR (75 MHz, Acetone-d6): δ 162.5, 154.0 (br), 145.4, 136.6 (br), 129.6, 122.6, 114.4, 113.2, 45.1, 36.0, 32.9, 27.4, 26.9, 12.9 ppm. HRMS calc. for C20H20N4O [M+H]+: 341.2341, found 341.2347.

N-(4-Isopropyl-3-methylphenyl)-1-methyl-5-phenyl-1H-pyrazole-4-carboxamide (SI87)

Synthesis according to the General procedure I. 1-Methyl-5-phenyl-1H-pyrazole-4-carboxylic acid 46e (38.4 mg, 0.190 mmol), N-ethyl-N-isopropylphenylenediamine hydrochloride (35.3 mg, 0.190 mmol), HBTU (93.7 mg, 0.247 mmol, 1.3 equiv), DIPEA (99.3 µL, 0.570 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound SI87 (40.8 mg, 0.122 mmol, 64%) as a white solid. M.p. 153.0–154.3 °C. 1H NMR (300 MHz, DMSO-d6): δ 9.55 (s, 1H), 8.12 (s, 1H), 7.53–7.42 (m, 5H), 7.40–7.32 (m, 2H), 7.11 (d, 1H, 3J = 8.3 Hz), 3.68 (s, 3H), 3.02 (sep, 1H, 3J = 6.8 Hz), 2.23 (s, 3H), 1.13 (d, 6H, 3J = 6.8 Hz) ppm. 13C NMR (75 MHz, DMSO-d6): δ 161.0, 144.4, 141.7, 138.5, 137.0, 135.0, 130.5, 129.6, 129.3, 128.6, 125.0, 121.9, 118.3, 116.6, 37.6, 28.7, 23.6, 19.5 ppm. HRMS calc. for C23H24N3O [M+H]+: 334.1919, found 334.1919.

N-[4-(Diethylamino)phenyl]-1-phenyl-1H-pyrazole-5-carboxamide (SI88)

Synthesis according to the General procedure I. 1-Phenyl-1H-pyrazole-5-carboxylic acid (51.2 mg, 0.272 mmol), N,N-diethyl-p-phenylenediamine 17 (45.2 µL, 0.272 mmol), HBTU (134 mg, 0.354 mmol, 1.3 equiv), DIPEA (94.4 µL, 0.544 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H2O 10+1) without chromatography on silica gel gave compound SI88 (63.0 mg, 0.188 mmol, 69%) as yellow needles. M.p. 129.3–130.7 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.21 (s, 1H), 7.77 (d, 1H, 3J = 1.9 Hz), 7.50–7.35 (m, 7H), 6.97 (d, 1H, 3J = 1.9 Hz), 6.62 (m, 2H), 3.29 (q, 4H, 3J = 7.0 Hz), 1.06 (t, 6H, 3J = 7.0 Hz) ppm. 13C NMR (75 MHz, DMSO-d6): δ 157.3, 144.5, 140.0, 139.4, 137.6, 128.7, 127.5, 126.9, 124.1, 121.8, 111.7, 109.0, 43.7, 12.3 ppm. HRMS calc. for C20H23N4O [M+H]+: 335.1872, found 335.1875.
**N-[4-(Diethylamino)phenyl]-3-phenyl-1H-pyrazole-4-carboxamide (SI89)**

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction was performed under a microwave heating (70 °C, 60 min). 3-Phenyl-1H-pyrazole-4-carboxylic acid (188 mg, 1.00 mmol), N,N-diethyl-p-phenylenediamine hydrochloride (256 mg, 1.18 mmol, 1.2 equiv), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.871 mL, 5.00 mmol, 5 equiv), DMF (4 mL). Solvent for extraction: ethyl acetate. Automated chromatography on silica gel gave compound SI89 (83.0 mg, 0.248 mmol, 25%) as an amorphous white solid. \(^1H\) NMR (300 MHz, Acetone-\(d_6\)): \(\delta\) 12.44 (bs, 1H), 8.66 (bs, 1H), 8.13 (bs, 1H), 7.89–7.82 (m, 2H), 7.50–7.33 (m, 5H), 6.66 (m, 2H), 3.35 (q, 4H, \(^3J = 7.0\) Hz), 1.12 (t, 3H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 162.1, 145.5, 129.6, 129.6, 129.4, 129.1, 129.0, 128.8, 128.6, 122.4, 117.0, 113.1, 45.1, 12.9 ppm. HRMS calc. for C\(_{20}\)H\(_{23}\)N\(_4\)O \([\text{M+H]}^+\): 335.1872, found 335.1882.

**N-(4-Oxo-2-phenyl-4H-chromen-6-yl)-3-phenyl-1H-pyrazole-4-carboxamide (SI90)**

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 7 d. 3-Phenyl-1H-pyrazole-4-carboxylic acid (99.5 mg, 0.529 mmol), 6-aminoflavone (126 mg, 0.529 mmol), HBTU (261 mg, 0.688 mmol, 1.3 equiv), DIPEA (0.184 mL, 1.06 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate and brine. Chromatography on silica gel gave compound SI90 (41.0 mg, 0.101 mmol, 19%) as a yellow solid. M.p. 272.4–276.2 °C (decomp.). \(^1H\) NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 13.65–13.10 (bd, 1H), 10.25 (s, 1H), 8.45 (d, 1H, \(^4J = 2.6\) Hz), 8.42–8.20 (bs, 1H), 8.15–8.03 (m, 3H), 7.82–7.72 (m, 3H), 7.65–7.54 (m, 3H), 7.50–7.34 (m, 3H), 7.01 (s, 1H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 176.9, 162.3, 162.1 (b), 151.6, 136.8, 136.7, 131.7, 131.2, 129.1, 128.4, 128.0, 126.3, 126.2, 123.4, 118.8, 114.3 (b), 113.9, 106.4, 10.2 ppm. HRMS calc. for C\(_{25}\)H\(_{18}\)N\(_3\)O\(_3\) \([\text{M+H]}^+\): 408.1348, found 408.1349.
(E)-N-[4-(Dimethylamino)benzylidene]-5-(4-methoxyphenyl)-1H-pyrazol-3-amine (SI91)

Synthesis according to the General procedure III. 4-(Dimethylamino)benzaldehyde (74.6 mg, 0.500 mmol), 3-amino-5-(4-methoxyphenyl)pyrazole (94.6 mg, 0.500 mmol), Na₂SO₄ (142 mg, 1.00 mmol), AcOH (5.7 µL, 0.10 mmol, 0.2 equiv), toluene (2 mL). Chromatography on silica gel gave compound SI91 (101 mg, 0.315 mmol, 63%) as a yellow solid. M.p. 163.7–164.8 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 12.82 (bs, 1H), 8.69 (bs, 1H), 7.80–7.65 (m, 4H), 7.00 (bs, 2H), 6.79 (m, 2H), 6.64 (s, 1H), 3.79 (s, 3H), 3.01 (s, 6H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 160.2, 159.1, 152.4, 150.2, 142.7, 123.8, 122.1, 130.0, 126.2, 111.0, 114.2, 111.5, 55.1, 39.6 ppm. HRMS calc. for C₁₉H₂₁N₄O [M+H]+: 321.1715, found 321.1717.

N-[4-(Dimethylamino)benzyl]-5-(4-methoxyphenyl)-1H-pyrazol-3-amine (SI92)

(E)-N-[4-(Dimethylamino)benzylidene]-5-(4-methoxyphenyl)-1H-pyrazol-3-amine SI91 (49.3 mg, 154 mmol) was dissolved under argon in a mixture of THF (1.3 mL) and MeOH (0.80 mL). Sodium cyanoborohydride (23.3 mg, 0.615 mmol, 4 equiv) was added, and the reaction mixture was stirred for 5 d at room temperature. A saturated solution of sodium hydrogen carbonate in H₂O (5mL) was added and 20 min later EtOAc and water. The phases were separated and the organic phase was washed twice with water. The solvent was removed with a rotary evaporator and the residue was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate gave compound SI92 (39.6 mg, 0.123 mmol, 80%) as a beige solid. M.p. 154.4–158.3 °C. ¹H NMR (300 MHz, Acetone-d₆): δ 10.95 (bs, 1H), 7.62 (m, 2H), 7.25 (m, 2H), 6.94 (m, 2H), 6.70 (m, 2H), 5.83 (s, 1H), 4.79 (bs, 1H), 4.23 (s, 2H), 3.81 (s, 3H), 2.89 (s, 6H) ppm. ¹³C NMR (75 MHz, Acetone-d₆): δ 160.2, 156.9 (br), 150.9, 146.2 (br), 129.7, 129.4, 127.1, 125.7, 87.3, 114.9, 113.4, 55.6, 49.2, 40.8 ppm. HRMS calc. for C₁₉H₂₃N₄O [M+H]+: 323.1872, found 323.1873.
(E)-N-[4-(Dimethylamino)benzylidene]-1,3-diphenyl-1H-pyrazol-5-amine (SI93)

