Discovery of antibiotics and their targets in multidrug-resistant bacteria

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Chapter 3

Hit optimization provides a submicromolar potent MRSA antibiotic

Introduction

The emergence of multidrug resistant bacteria in parallel with a dearth of new antibiotic drug approvals has the potential to become one of the biggest health care problems of the 21st century.[1–3] Among Gram-positive pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be one of the most worrisome. Recent data indicate that drug-resistant staphylococcal infections, due predominantly to MRSA, were associated with a staggering 750,000 deaths worldwide in 2019.[4] For this reason, the WHO has recently placed MRSA, as well as vancomycin-resistant *S. aureus* (VRSA)[5] on the high-priority list for research & development of new antibiotics. With the emergence of new strains with additional resistance to the most recently approved antibiotics linezolid[6] and daptomycin[7,8], it is anticipated that

MRSA infections will become increasingly untreatable in the near future. Therefore, new antibiotics with novel modes-of-action (MoA) are urgently required to counteract this type of antimicrobial drug resistance.

In Chapter 2, a diverse chemical library was screened to identify molecules with antibacterial activity against MRSA (Figure 3.1). Benzyl (4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)carbamate, or hit **1**, was identified as the most potent hit. Compound **1** has previously been reported as a covalent inhibitor of human lipases.[9,10] The oxadiazolone group was hypothesized to function as an electrophilic trap for catalytically active serines.

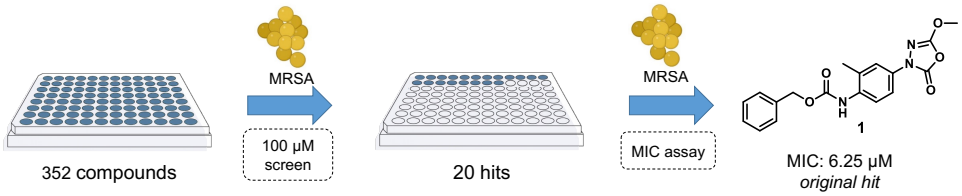


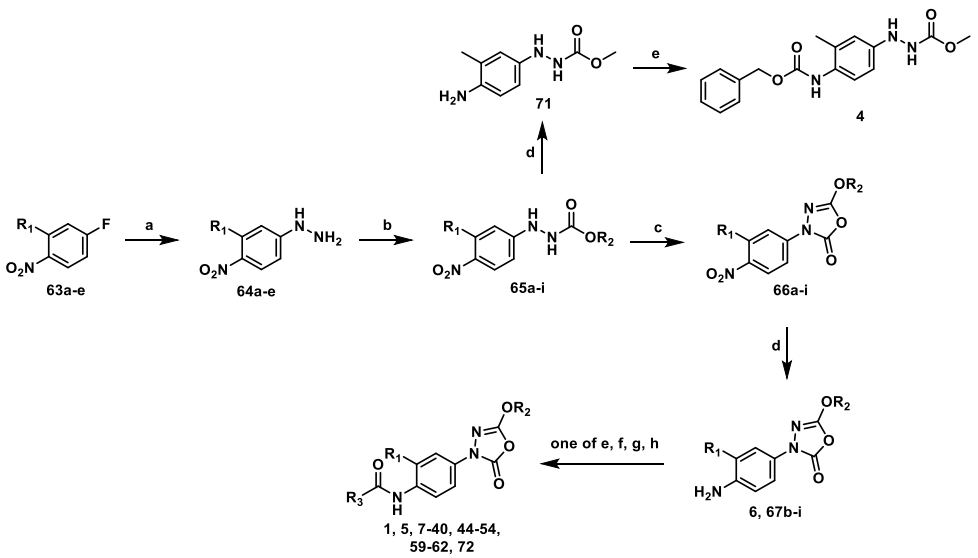
Figure 3.1 | Summary of the in-house library screen in Chapter 2 that led to compound **1**.