Synthesis according to the General procedure III. Deviating from the General procedure III, the reaction mixture was first heated at 70 °C for 3 h. Then p-toluenesulfonic acid was added and the reaction mixture was heated at 70 °C for 2 h. 4-(Dimethylamino)benzaldehyde (74.6 mg, 0.500 mmol), 5-amino-1,3-diphenyl-1H-pyrazole (118 mg, 1.00 mmol), Na₂SO₄ (142 mg, 1.00 mmol), AcOH (5.7 µL, 0.10 mmol, 0.2 equiv), p-toluenesulfonic acid (9.5 mg, 0.050 mmol, 0.1 equiv), toluene (2 mL). Recrystallization (toluene/hexane 1+1) after chromatography on silica gel gave compound SI93 (107 mg, 0.292 mmol, 58%) as yellow needles. M.p. 170.1–171.6 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 8.76 (s, 1H), 7.94–7.84 (m, 4H), 7.74 (m, 2H), 7.57–7.32 (m, 2H), 7.00 (s, 1H), 6.82 (m, 2H), 3.03 (s, 6H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 161.6, 152.9, 152.3, 150.2, 139.4, 133.1, 130.7, 128.6, 128.6, 127.9, 126.3, 125.1, 123.4, 122.9, 111.5, 90.6, 39.6 ppm. HRMS calc. for C₂₄H₂₃N₄ [M+H]+: 367.1923, found 367.1922.

N-[4-(Dimethylamino)benzyl]-1,3-diphenyl-1H-pyrazol-5-amine (SI94)

(E)-N-[4-(Dimethylamino)benzylidene]-1,3-diphenyl-1H-pyrazol-5-amine SI93 (62.5 mg, 171 mmol) was dissolved under argon in a mixture of THF (1.3 mL) and MeOH (0.80 mL). Sodium cyanoborohydride (25.8 mg, 0.682 mmol, 4 equiv) was added, and the reaction mixture was stirred for 5 d at room temperature. A saturated solution of sodium hydrogen carbonate in H₂O (5mL) was added and 20 min later EtOAc and water. The phases were separated and the organic phase was washed twice with water. The solvent was removed with a rotary evaporator and the residue was subjected to automated preparative chromatography. The chromatography on silica gel with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate, gave compound SI94 (62.1 mg, 0.169 mmol, 99%) as a beige solid. M.p. 127.3–129.4 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 7.75–7.70 (m, 2H), 7.66–7.61 (m, 2H), 7.55–7.47 (m, 2H), 7.39–7.31 (m, 3H), 7.30–7.20 (m, 3H), 6.70–6.64 (m, 2H), 5.97 (t, 1H, J = 5.8 Hz), 5.95 (s, 1H), 4.14 (d, 2H, J = 5.8 Hz), 2.83 (s, 6H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 150.0, 149.6, 149.5, 139.2, 138.1, 133.5, 128.4, 128.3,
127.5, 126.9, 126.5, 125.0, 123.3, 112.3, 85.6, 48.2, 40.2 ppm. HRMS calc. for C_{24}H_{25}N_{4} [M+H]^+: 369.2079, found 369.2076.

**(E)-4-[[5-Amino-3-(4-methoxyphenyl)-1H-pyrazol-4-yl]diazenyl]benzoic acid (SI95)**

![Reaction Scheme](image)

3-(4-Methoxyphenyl)-1H-pyrazol-5-amine (189 mg, 1.00 mmol) was dissolved in ethanol (12.5 mL). To this solution, sodium acetate (246 mg, 3.00 mmol, 3 equiv) and acetic acid (0.172 mL, 3.00 mmol, 3 equiv) were added, and the solution was cooled to 0 °C in an ice bath. Further, a solution of sodium nitrite (79.4 mg, 1.15 mmol) in water (1.5 mL) was prepared and cooled to 0 °C. 4-Aminobenzoic acid (158 mg, 1.15 mmol) was dissolved in an equimixture of conc. hydrochloric acid and water (3.0 mL) and cooled to 0 °C in an ice bath. To this white slurry, the sodium nitrite solution was added slowly at 0 °C during a period of 20 min via a syringe. This mixture was added during a period of 30 min to the 3-(4-methoxyphenyl)-1H-pyrazol-5-amine solution via a syringe. Simultaneously three portions of sodium acetate (246 mg, 246 mg and 492 mg) were added to the reaction mixture after 10 min, 20 min and 30 min, respectively. The reaction mixture was stirred for 70 min. Ethyl acetate was added, and the organic phase was washed once with water and extracted twice with a 0.5 M solution of sodium hydroxide in water. The aqueous phase was neutralized with 1 M hydrochloric acid and the resulting suspension was filtered. The crude solid material was dried *in vacuo* and purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of methanol in ethyl acetate, starting with 0% of methanol, increasing to 10% methanol and long isocratic continuation with 10% methanol to give compound **SI95** (131 mg, 0.388 mmol, 39%) as an orange resin.\(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 12.53 (bs, 2H), 8.09–8.00 (m, 4H), 7.78 (m, 2H), 7.20 (bs, 2H), 7.06 (m, 2H), 3.82 (s, 3H) ppm. \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 167.2, 159.4, 155.9, 130.4, 129.9, 128.7, 124.0, 122.9, 120.6, 113.9, 55.1 ppm. HRMS calc. for C_{17}H_{16}N_{5}O_{3} [M+H]^+: 338.1253, found 338.1252.
(E)-Butyl 4-[[5-amino-3-(4-methoxyphenyl)-1H-pyrazol-4-yl]diazenyl]benzoate (SI96)

(E)-4-[[5-Amino-3-(4-methoxyphenyl)-1H-pyrazol-4-yl]diazenyl]benzoic acid SI95 (40.0 mg, 0.119 mmol) was dissolved in 1-butanol (2 mL). Anhydrous sodium sulfate (400 mg) and acetyl chloride (27.7 µL, 0.390 mmol) were added, and the reaction mixture was refluxed for 7 h. Water and ethyl acetate were added and the phases were separated. The organic phase was washed three times with a 5% solution of sodium hydrogen carbonate in water and three times with water until the water remained neutral. The solvent was removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing ethyl acetate starting with 100% n-hexane to give compound SI96 (13.7 mg, 0.0348 mmol, 29%) as an orange resin. ¹H NMR (300 MHz, DMSO-d₆): δ 12.11 (bs, 1H), 8.10–8.01 (m, 4H), 7.81 (m, 2H), 7.43 (bs, 2H), 7.06 (m, 2H), 4.29 (t, 2H, J = 6.5 Hz), 3.82 (s, 3H), 1.77–1.66 (m, 2H), 1.51–1.38 (m, 2H), 0.95 (t, 3H, J = 7.4 Hz) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 165.4, 159.5, 156.3, 132.7, 131.2, 130.2, 129.0, 128.7, 128.2, 120.8, 113.9, 64.3, 55.1, 30.2, 18.7, 13.5 ppm. HRMS calc. for C₂₁H₂₄N₅O₃ [M+H]⁺: 394.1879, found 394.1882.

(E)-4-[(4-Nitrophenyl)diazenyl]-1,3-diphenyl-1H-pyrazol-5-amine (SI97)

5-Amino-1,3-diphenyl-1H-pyrazole (0.100 g, 0.425 mmol) was dissolved in ethanol (3 mL). To this solution, sodium acetate (105 mg, 1.28 mmol, 3 equiv) and acetic acid (72.9 µL, 1.28 mmol, 3 equiv) were added, and the resulting solution was cooled to 0 °C in an ice bath. A solution of sodium nitrite (29.3 mg, 0.425 mmol) in water (0.5 mL) was prepared and cooled to 0 °C. p-Nitroaniline (58.7 mg, 0.425 mmol) was dissolved in an equimixture of concentrated hydrochloric acid and water (1 mL) and cooled to 0 °C in an ice bath. To this solution, the sodium nitrite solution was added slowly during a period of 30 min. After stirring the reaction mixture for 10 min, it was added during a period of 15 min to the 5-amino-1,3-diphenyl-1H-pyrazole solution in ethanol. Simultaneously, sodium acetate (800 mg) was added to the reaction mixture in small portions. The reaction mixture was stirred for 2 h. Ethyl acetate was added, and the organic phase was washed three times with water. The organic solvents were removed with a rotary evaporator, and the crude product was purified by column chromatography on silica gel (toluene/ethyl acetate 4:1). The product was recrystallized from a mixture of 2-propanol (12 mL) and ethyl acetate (2 mL) to yield compound SI97 (108 mg, 0.281 mmol, 66%) as orange crystals. M.p. 209.7–211.1
°C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 8.34 (m, 2H), 8.18–8.13 (m, 2H), 8.08 (s, 2H), 7.96 (m, 2H), 7.72–7.42 (m, 8H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 157.2, 148.8, 145.8, 139.8, 137.2, 131.5, 129.6, 128.9, 128.5, 128.1, 127.9, 125.0, 124.1, 123.4, 121.5 ppm. HRMS calc. for C$_{21}$H$_{17}$N$_6$O$_2$ [M+H]$^+$: 385.1413, found 385.1412.

1-[5-(4-Methoxyphenyl)-1H-pyrazol-3-yl]-3-[4-(trifluoromethyl)phenyl]urea (SI98)

Synthesis according to the General procedure IV. Deviating from the General procedure IV, anhydrous tetrahydrofuran was used as a solvent. 3-Amino-5-(4-methoxyphenyl)pyrazole (94.6 mg, 0.500 mmol), 4-(trifluoromethyl)phenyl isocyanate (71.4 µL, 0.500 mmol), THF (1.5 mL). Automated chromatography on silica gel gave compound SI98 (149 mg, 0.396 mmol, 79%) as fine white needles. M.p. 213.6–214.8 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.35 (s, 1H), 7.76–7.68 (m, 4H), 7.65–7.59 (m, 2H), 6.94 (m, 2H), 5.71 (s, 1H), 5.50 (s, 2H), 3.84 (s, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 160.8, 153.3, 150.7, 150.4, 140.3, 127.8, 126.6 (q, $J = 3.8$ Hz), 124.9, 124.3 (q, $J = 271.6$ Hz), 119.6, 114.3, 87.0, 55.6 ppm. HRMS calc. for C$_{18}$H$_{16}$F$_3$N$_4$O$_2$ [M+H]$^+$: 377.1225, found 377.1220.

3-Amino-N,5-bis(4-methoxyphenyl)-1H-pyrazole-1-carboxamide (SI99)

Synthesis according to the General procedure IV. Deviating from the General procedure IV, anhydrous tetrahydrofuran was used as a solvent. 3-Amino-5-(4-methoxyphenyl)pyrazole (94.6 mg, 0.500 mmol), 4-methoxyphenyl isocyanate (64.4 µL, 0.500 mmol), THF (2 mL). Automated chromatography on silica gel gave compound SI99 (145 mg, 0.428 mmol, 86%) as a white solid. M.p. 216.5–218.3 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 9.79 (s, 1H), 7.86 (m, 2H), 7.59 (m, 2H), 6.99 (m, 2H), 6.95 (m, 2H), 6.54 (s, 2H), 5.76 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 159.7, 155.9, 151.5, 151.4, 150.6, 130.2, 127.4, 124.9, 122.7, 113.8, 84.6, 55.2, 55.1 ppm. HRMS calc. for C$_{18}$H$_{19}$N$_4$O$_3$ [M+H]$^+$: 339.1457, found 339.1459.
N-(4-Oxo-2-phenyl-4H-chromen-6-yl)isothiazole-4-carboxamide (SI100)

Synthesis according to the General procedure I. Isothiazole-4-carboxylic acid 46s (32.3 mg, 0.250 mmol), 6-aminoflavone 5g (59.3 mg, 0.250 mmol), HBTU (123 mg, 0.325 mmol, 1.3 equiv), DIPEA (87.1 µL, 0.500 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: ethyl acetate and water containing 50% brine. Chromatography on silica gel gave compound SI100 (33.4 mg, 0.0959 mmol, 38%) as a yellow solid. M.p. 283.6–288.5 °C (decomp.). 1H NMR (300 MHz, DMSO-d6): δ 10.72 (s, 1H), 9.30 (d, 1H, 4J = 2.0 Hz), 8.67 (d, 1H, 4J = 2.7 Hz), 8.56 (d, 1H), 8.42 (dd, 1H, 3J = 9.1 Hz), 8.15–8.08 (m, 2H), 7.81 (d, 1H), 7.66–7.56 (m, 3H), 7.03 (s, 1H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 176.9, 162.3, 159.3, 151.6, 150.3, 150.3, 136.0, 131.7, 131.2, 129.1, 127.1, 126.4, 125.9, 123.4, 118.8, 114.9, 106.5 ppm. HRMS calc. for C19H13N2O3S [M+H]+: 349.0647, found 349.0649.

5-Methyl-N-(4-oxo-2-phenyl-4H-chromen-6-yl)-2-phenylfuran-3-carboxamide (SI101)

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 3 d. 5-Methyl-2-phenylfuran-3-carboxylic acid (31.9 mg, 0.158 mmol), 6-aminoflavone 5g (37.4 mg, 0.158 mmol), HBTU (77.9 mg, 0.205 mmol, 1.3 equiv), DIPEA (55.0 µL, 0.316 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (2:1). Chromatography on silica gel gave compound SI101 (27.1 mg, 0.0643 mmol, 41%) as a slightly yellow solid. M.p. 217.3–219.7 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.37 (s, 1H), 8.49 (d, 1H, 4J = 2.7 Hz), 8.14–8.07 (m, 3H), 7.87–7.82 (m, 2H), 7.79 (d, 1H, 3J = 9.1 Hz), 7.66–7.55, 7.48–7.32 (each m, each 3H), 7.02 (s, 1H), 6.70 (q, 4J = 1.1 Hz), 2.40 (d, 3H, 4J = 1.0 Hz) ppm. 13C NMR (75 MHz, DMSO-d6): δ 176.9, 162.4, 162.3, 151.8, 151.5, 150.9, 136.5, 131.7, 131.1, 129.7, 129.1, 128.3, 126.5, 126.5, 126.3, 123.4, 118.9, 118.5, 114.3, 108.2, 106.5, 13.1 ppm. HRMS calc. for C27H20NO4 [M+H]+: 422.1392, found 422.1392.
Synthesis according to the General procedure I. 5-Phenylloxazole-4-carboxylic acid 46a (44.7 mg, 0.236 mmol), 6-aminoflavone 5g (56.1 mg, 0.236 mmol), HBTU (116 mg, 0.307 mmol, 1.3 equiv), DIPEA (82.2 µL, 0.472 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (2:1). Chromatography on silica gel gave compound SI102 (28.9 mg, 0.0708 mmol, 30%) as a yellow solid. M.p. 227.3–228.8 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.61 (s, 1H), 8.72 (s, 1H), 8.69 (d, 1H, J = 2.6 Hz), 8.23–8.17 (m, 3H), 8.14–8.07 (m, 2H), 7.80 (d, 1H, J = 9.1 Hz), 7.65–7.48 (m, 6H), 7.04 (s, 1H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 176.9, 162.3, 159.7, 152.2, 152.0, 150.3, 135.9, 131.7, 131.1, 130.1, 129.1, 128.7, 128.5, 127.9, 127.2, 126.7, 126.3, 123.4, 118.8, 114.9, 106.5 ppm. HRMS calc. for C25H17N2O4 [M+H]+: 409.1188, found 409.1187.

3,5-Bis(methylthio)-N-(4-oxo-2-phenyl-4H-chromen-6-yl)isothiazole-4-carboxamide (SI103)

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 3 d at room temperature. 3,5-Bis(methylthio)isothiazole-4-carboxylic acid 46w (27.0 mg, 0.122 mmol), 6-aminoflavone 5g (37.6 mg, 0.122 mmol), HBTU (60.3 mg, 0.159 mmol, 1.3 equiv), DIPEA (42.5 µL, 0.244 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: ethyl acetate and water containing 50% brine. Chromatography on silica gel gave compound SI103 (6.7 mg, 0.015 mmol, 12%) as a yellow solid. M.p. 245.3–270.7 °C (decomp.). 1H NMR (300 MHz, DMSO-d6): δ 10.40 (s, 1H), 8.42 (d, 1H, J = 2.7 Hz), 8.15–8.09 (m, 2H), 8.06 (dd, 1H, J = 9.1 Hz, J = 2.7 Hz), 7.82 (d, 1H, J = 9.1 Hz), 7.66–7.56 (m, 3H), 7.03 (s, 1H), 2.68 (s, 3H), 2.58 (s, 3H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 176.8, 169.6, 163.2, 162.4, 160.3, 152.2, 136.1, 131.7, 131.1, 129.1, 126.4, 126.3, 123.5, 119.1, 114.2, 112.7, 106.5, 18.4, 12.1, 11.9 ppm. HRMS calc. for C23H17N2O3S3 [M+H]+: 441.0401, found 441.0401.
N-(4-Oxo-2-phenyl-4H-chromen-6-yl)-4-phenyl-1,2,3-thiadiazole-5-carboxamide (SI104)

Synthesis according to the General procedure I. 4-Phenyl-1,2,3-thiadiazole-5-carboxylic acid 46n (31.9 mg, 0.158 mmol), 6-aminoflavone 5g (34.1 mg, 0.158 mmol), HBTU (71.0 mg, 0.187 mmol, 1.3 equiv), DIPEA (50.2 µL, 0.288 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (1:1). Chromatography on silica gel gave compound SI104 (33.8 mg, 0.0794 mmol, 55%) as a yellow solid. M.p. 222.2–223.9 °C (decomp.). 1H NMR (300 MHz, DMSO-d6): δ 11.29 (s, 1H), 8.42 (d, 1H, J = 2.6 Hz), 8.15–8.07 (m, 2H), 7.99–7.89 (m, 3H), 7.83 (d, 1H, J = 9.1 Hz), 7.66–7.47 (m, 6H), 7.05 (s, 1H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 176.7, 162.5, 159.1, 158.3, 152.4, 144.2, 135.5, 131.8, 131.0, 129.9, 129.7, 129.1, 129.0, 128.2, 126.3, 123.5, 119.4, 114.5, 106.5 ppm. HRMS calc. for C_{24}H_{16}N_{3}O_{5}S [M+H]^+: 426.0912, found 426.0913.