Here, the structure-activity relationship (SAR) of hit **1** is reported. Identification of moieties essential for antibiotic activity led to the identification of compound **38** as a submicromolar active MRSA inhibitor with high activity against multidrug resistant clinical isolates.

Results and discussion

Various synthetic routes were followed to generate compounds **2**-**62** as derivatives of hit **1**. The antibacterial activity of these compounds was subsequently evaluated using the minimum inhibitory concentration (MIC) assay described in Chapter 2. Both the MRSA USA300 strain and the methicillin-susceptible *S. aureus* (MSSA, referred to as: SA) strain 29213 were used for biological evaluation of the compounds.

The general synthetic route (depicted in Scheme 3.1) started with 2-substituted 4-fluoronitrobenzenes **63a-e**, on which a nucleophilic aromatic substitution with hydrazine resulted in compounds **64a-e**. The hydrazines were then reacted with a variety of alkyl chloroformates to form carbazates **65a-i**, which then could be cyclized using phosgene to a series of 5-alkoxy-1,3,4-oxadiazol-2(3*H*)-ones (**66a-i**), or oxadiazolones for short. The last steps involved reduction of the nitrophenyl to an aniline (**6**, **67b-i**, and **71**), which could then be coupled to range of substituents using either amide coupling methods, or nucleophilic acyl substitution with chloroformates or acyl chlorides to give compounds **4**, **5**, **7**-**40**, **44**-**54**, **59**-**62**, and **72**. Compounds (**2**, **3**, **41**-**43**, **55**-**58**) were synthesized according to the synthetic routes at the end of this chapter (Scheme S3.1-8).



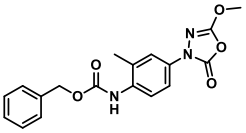
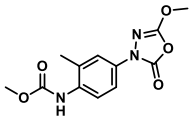
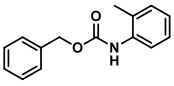
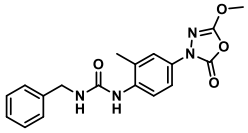
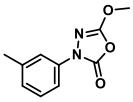
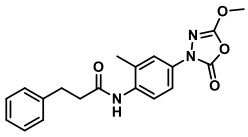
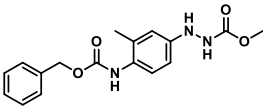
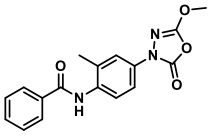
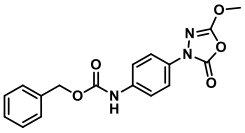
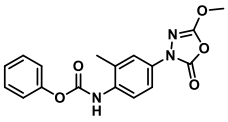
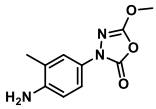
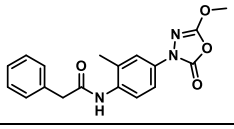
Scheme 3.1 | General synthetic route for compound **1** analogues. Reagents and conditions: a) NH_2-NH_2, EtOH, 80°C, 19% – 60%, or, NH_2-NH_2, NMP, 0°C/65°C, 74% – 77%; b) R_2COCl, pyridine, DCM or NMP, 0°C, 45% – 94%; c) triphosgene, pyridine, DCM, 0°C, 17% – 87%; d) H_2, Pd/C, MeOH/DCM, RT, 17% – 99%; e) R_3COCl, DCM, 0°C, 26 – 99%; f) R_3COOH, HOBt, EDC, DCM, 0°C, 17% – 61%; g) R_3COOH, HATU, DIPEA, DMF, RT, 22% – 58%; h) R_3COOH, PyAOP, DIPEA, ACN, 9% – 95%.

First, a disjunctive approach was used to determine which structural motifs of hit **1** were essential for its antibacterial activity. To this end, compounds **2**-**12** were evaluated in the MIC assay (Table 3.1).