3-Methyl-N-(4-oxo-2-phenyl-4H-chromen-6-yl)-5-phenylisoxazole-4-carboxamide (SI105)

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 4 d. 3-Methyl-5-phenylisoxazole-4-carboxylic acid (105 mg, 0.516 mmol), 6-aminoflavone 5g (122 mg, 0.515 mmol), HBTU (254 mg, 0.671 mmol, 1.3 equiv), DIPEA (0.180 mL, 1.03 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate/diethyl ether (1:1) and water containing 30% brine. Chromatography on silica gel gave compound SI105 (162 mg, 0.383 mmol, 74%) as slightly yellow crystals. M.p. 215.2–217.8 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.86 (s, 1H), 8.46 (d, 1H, J = 2.7 Hz), 8.16–8.08 (m, 2H), 8.00 (dd, 1H, J = 2.7 Hz, J = 9.1 Hz), 7.87–7.79 (m, 3H), 7.66–7.52 (m, 6H), 7.05 (s, 1H), 2.41 (s, 3H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 176.8, 166.5, 162.4, 160.3, 159.0, 152.1, 135.9, 131.8, 131.1, 131.0, 129.2, 129.1, 126.8, 126.3, 126.3, 126.2, 123.5, 119.3, 114.2, 113.0, 106.5, 10.2 ppm. HRMS calc. for C_{28}H_{19}N_{2}O_{4} [M+H]^+: 423.1345, found 423.1346.

3-[4-(Diethylamino)benzamido]benzofuran-2-carboxamide (SI106)

Synthesis according to the General procedure II. Deviating from the General procedure II, the oxalyl chloride solution was stirred at room temperature for 1 h, and DIPEA was added to the pyridine solution. 4-(Diethylamino)benzoic acid 29 (387 mg, 2.00 mmol), 3-aminobenzofuran-2-carboxamide (352 mg, 2.00 mmol), a 2 M solution of oxalyl chloride in DCM (4.00 mL, 8.00 mmol, 4 equiv), DMF (16.7 µL, 0.200 mmol, 0.1 equiv), DCM (3 mL), DIPEA (0.522 mL, 3.00 mmol, 1.5 equiv), pyridine (5 mL). Solvent for extraction: ethyl acetate. Recrystallization (MeOH/H_{2}O 20+1) after chromatography on silica gel gave compound SI106 (207 mg, 0.589 mmol,
29%) as slightly yellow needles. M.p. 191.3–192.6 °C. 1H NMR (300 MHz, DMSO-d6): δ 10.88 (s, 1H), 8.37 (ddd, 1H, 3J = 8.1 Hz, 4J = 1.4 Hz, 5J = 0.7 Hz), 8.21 (bs, 1H), 7.92 (bs, 1H), 7.81 (m, 2H), 7.59 (ddd≈dt, 1H, 3J = 8.4 Hz, 4J = 1.3), 7.52 (ddd, 1H, 3J = 7.0 Hz), 7.33 (ddd, 1H), 6.78 (m, 2H), 3.42 (q, 4H, 3J = 7.0 Hz), 1.13 (t, 6H, 3J = 7.0 Hz) ppm.

13C NMR (75 MHz, DMSO-d6): δ 163.8, 162.7, 152.7, 150.3, 133.1, 129.3, 127.9, 127.8, 126.2, 122.9, 122.0, 118.4, 111.8, 110.5, 43.8, 12.4 ppm. HRMS calc. for C20H22N3O3 [M+H]+: 352.1661 found 352.1667.

1-[4-[(5-(4-Isobutylphenyl)isoxazol-3-yl)methoxy]phenyl]ethanone (SI107)

[5-(4-Isobutylphenyl)isoxazol-3-yl]methanol (0.100 g, 0.432 mmol), 4′-hydroxyacetophenone (70.2 mg, 0.518 mmol, 1.2 equiv) and triphenylphosphine (136 mg, 0.518 mmol, 1.2 equiv) were dissolved in anhydrous THF (2 mL) under argon and cooled to 0 °C in an ice bath. Diisopropyl azodicarboxylate (0.102 mL, 0.518 mmol, 1.2 equiv) was added, and the reaction mixture was stirred for 1 h at 0 °C and overnight at room temperature. Ethyl acetate was added, and the organic phase was washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing ethyl acetate starting with 100% n-hexane to give compound SI107 (128 mg, 0.366 mmol, 85%) as white crystals. M.p. 109.7–110.3 °C. 1H NMR (300 MHz, DMSO-d6): δ 7.96 (m, 2H), 7.79 (m, 2H), 7.32 (m, 2H), 7.19 (m, 2H), 7.09 (s, 1H), 5.35 (s, 2H), 2.52 (s, 3H), 2.51 (d, 2H, 3J = 6.7 Hz), 1.87 (dsept≈sept, 1H, 3J = Hz), 0.87 (d, 6H) ppm. 13C NMR (75 MHz, DMSO-d6): δ 196.2, 169.7, 161.5, 160.8, 144.0, 130.5, 130.4, 129.7, 125.4, 124.2, 114.6, 99.3, 61.4, 44.3, 29.4, 26.4, 22.0 ppm. HRMS calc. for C22H24NO3[M+H]+: 350.1758, found 350.1756.
Synthesis of compounds in Tables 6-8 (compounds not included in Schemes 1-4 and Table 1)

**N-[4-[Ethyl(isopropyl)amino]phenyl]isothiazole-4-carboxamide (61)**

Synthesis according to the General procedure I. Isothiazole-4-carboxylic acid 46s (0.100 g, 0.774 mmol), N-ethyl-N-isopropylphenylenediamine hydrochloride (166 mg, 0.773 mmol), HBTU (381 mg, 1.01 mmol, 1.3 equiv), DIPEA (0.404 mL, 2.32 mmol, 3 equiv), DMF (1.5 mL). Solvent for extraction: ethyl acetate and water containing 50% brine. Chromatography on silica gel gave compound 61 (184 mg, 0.636 mmol, 82%) as a yellowish oil. $^1$H NMR (300 MHz, Acetone-$d_6$): $\delta$ 9.38 (br s, 1H), 9.11 (d, 1H, $^4J = 2.1$ Hz), 8.31 (d, 1H, $^4J = 2.1$ Hz), 7.69 (m, 2H), 6.79 (m, 2H), 4.05 (sep, 1H, $^3J = 6.6$ Hz), 3.27 (q, 2H, $^3J = 7.0$ Hz), 1.18 (d, 6H, $^3J = 6.6$ Hz), 1.14 (t, 3H, $^3J = 7.0$ Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 158.3, 154.7, 151.1, 144.9, 127.4, 124.4, 121.9, 112.9, 47.9, 37.4, 19.7, 14.8 ppm. HRMS calc. for $C_{15}H_{20}N_{3}S$ [M+H]$: 290.1327$, found 290.1334.

**N-[4-[Ethyl(isopropyl)amino]phenyl]-3-methyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)isoxazole-4-carboxamide (62)**

Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 4 d and the coupling reagent 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) was used instead of HBTU. 3-Methyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)isoxazole-4-carboxylic acid 46c (25.5 mg, 0.113 mmol), N-ethyl-N-isopropylphenylenediamine hydrochloride (24.3 mg, 0.113 mmol), HATU (55.9 mg, 0.147 mmol, 1.3 equiv), DIPEA (59.0 $\mu$L, 0.339 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether and a mixture of water and brine (4:1). Chromatography on silica gel gave compound SI-107 (42.0 mg, 0.109 mmol, 96%) as an orange resin. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.13 (s, 1H), 7.41 (m, 2H), 6.73 (m, 2H), 4.00 (sep, 1H, $J = 6.6$ Hz), 3.20 (q, 2H, $J = 6.9$ Hz), 2.89 (s, 3H), 2.47 (s, 3H), 1.12 (d, 6H, $J = 6.6$ Hz), 1.08 (t, 3H, $J = 6.9$ Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 158.9, 158.5, 158.0, 157.8, 145.4, 134.2, 126.7, 121.7, 117.6, 112.7, 47.9, 37.3, 19.7, 14.7, 14.0, 10.4 ppm. HRMS calc. for $C_{19}H_{24}N_{3}O_{2}$S [M+H]$: 386.1651$, found 386.1651.