Compound **2**, which lacked the oxadiazolone group, showed a complete loss of activity. Uncyclized oxadiazolone (**4**) also demonstrated no activity. This indicated that the oxadiazolone is required for activity, and might suggest that its electrophilic center covalently interacts with nucleophilic amino acids in bacterial proteins. The methyl group on the central phenyl ring was favorable for the activity, as compound **5**, which has a hydrogen instead of a methyl, had a 4-fold reduced activity compared to hit **1**. Removal of the benzylcarbamate, swapping the benzylcarbamate for an amine and replacing the benzyl group for a methyl group strongly reduced potency as witnessed by compounds **3**, **6** and **7**, respectively. This indicated that an aromatic moiety on the left side of the molecule is favored.

Next, the carbamate group was substituted for a urea in compound **8**. This abolished the activity, while an amide substitution (**9**) was tolerated, albeit with a four-fold lower activity. Interestingly, a shortened amide linker (**10**) led only to a two-fold reduction in potency, while a carbamate linker (**11**) was not allowed. Removal of the oxygen to form amide **12** reduced the antibiotic activity by two-fold. Together, these data show that the carbamate is not essential for activity and can be swapped for an amide with minimal loss in potency. Compound **10** was chosen as the new chemical starting point, because of its simplified scaffold compared to **1**, thereby permitting a wider array of synthetic derivatizations with commercially available building blocks.

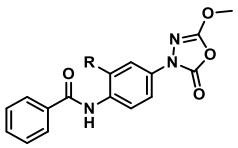
Table 3.1 | Dissecting the structure of hit **1** for antibacterial activity.

ID	Structure	MIC (μM) MRSA[a]	MIC (μM) SA[a]	ID	Structure	MIC (μM) MRSA	MIC (μM) SA
1		6.25	12.5	**7**		50	>50
2		>50	>50	**8**		>50	>50
3		>50	>50	**9**		25	>50
4		>50	>50	**10**		12.5	25
5		25	>50	**11**		>50	>50
6		>50	>50	**12**		12.5	50

[a]In this and subsequent tables: MRSA = MRSA USA300, SA = methicillin-susceptible *S. aureus* ATCC 29213.

To further query the role of the methyl on the central phenyl ring, compounds **13**-**16** were evaluated (Table 3.2). In line with compound **5**, removal of the methyl group (**13**) provided a loss of activity, while swapping the methyl for a methoxy- (**14**), chloro- (**15**), or cyano-substituent (**16**) gave a small loss in potency. This indicated that a small (non-polar) electron-donating substituent was optimal.

Table 3.2 | Central ring derivatives of **10**.



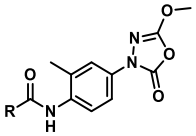
ID	R	MIC (μM)	
		MRSA	SA
10		12.5	25
13		>50	>50
14		25	>50
15		25	50
16		25	>50

To systematically study the electronic and hydrophobic effects of the distal phenyl ring in compound **10**, compounds **17**-**40** were evaluated. First, the effect of heteroatoms on the activity was investigated. Pyridines (**17**-**19**), pyrimidines (**20**, **21**) or pyrazines (**22**) did not show any activity, indicating that heterocycles with reduced electron density are not allowed. Of note, a *para* chloro substituted pyridin-2-yl (**23**) did show an increase in activity against MRSA.

Next, the effect of other small substituents on various positions of the ring inspired by the Topliss scheme[11] was investigated (**24**-**35**) (Table 3.3). *Para* chloro (**24**), methyl (**25**) and fluoro (**26**), but not methoxy (**27**) substituents gave also an increase in potency. A trifluoromethyl substituent (**28**) abolished the antimicrobial activity, which might be due to the size of the CF_3-group, or because of its strong electron-withdrawing effect.

Substitution on the *meta* position with a chloro (**29**), methoxy (**30**), and methyl (**31**) group improved potency or remained similar. Dichloro substitution (**32**) abolished activity, while ortho-substitution with a chloro (**33**), methoxy (**34**) or methyl (**35**) group led to a general decrease in activity.

Table 3.3 | Left ring variations on compound **10**.



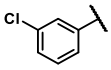
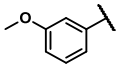
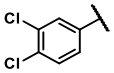
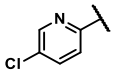
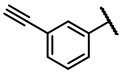
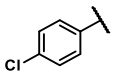
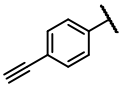
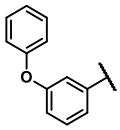
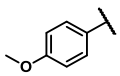
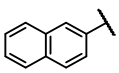
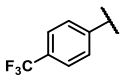
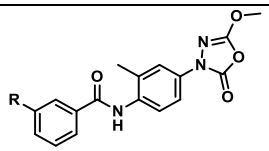
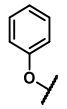
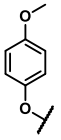
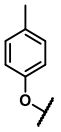
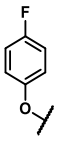
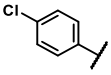
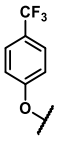
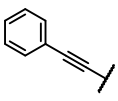
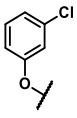
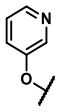
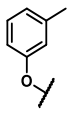
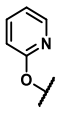
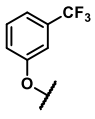
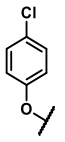
ID	R	MIC (μM) MRSA	MIC (μM) SA	ID	R	MIC (μM) MRSA	MIC (μM) SA
10		12.5	25	**29**		6.25	>50
17		>50	>50	**30**		6.25	12.5
18		50	>50	**31**		12.5	>50
19		>50	>50	**32**		>50	>50
20		>50	>50	**33**		12.5	25
21		>50	>50	**34**		>50	>50
22		>50	>50	**35**		25	>50
23		6.25	50	**36**		3.1	25
24		6.25	>50	**37**		25	>50
25		6.25	25-50	**38**		0.8	1.6
26		6.25	25	**39**		25	50
27		12.5	>50	**40**		1.6	>50
28		>50	>50				

Table 3.4 | Left ring variations on compound **38**.

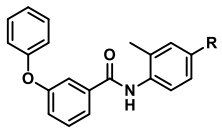


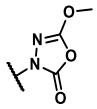
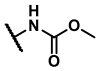
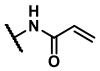
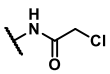
ID	R	MIC (μM)		ID	R	MIC (μM)	
		MRSA	SA			MRSA	SA
38		0.8	1.6	**48**		1.6	3.1
41		>12.5	>50	**49**		3.1	1.6
42		12.5	>50	**50**		1.6	3.1
43		>12.5	>50	**51**		3.1	>12.5
44		>12.5	>50	**52**		0.8–1.6	3.1–6.25
45		>12.5	>50	**53**		0.8	1.6–3.1
46		12.5	>50	**54**		1.6	>12.5
47		1.6	3.1				

Alkyne-bearing compound **36** (*meta*) showed a four-fold increase in activity, while **37** (*ortho*) was less potent. This suggested that the *meta* position was suitable for chemical expansion. Of note, alkyne **36** can potentially be used as ligation handle for activity-based protein profiling[12] (see Chapter 5). To explore the size of the binding pocket interacting with the substituents at the *meta* position, phenoxyphenyl derivative **38** was synthesized. Gratifyingly, compound **38** had submicromolar potency against MRSA (MIC = 0.8 μM) and was the most potent oxadiazolone identified in this study. Lastly, the ring system was expanded in naphthalenes **39** and **40**. The 1-naphthalene group (**39**) reduced activity, while a 2-naphthalene substituent (**40**) increased activity for MRSA (MIC = 1.6 μM), but had no activity against SA.

Compounds (**41**-**54**) were evaluated to systematically investigate the role of the phenoxy-group (Table 3.4). Biphenyl (**41**-**43**) analogs were either inactive or less active. A compound with an internal alkyne linker (**44**) also showed reduced activity. 2- or 3-pyridyl aryl ethers (**45** and **46**) were inactive, and *para* substituted analogs of **38** (**47**-**51**) were in general two-fold less active than compound **38**. *Meta* substituents (**52**-**54**) were well tolerated with m-methyl derivative **53** being on par with compound **38**.