**N-[4-[Ethyl(isopropyl)amino]phenyl]-3-methyl-5-phenylisoxazole-4-carboxamide (63)**

Synthesis according to the General procedure I. 3-Methyl-5-phenylisoxazole-4-carboxylic acid (102 mg, 0.500 mmol), N-ethyl-N-isopropylphenylenediamine hydrochloride (107 mg, 0.500 mmol), HBTU (247 mg, 0.650 mmol, 1.3 equiv), DIPEA (0.261 mL, 0.261 mmol, 3 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 63 (145 mg, 0.451
mmol, 90%) as yellow needles. M.p. 133.9–135.2 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.19 (s, 1H), 7.85–7.70 (m, 2H), 7.59–7.50 (m, 3H), 7.44 (m, 2H), 6.72 (m, 2H), 3.98 (sept, 1H, $^3$J = 6.6 Hz), 3.20 (q, 2H, $^3$J = 7.0 Hz), 2.35 (s, 3H). 1.12 (d, 6H, $^3$J = 6.6 Hz), 1.07 (t, 3H, $^3$J = 7.0 Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 165.5, 159.1, 158.9, 145.1, 130.7, 129.1, 127.5, 126.5, 126.5, 121.3, 113.7, 113.0, 48.0, 37.3, 19.7, 14.7, 10.1 ppm. HRMS calc. for C$_{22}$H$_{26}$N$_3$O$_2$ [M+H]$^+$: 364.2025, found 364.2026.

$(E)$-N-4-[(Dimethylamino)benzyldene]-5-methyl-3-phenylisoxazol-4-amine (SI108)

Synthesis according to the General procedure III. Deviating from the General procedure III, reaction mixture was heated at 100 °C for 9 h. 4-[(Dimethylamino)benzaldehyde, (214 mg, 1.43 mmol), 5-methyl-3-phenylisoxazol-4-amine 28 (0.250 g, 1.43 mmol), Na$_2$SO$_4$ (509 mg, 3.58 mmol, 2.5 equiv), AcOH (20.5 μL, 0.358 mmol, 0.25 equiv), toluene (2.5 mL). Recrystallization (ethyl acetate) after chromatography on silica gel gave compound SI108 (142 mg, 0.465 mmol, 32%) as yellowish crystals. M.p. 155.2–158.6 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 8.40 (s, 1H), 7.95–7.87 (m, 2H), 7.72 (m, 2H), 7.52–7.45 (m, 3H), 6.80 (m, 2H), 3.01 (s, 6H), 2.48 (s, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 163.3, 156.7, 156.4, 152.6, 130.0, 129.5, 128.9, 128.6, 128.5, 127.5, 123.4, 111.5, 39.6, 11.1 ppm. HRMS calc. for C$_{19}$H$_{20}$N$_3$O [M+H]$^+$: 306.1606, found 306.1608.

N-4-[(Dimethylamino)benzyl]-5-methyl-3-phenylisoxazol-4-amine (SI109)

$(E)$-N-4-[(Dimethylamino)benzyldene]-5-methyl-3-phenylisoxazol-4-amine SI108 (90.0 mg, 0.295 mmol) was dissolved in absolute methanol (1 mL) under argon. Sodium cyanoborohydride (22.2 mg, 0.354 mmol) was added, and the reaction mixture was stirred overnight at room temperature. THF (1 mL) was added, and stirring was continued overnight. The second portion of sodium cyanoborohydride (11.1 mg, 0.177 mmol) was added, and the reaction mixture was heated at 40 °C for 3 d. The third portion of sodium cyanoborohydride (44.4 mg, 0.708 mmol) was added and stirring at 40 °C was continued for 2 d. Then sodium borohydride (12.3 mg, 0.325 mmol) was added and heating was continued for 2 d. The second portion of sodium borohydride (12.3 mg, 0.325 mmol) was added, and heating was continued for 4 d. First, a small amount of water was added, and after 15
min ethyl acetate and water were added. The phases were separated and the organic phase was washed twice with water. The solvent was removed with a rotary evaporator and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate to give compound SI109 (41.0 mg, 0.133 mmol, 45%) as a colorless oil. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.93–7.84 (m, 2H), 7.55–7.45 (m, 3H), 6.61 (m, 2H), 4.30 (t, 1H, $^3J = 6.9$ Hz), 3.72 (s, 6H), 2.16 (s, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 159.1, 157.3, 149.5, 129.4, 129.3, 128.7, 128.6, 127.3, 127.0, 123.1, 112.1, 51.4, 40.1, 10.1 ppm. HRMS calc. for C$_{19}$H$_{22}$N$_3$O [M+H]$^+$: 308.1763, found 308.1768.

$N$-[4-(Dimethylamino)benzyl]-$N$-(5-methyl-3-phenylisoxazol-4-yl)acetamide (64)

![Chemical structure of compound SI109 and 64](image)

To a solution of $N$-[4-(dimethylamino)benzyl]-5-methyl-3-phenylisoxazol-4-amine SI109 (26.0 mg, 0.0846 mmol) and triethylamine (29.5 µL, 0.212 mmol, 2.5 equiv) in absolute DCM (0.3 mL) was added acetyl chloride (9.0 µL, 0.13 mmol, 1.5 equiv) under argon. The reaction mixture was stirred for 1 h at room temperature. Triethylamine (29.5 µL, 0.212 mmol, 2.5 equiv) and acetyl chloride (9.0 µL, 0.13 mmol, 1.5 equiv) were added and stirring was continued overnight. Finally, DCM (0.5 mL), triethylamine (89 µL, 0.64 mmol, 7.5 equiv) and acetyl chloride (27 µL, 0.38 mmol, 4.5 equiv) were added and stirring was continued for 2 h. A 5% solution of sodium hydrogen carbonate in water and ethyl acetate were added, the phases were separated, and the organic phase was washed twice with water. The organic solvent was removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate gave compound 64 (11.8 mg, 33.8 µmol, 40%) as a colorless oil. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.62–7.44 (m, 5H), 6.93 (m, 2H), 6.58 (m, 2H), 5.17 (d, 1H, $^3J = 13.7$ Hz), 3.73 (d, 1H), 2.84 (s, 6H), 1.83 (s, 3H), 1.81 (s, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 170.0, 167.6, 158.0, 150.0, 130.4, 130.2, 129.3, 127.5, 126.6, 123.8, 117.3, 112.0, 49.9, 40.1, 21.9, 10.0 ppm. HRMS calc. for C$_{21}$H$_{24}$N$_3$O$_2$ [M+H]$^+$: 350.1869, found 350.1869.
N-[4-(Diethylamino)phenyl]-3-methyl-5-phenylisoxazole-4-carboxamide (65)

Synthesis according to the General procedure I. 3-Methyl-5-phenyl-4-isoxazolecarboxylic acid (102 mg, 0.500 mmol), \(N,N\)-diethyl-p-phenylenediamine 17 (83.1 \(\mu\)L, 0.500 mmol), HBTU (246.5 mg, 0.650 mmol, 1.3 equiv), DIPEA (0.174 mL, 1.00 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H\(_2\)O 10+1) without chromatography on silica gel gave compound 65 (150 mg, 0.428 mmol, 86%) as yellow needles. M.p. 159.0–160.2 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.18 (s, 1H), 7.85–7.78 (m, 2H), 7.57–7.51 (m, 3H), 7.43 (m, 2H), 6.65 (m, 2H), 3.31 (q, 4H, \(J = 7.0\) Hz), 2.35 (s, 3H), 1.07 (t, 6H, \(J = 7.0\) Hz) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 165.5, 159.0, 158.9, 144.6, 130.7, 129.1, 127.1, 126.5, 126.5, 121.5, 113.8, 111.8, 43.7, 12.3, 10.1 ppm. HRMS calc. for C\(_{21}\)H\(_{24}\)N\(_3\)O\(_2\) [M+H]\(^+\): 350.1869, found 350.1870.

N-(5-Methyl-3-phenylisoxazol-4-yl)-4-(4-methylpiperazin-1-yl)benzamide (67)

4-(4-Methylpiperazin-1-yl)benzoic acid (75.0 mg, 0.340 mmol) was dissolved in anhydrous dichloromethane (3 mL) under argon. Oxalyl chloride (0.146 mL, 1.70 mmol, 5 equiv) was added, and the reaction mixture was stirred at room temperature for 2 h. The organic solvents were removed with a rotary evaporator, and the residue was dissolved in anhydrous pyridine (2 mL). To this solution, 5-methyl-3-phenylisoxazol-4-amine 28 (59.3 mg, 0.340 mmol) and DIPEA (0.178 mL, 1.02 mmol, 3 equiv) were added, and the resulting mixture was stirred at room temperature overnight. Then HBTU (155 mg, 0.408 mmol, 1.2 equiv) and DIPEA (178 \(\mu\)L, 1.02 mmol, 3 equiv) were added, and the reaction mixture was stirred at room temperature for 3 d. HBTU (77.0 mg, 0.204 mmol, 0.6 equiv) were added and the reaction mixture was heated at 80 °C for 7 h. Ethyl acetate was added and the organic phase was washed three times with a mixture of water and brine (1+1). The automated chromatography on silica gel was performed with an increasing gradient of ethyl acetate in \(n\)-hexane, starting with 0% of ethyl acetate. Recrystallization (MeOH/H\(_2\)O 10+1) gave compound 67 (0.040 g, (0.106 mmol, 31%) as beige needles. M.p. 192.0–194.4 °C (decomp.). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.74 (m, 2H), 7.68–7.61 (m, 2H), 7.44–7.35 (m, 3H), 7.12 (s, 1H), 6.89 (m, 2H), 3.33 (m, 4H), 2.55 (m, 4H), 2.42 (s, 3H), 2.34 (s, 3H) ppm. \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 166.3, 159.3, 154.0, 130.1, 129.2, 129.1, 128.5, 127.9, 122.6, 114.3, 112.5, 54.9, 47.7, 46.3, 12.1 ppm. HRMS calc. for C\(_{22}\)H\(_{25}\)N\(_4\)O\(_2\) [M+H]\(^+\): 377.1978, found 377.1974.
Methyl 4-(N,5-dimethyl-3-phenylisoxazole-4-carboxamido)benzoate (SI110)

Methyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate **11** (183 mg, 0.543 mmol) was dissolved under argon in absolute DMF (4 mL). A 60% suspension of sodium hydride in mineral oil (23.9 mg, 0.597 mmol, 1.1 equiv) was added, and the reaction mixture was stirred for 3 h at room temperature. Iodomethane (50.7 µL, 0.815 mmol, 1.5 equiv) was added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with diethyl ether and washed three times with a mixture of water and brine (3:1). The solvent was removed at a rotary evaporator and the residue was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate gave compound **SI110** (0.180 g, 0.514 mmol, 95%) as a colorless oil. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.76 (m, 2H), 7.75–7.41 (m, 3H), 7.37–7.31 (m, 2H), 6.92 (m, 2H), 3.82 (s, 3H), 3.33 (s, 3H), 2.41 (s, 3H) ppm. ¹³C NMR (75 MHz, DMSO-*d*₆): δ 170.5, 165.9, 162.5, 160.0, 147.1, 130.5, 129.9, 129.4, 128.3, 127.6, 127.5, 126.3, 112.4, 52.6, 37.2, 12.0 ppm. HRMS calc. for C₂₀H₁₉N₂O₄ [M+H]⁺: 351.1345, found 351.1352.

4-(N,5-Dimethyl-3-phenylisoxazole-4-carboxamido)benzoic acid (68)

Methyl 4-(N,5-dimethyl-3-phenylisoxazole-4-carboxamido)benzoate **SI110** (129 mg, 0.368 mmol) was dissolved in an equimixture of THF, MeOH and water (6 mL). Lithium hydroxide hydrate (18.5 mg, 0.442 mmol) was added, and the reaction mixture was stirred overnight at room temperature. Diethyl ether was added and the organic phase was extracted twice with water. The combined aqueous phases were acidified with a 1 M solution of HCl in H₂O and extracted with ethyl acetate. The organic phase was washed four times with water until the aqueous phase remained neutral. Evaporation of the organic phase with a rotary evaporator and drying *in vacuo* gave compound **68** (98.5 mg, 0.293
mmol, 80%) as a white solid. M.p. 219.5–220.7 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 12.92 (bs, 1H), 7.63 (m, 2H), 7.53–7.40 (m, 3H), 7.37–7.30 (m, 2H), 6.88 (m, 2H), 3.31 (s, 3H), 2.39 (s, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 169.8, 166.4, 162.0, 159.5, 146.2, 130.0, 129.6, 128.8, 128.3, 127.8, 127.0, 125.6, 111.9, 36.7, 11.5 ppm. HRMS calc. for C$_{19}$H$_{17}$N$_2$O$_4$ [M+H]$^+$: 337.1188, found 337.1195.

Methyl 1-phenethyl-4-phenyl-1H-1,2,3-triazole-5-carboxylate (SI111)

(2-Bromoethyl)benzene (0.137 mL, 1.00 mmol) was dissolved in ethanol (2 mL). Sodium azide (65.0 mg, 1.00 mmol) was added, and the reaction mixture was stirred under reflux conditions overnight. Ethanol was removed with a rotary evaporator. Methyl phenylpropiolate (0.160 g, 1.00 mmol) and toluene (2 mL) were added and the reaction mixture was heated at 110 °C under reflux conditions for 3 d. The reaction mixture was diluted with ethyl acetate and washed three times with water. The organic solvent was removed with a rotary evaporator. The crude product was purified by automated chromatography on silica gel, using a gradient of increasing ethyl acetate starting with 100% n-hexane to give compound SI111 (76.4 mg, 0.249 mmol, 25%) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.72–7.65 (m, 2H), 7.47–7.38 (m, 3H), 7.34–7.17 (m, 5H), 4.96 (m, 1H), 3.78 (s, 3H), 3.24 (m, 1H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 159.8, 150.3, 137.1, 130.5, 129.5, 129.1, 128.9, 128.2, 127.1, 50.4, 50.2, 37.2 ppm. HRMS calc. for C$_{18}$H$_{18}$N$_3$O$_2$ [M+H]$^+$: 308.1399, found 308.1400.

N-[4-(Diethylamino)phenyl]-1-phenethyl-4-phenyl-1H-1,2,3-triazole-5-carboxamide (71)

Synthesis according to the General procedure VI. Methyl 1-phenethyl-4-phenyl-1H-1,2,3-triazole-5-carboxylate SI111 (55.1 mg, 0.179 mmol), LiOH·H$_2$O (11.3 mg, 0.269 mmol, 1.5 equiv), solvent volume: 200 µL each, N,N-Diethyl-p-phenylenediamine 17 (29.8 µL, 0.179 mmol), HBTU (97.1 mg, 0.256 mmol, 1.3 equiv), DIPEA (62.4 µL, 0.358 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound 71 (25.4 mg, 0.0578 mmol, 32%) as a greenish solid. M.p. 138.4–139.8 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.58 (s, 1H), 7.79–7.74 (m, 2H), 7.50–7.17 (m, 10H), 6.68 (m, 2H), 4.70 (t, 1H, $^3$J = 7.4 Hz), 3.32 (q, 4H, $^3$J = 7.0 Hz), 3.20 (t, 1H), 1.09 (t, 6H, $^3$J = 7.0 Hz) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 157.0, 144.9, 143.4, 137.2, 130.1, 129.8, 128.8, 128.6, 128.4, 128.3, 126.6, 126.3, 126.3, 121.8, 111.6, 50.1, 43.7, 35.4, 12.3 ppm. HRMS calc. for C$_{27}$H$_{30}$N$_5$O [M+H]$^+$: 440.2450, found 440.2452.
[3-Amino-5-(4-methoxyphenyl)-1H-pyrazol-1-yl][4-(tert-butyl)phenyl]methanone (SI112) and 4-(tert-butyl)-N-[5-(4-methoxyphenyl)-1H-pyrazol-3-yl]benzamide (72)

Synthesis according to the General procedure I. 4-(tert-Butyl)benzoic acid (178 mg, 1.00 mmol), 5-(4-methoxyphenyl)-1H-pyrazol-3-amine (189 mg, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate. Automated chromatography on silica gel and subsequent recrystallization (EtOH/H₂O 19+1) gave compound SI112 (217 mg, 0.621 mmol, 62%) as white plates and compound 72 (13.0 mg, 0.037 mmol, 4%) as a white solid. Compound SI112: M.p. 142.0–143.6 ºC. 1H NMR (300 MHz, DMSO-d₆): δ 8.07 (m, 2H), 7.70 (m, 2H), 7.57 (m, 2H), 6.98 (m, 2H), 6.78 (s, 2H), 5.83 (s, 1H), 3.78 (s, 3H), 1.34 (s, 9H) ppm. 13C NMR (75 MHz, DMSO-d₆): δ 168.9, 159.9, 155.3, 153.8, 130.9, 130.3, 127.3, 124.6, 124.6, 114.0, 84.5, 55.1, 34.7, 30.8 ppm. HRMS calc. for C₂₁H₂₂N₂O₂ [M+H]+: 350.1869, found 350.1873. Compound 72: M.p. 232.1–232.4 ºC. 1H NMR (300 MHz, DMSO-d₆): δ 11.87 (br s, 1H), 9.85 (s, 1H), 8.04 (m, 2H), 7.73 (m, 2H), 7.57 (m, 2H), 7.02 (m, 2H), 6.94 (br s, 1H), 3.85 (s, 3H), 1.36 (s, 9H) ppm. 13C NMR (75 MHz, DMSO-d₆): δ 165.2, 160.7, 155.9, 148.0, 145.1, 132.5, 128.3, 127.5, 126.2, 124.5, 115.2, 93.7, 55.7, 35.5, 31.4 ppm. HRMS calc. for C₂₁H₂₂N₂O₂ [M+H]+: 350.1869, found 350.1875.

3',5-Dimethyl-N-(4-oxo-2-phenyl-4H-chromen-6-yl)-3,5'-biisoxazole-4'-carboxamide (73)

Synthesis according to the General procedure I. Deviating from the General procedure I, HATU was used as coupling reagent and due to the poor solubility of the product a different work-up procedure was used after stirring the reaction mixture overnight. MeOH (2 mL) was added and the suspension was filtered, washed with water and MeOH and dried in vacuo. 3-Methyl-5-(5-methylisoxazol-3-yl)isoxazole-4-carboxylic acid (40.8 mg, 0.196 mmol), 6-aminoflavone 5g (46.5 mg, 0.196 mmol), HATU (96.9 mg, 0.155 mmol, 1.3 equiv), DIPEA (68.3 µL, 0.392 mmol, 2 equiv), DMF (2 mL). Filtration gave compound 73 (66.4 mg, 0.0817 mmol, 61%) as a white solid. M.p. 274.4–277.6 ºC. 1H NMR (300 MHz, DMSO-d₆): δ 11.16 (s, 1H), 8.37 (d, 1H, J = 2.7 Hz), 8.20 (dd, 1H, J = 9.1 Hz), 8.02–7.94 (m, 2H), 7.64 (d, 1H), 7.60–7.51 (m, 3H), 6.80 (s, 1H), 6.69 (q, 1H, J = 9.0 Hz), 2.67 (s, 3H), 2.62 (d, 3H) ppm. 13C NMR (75 MHz, DMSO-d₆): δ 177.5, 172.1, 163.2, 163.0, 158.4, 156.4, 153.6, 152.9, 153.8, 131.9, 131.5, 129.0, 126.4, 126.2, 124.3, 118.8, 115.1, 113.9, 107.0, 101.7, 12.1 ppm. HRMS calc. for C₂₄H₁₉N₃O₅ [M+H]+: 428.1246, found 428.1249.
**N-[4-(Ethyl(isopropyl)amino)phenyl]-3',5-dimethyl-[3,5'-biisoxazole]-4'-carboxamide (74)**

Synthesis according to the General procedure I. Deviating from the General procedure I, HATU was used as coupling reagent. 3-Methyl-5-(5-methylisoxazol-3-yl)isoxazole-4-carboxylic acid (28.5 mg, 0.137 mmol), N-ethyl-N-isopropylphenylenediamine hydrochloride (29.4 mg, 0.137 mmol), HATU (67.7 mg, 0.178 mmol, 1.3 equiv), DIPEA (71.6 µL, 0.411 mmol, 3 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H₂O 10+1) without chromatography on silica gel gave compound 74 (30.1 mg, 0.0817 mmol, 60%) as fine yellow needles. M.p. 111.2–114.5 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 10.22 (s, 1H), 7.44 (m, 2H), 6.76–6.69 (m, 3H), 3.98 (sept, 1H, 3J = 6.0 Hz), 3.20 (q, 4H, 3J = 7.0 Hz), 2.51 (d, 3H, 4J = 0.9 Hz), 2.40 (s, 3H), 1.12 (d, 6H, 1J = 6.0 Hz), 1.08 (t, 6H, 3J = 7.0 Hz) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 171.5, 159.4, 157.4, 156.7, 151.8, 127.4, 121.3, 116.5, 113.0, 101.0, 48.0, 37.3, 19.7, 14.7, 11.7, 10.2 ppm. HRMS calc. for C₂₀H₂₈N₄O [M+H]⁺: 369.1927, found 369.1927.

**(E)-N¹-[3-(4-Fluorophenyl)-1H-pyrazol-4-yl]methylene]-N⁴,N⁴-dimethylbenzene-1,4-diamine (75)**

Synthesis according to the General procedure III. Deviating from the General procedure III, no acid catalyst was added, and the reaction mixture was heated at 70 °C overnight. 3-(4-Fluorophenyl)-1H-pyrazole-4-carbaldehyde (0.190 g, 1.00 mmol), N,N-dimethyl-p-phenylenediamine 42 (136 mg, 1 equiv), Na₂SO₄ (0.200 g, 1.41 mmol), toluene (3 mL). Recrystallization (hexane/benzene 1+1) after chromatography on silica gel gave compound 75 (241 mg, 0.782 mmol, 78%) as a yellow solid. M.p. 100.6–108.3 °C. ¹H NMR (300 MHz, DMSO-d₆): δ 13.39 (bs, 1H), 8.47 (s, 1H), 8.20 (bs, 1H), 7.78 (m, 2H), 7.34 (m, 2H), 7.12 (m, 2H), 6.72 (m, 2H), 2.89 (s, 6H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ 162.1 (d, J = 245.6 Hz), 148.9, 148.3, 141.1, 130.5 (d, J = 8.2 Hz), 128.2, 121.6, 117.4, 115.6 (d, J = 21.3 Hz), 112.8, 40.3 ppm. HRMS calc. for C₁₈H₁₅FN₄ [M+H]⁺: 309.1515, found 309.1515.

**2-Cyanoethyl 4-(5-methyl-3-phenyloxazole-4-carboxamido)benzoate (76)**

Synthesis according to the General procedure VII. Deviating from the General procedure VII, the product was recrystallized from MeOH after chromatography. 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid 12 (39.4 mg, 0.122 mmol), 3-hydroxypropionitrile (25.1 µL, 0.367 mmol, 3 equiv), HBTU (60.1 mg, 0.159 mmol, 1.3 equiv), DIPEA (42.5 µL, 0.244 mmol, 2 equiv), DMF (1 mL). Reaction time: overnight. Solvent for extraction: diethyl ether and water. Recrystallization gave compound 76 (28.6 mg, 0.0762 mmol, 62%) as white crystals.
M.p. 156.3–157.2 °C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.74 (s, 1H), 7.96 (m, 2H), 7.77 (m, 2H), 7.70–7.62 (m, 2H), 7.52–7.43 (m, 3H), 4.43 (t, 2H, \(^3\)J = 6.0 Hz), 3.01 (t, 2H, \(^3\)J = 6.0 Hz), 2.58 (s, 3H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 170.3, 164.7, 160.4, 160.2, 143.2, 130.4, 130.1, 128.8, 127.9, 127.7, 124.2, 119.2, 118.4, 112.9, 59.5, 17.5, 11.9 ppm. HRMS calc. for \(\text{C}_{21}\text{H}_{18}\text{N}_3\text{O}_4\ [\text{M+H}]^+\): 376.1297, found 376.1298.

\(\text{N,N-Diethyl-4-(5-methyl-3-phenylisoxazole-4-carboxamido)-N-(prop-2-yn-1-yl)benzen-aminium bromide (77)}\)

\(\text{N-[4-(Dimethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide 1 (0.200 g, 0.572 mmol)}\) was dissolved in a mixture of methanol (3 mL) and ethyl acetate (2 mL). An 80% solution of propargyl bromide in toluene (0.127 mL, 1.14 mmol, 2 equiv) was added, and the reaction mixture was stirred at room temperature for 4 d. Then the reaction mixture was heated at 70 °C overnight. An 80% solution of propargyl bromide in toluene (0.255 mL, 2.29 mmol) was added, and the reaction mixture was heated at 70 °C for 40 h. The organic solvents were evaporated with a rotary evaporator. Diethyl ether and water were added. The aqueous phase was separated and washed once with diethyl ether. Evaporation of the aqueous phase with a rotary evaporator gave compound 77 (154 mg, 0.329 mmol, 58%) as pink crystals. M.p. 162.9–165.1 °C (decomp.). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.81 (s, 1H), 7.91–7.82 (m, 4H), 7.72–7.65 (m, 2H), 7.54–7.45 (m, 3H), 4.98 (d, 2H, \(J = 2.5\) Hz, \(\text{CH}_2\text{CCH}\)), 3.99 (t, 1H), 3.97 (q, 4H, \(^3\)J = 7.0 Hz), 2.61 (s, 3H), 1.09 (t, 6H) ppm. \(^13\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 170.3, 160.4, 160.2, 139.8, 135.8, 130.1, 128.8, 127.8, 127.7, 123.2, 120.3, 112.8, 82.9, 72.2, 58.6, 49.2, 12.0, 8.0, ppm. HRMS calc. for the cation \(\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}_2^+ [\text{M}]^+\): 388.2025, found 388.2026.
3-(2-Chlorophenyl)-N-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide 39k (51.0 mg, 0.131 mmol) was dissolved under argon in absolute DMF (1 mL) and the solution was degassed. Copper(I) iodide (25.0 mg, 0.131 mmol) and potassium carbonate (18.1 mg, 0.131 mmol) were added under argon. The reaction mixture was irradiated in a microwave reactor to 140 °C for 2.5 h. DCM was added, and the organic phase was washed twice with water. The solvent was removed with a rotary evaporator, and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in n-hexane, starting with 0% of ethyl acetate gave compound 78 (5.70 mg, 0.0164 mmol, 13%) as a white solid. M.p. 225.3–227.2 °C. $^1$H NMR (300 MHz, CD$_2$Cl$_2$): $\delta$ 8.16 (ddd, 1H, $^4J$ = 0.5 Hz, $^3J$ = 1.7 Hz, $^3J$ = 7.8 Hz), 7.37 (ddd, 1H, $^4J$ = 1.7 Hz, $^3J$ = 7.3 Hz, $^3J$ = 8.8 Hz), 7.21 (ddd, 1H, $^4J$ = 1.2 Hz, $^3J$ = 7.3 Hz, $^3J$ = 7.8 Hz), 7.03 (m, 2H), 6.82 (m, 2H), 6.75 (m, 1H), 3.44 (q, 4H, $^3J$ = 7.1 Hz), 2.86 (s, 3H), 1.23 (t, 6H, 7.1 Hz) ppm. $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$): $\delta$ 175.1, 159.6, 157.3, 148.5, 143.3, 131.9, 130.4, 125.0, 124.7, 123.2, 118.4, 112.8, 112.4, 108.2, 45.1, 13.2, 12.9 ppm. HRMS calc. for C$_{21}$H$_{22}$N$_3$O$_2$ [M+H]$^+$: 348.1712, found 348.1715.
Table S1. List of commercial compounds and suppliers

| Structure                                                                 | Cmpd | Supplier   | Supplier id |
|---------------------------------------------------------------------------|------|------------|-------------|
| ![Structure image](image1) N-[4-(diethylamino)phenyl]cyclopentanecarboxamide | 57   | ChemBridge | 7264871     |
| ![Structure image](image2) N-(4-acetylphenyl)-5-(furan-2-yl)isoxazole-3-carboxamide | 70   | ChemBridge | 9249938     |
| ![Structure image](image3) N-(4-cyanophenyl)-5-(furan-2-yl)isoxazole-3-carboxamide | SI113 | ChemBridge | 9265701     |
| ![Structure image](image4) N-(sec-butyl)-5-(furan-2-yl)isoxazole-3-carboxamide | 69   | ChemDiv    | C226-1747   |
| ![Structure image](image5) N,N-diethyl-5-(thiophen-2-yl)isoxazole-3-carboxamide | SI114 | ChemDiv    | C226-1870   |
| Chemical Structure | SI115 | ChemDiv | F082-0953 |
|-------------------|-------|---------|-----------|
| 3-(5-bromothiophen-2-yl)-N-(3-chloro-4-methoxyphenyl)-5-methylisoxazole-4-carboxamide |

| Chemical Structure | SI116 | ChemDiv | F082-0919 |
|-------------------|-------|---------|-----------|
| 3-(5-bromothiophen-2-yl)-N-(4-isopropylphenyl)-5-methylisoxazole-4-carboxamide |

| Chemical Structure | SI117 | ChemDiv | F082-0893 |
|-------------------|-------|---------|-----------|
| 3-(5-bromothiophen-2-yl)-N-cyclopropyl-5-methylisoxazole-4-carboxamide |

| Chemical Structure | SI118 | ChemDiv | G639-0128 |
|-------------------|-------|---------|-----------|
| N-(4-cyanophenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxamide |

| Chemical Structure | SI119 | ChemDiv | G365-0453 |
|-------------------|-------|---------|-----------|
| N-(4-isopropylphenyl)-1,4-dihydropyrimidino[4,3-c]pyrazole-3-carboxamide |
| Compound Description                                                                 | Code | Source   | Code      |
|-------------------------------------------------------------------------------------|------|----------|-----------|
| $N$-(4-isopropylphenyl)-4,5-dihydrothieno[3',2':3,4]benzo[1,2-\textit{d}]isoxazole-3-carboxamide | 66   | ChemDiv  | G213-0088 |
| $N$-[4-(diethylamino)phenyl]-5-(furan-2-yl)-1\textit{H}-pyrazole-3-carboxamide       | SI120| Enamine  | Z317775470|
| $N$-(3-oxo-3,4-dihydro-2\textit{H}-benzo[\textit{b}][1,4]oxazin-6-yl)-5-phenyl-1\textit{H}-pyrazole-3-carboxamide | SI121| Enamine  | Z117445894|
| $N$-(2,2-difluorobenzo[\textit{d}][1,3]dioxol-5-yl)-5-(furan-2-yl)isoxazole-3-carboxamide | SI122| Enamine  | Z220530528|
| 3-methoxy-4-methyl-$N$-[3-(pyridin-4-yl)-1\textit{H}-pyrazol-5-yl]benzamide           | SI123| Enamine  | Z979287910|
| Compound                                                                 | Enamine | Z Number     |
|-------------------------------------------------------------------------|---------|--------------|
| $N$-(3-chloro-4-fluorophenyl)-5-(furan-2-yl)isoxazole-4-carboxamide       | SI124   | Z1505509423  |
| $N$-(2-ethyl-2-methylbenzo[d][1,3]dioxol-5-yl)-5-(5-methylfuran-2-yl)isoxazole-4-carboxamide | SI125   | Z1873649946  |
| ethyl 4-(3-phenylisoxazole-5-carboxamido)-1H-pyrrole-2-carboxylate       | SI126   | Z1286345678  |
| 4-(5-chlorothiophen-2-yl)-$N$-(4-(1,1-dioxidoisothiazolidin-2-yl)phenyl)-1H-pyrrole-3-carboxamide | SI127   | Z821502624   |
| $N$-[3-(thiophen-2-yl)-1H-pyrrozol-5-yl]benzamide                        | SI128   | Z759027002   |
| $N$-[4-(dimethylamino)-3,5-difluorophenyl]-5-(furan-2-yl)isoxazole-3-carboxamide | SI129   | Z810678144   |
| Chemical Structure | ID | Supplier | Number |
|--------------------|----|----------|--------|
| ![Chemistr1](image1) | SI130 | Enamine | Z117578254 |
| ![Chemistr2](image2) | SI131 | ChemDiv | G794-1887 |
| ![Chemistr3](image3) | SI132 | ChemDiv | C791-0005 |
| ![Chemistr4](image4) | 59 | Enamine | Z1437204853 |
| ![Chemistr5](image5) | SI133 | Maybridge | SPB03214 |
| ![Chemistr6](image6) | SI134 | Maybridge | SPB03211 |
| Chemical Structure | Description | Supplier | Code |
|--------------------|-------------|----------|------|
| ![Chemical Structure](image1.png) | 3',5-dimethyl-N-[4-(trifluoromethyl)phenyl]-[3,5'-bi-oxazole]-4'-carboxamide | Maybridge | SI135 |
| ![Chemical Structure](image2.png) | N-(3-chlorophenyl)-3',5-dimethyl-[3,5'-bi-oxazole]-4'-carboxamide | Maybridge | SI136 |
[3-Amino-5-(4-methoxyphenyl)-1H-pyrazol-1-yl] (5-methyl-3-phenylisoxazol-4-yl) methanone SI137

\[
\text{\begin{center}
\includegraphics[width=0.4\textwidth]{si137.png}
\end{center}}
\]

Synthesis previously described\textsuperscript{a}

\textsuperscript{a}Karhu, S. T.; Välimäki, M. J.; Jumppanen, M.; Kinnunen, S. M.; Pohjolainen, L.; Leigh, R. S.; Auno, S.; Földes, G.; Boije af Gennäs, G.; Yli-Kauhaluoma, J.; Ruskoaho, H.; Talman, V. Stem Cells Are the Most Sensitive Screening Tool to Identify Toxicity of GATA4-Targeted Novel Small-Molecule Compounds. Arch. Toxicol. 2018, 92 (9), 2897–2911.

Hierarchical clustering

To identify compounds which inhibit the GATA4-NKX2-5 transcriptional synergy but have no effect on either NKX2-5 or GATA4 transcriptional activity, we performed hierarchical clustering for biological data to get two-dimensional presentation of the three-dimensional activity data. It has been shown previously\textsuperscript{b} that cluster analysis can be used to identify compounds with a similar activity pattern, since they are close to each other in an activity space determined by activity measures. Hierarchical clustering of the activity patterns of selected compounds is presented in SFigure 1. We identified two potentially interesting groups of compounds with different activity patterns based on hierarchical clustering. In the first group, there are two novel compounds which inhibited transcriptional synergy of GATA4 and NKX2-5 without affecting GATA4 transcriptional activity similar to that of compound 3. In the second group, compounds 39k and 47l did not affect NKX2-5 transcriptional activity. In addition, compound 39k slightly increased GATA4 transcriptional activity at 10 µM concentration. A common structural feature for all selective (i.e. not affecting GATA4 transcriptional activity) inhibitors of GATA4-NKX2-5 transcriptional synergy is a hydrogen bond acceptor in the \textit{para} position in the northern part benzene ring.
Supporting Figure 1. Hierarchical clustering of the activity patterns of compounds. Euclidean distance was used as a distance metric for cluster analysis. The activity of the compound in each luciferase reporter assay is colored according inhibition/enhancement percentage. Color codes: gray (0-65% of control), orange (65-90% of control), blue (90-110% of control), green (110-250% of control). MTT cell viability assay (not used as a parameter in the clustering); red (cell viability >90%), light blue (cell viability <90%) and white not determined (ND).

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