Table 3.5 | Warhead derivatives of compound **38.**

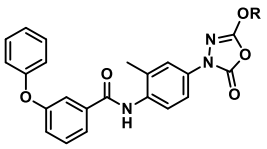


ID	R	MIC (μM)	
		MRSA	SA
38		0.8	1.6
55		>12.5	>12.5
56		>12.5	>12.5
57		>12.5	>12.5
58		>12.5	>12.5

Next, the role of the oxadiazolone was revisited. Following the hypothesis that the oxadiazolone is an electrophilic trap, several other electrophilic warheads were introduced (Table 3.5).[13] Introduction of methylcarbamate, acrylamide, chloroacetamide, and isothiocyanate groups (**55**-**58**) removed activity completely.

Finally, the effect of the methoxy side chain of the oxadiazolone was investigated using compounds **59**-**62** (Table 3.6), following changes found in an antibacterial study of oxadiazolones against *Mycobacteria*.[14] No improvements in potency were found. Ethyl derivative **59** was equally potent as **38** against MRSA, but showed reduced potency against SA. Isobutyl (**60**) relinquished activity, whereas butyl (**61**) and methoxyethyl (**62**) analogs showed slightly decreased potency against MRSA, but no measurable activity against SA.

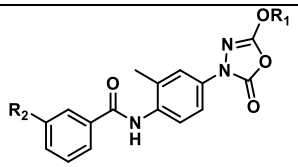
Table 3.6 | Oxadiazolone side chain variations of compound **38**.

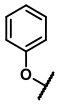
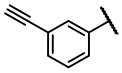
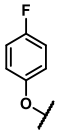
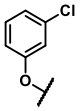
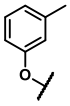
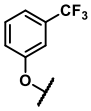
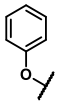
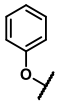
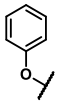
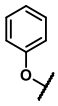


ID	R	MIC (μM)	
		MRSA	SA
38		0.8	1.6
59		0.8	3.1
60		>12.5	>12.5
61		1.6	>12.5
62		3.1	>12.5

The most potent compounds and a negative control (**60**)were tested for cytotoxicity against a human liver (HepG2) and kidney (HEK293T) cell lines, using an MTT assay which measures metabolic activity as an indicator of cell viability, proliferation, and compound cytotoxicity (Table 3.7). Compound **38** had the lowest human cell cytotoxicity, as is indicated by the selectivity ratio in both cell lines (selectivity ratio is defined as human cell toxicity concentration/MIC). Interestingly, inactive compound **60** also showed no cytotoxicity.

Table 3.7 | Human cytotoxicity testing on selected derivatives.



ID	R_1	R_2	CC_{50} (μM)[a] HEK293T	CC_{50} (μM)[a] HepG2	MIC MRSA (μM)	Selectivity ratio (HEK293T/ MRSA)	Selectivity ratio (HepG2/ MRSA)
38			8.4	16.2	0.8	10.5	20.3
36			10.2	>50	3.1	3.3	>16.1
50			8.2	25	1.6	5.1	15.6
52			4.4	11	0.8–1.6	2.7-5.5	6.9-13.8
53			3.9	6.3	0.8	4.9	7.9
54			15	11	1.6	9.4	6.9
59			9.4	7.2	0.8	11.8	9.0
60			>50	>50	>12.5	-	-
61			16	>50	1.6	10.0	>31.3
62			4.6	7.0	3.1	1.5	2.3

[a]CC_{50} = 50% cytotoxic concentration.

In view of the excellent profile, compound **38** was selected as lead molecule for further profiling. Compound **38** did not show any hemolytic activity (Figure S3.1). In addition, it was highly potent against a variety of *S. aureus* strains, including vancomycin-resistant strains and clinical isolates (Table 3.8). There was no activity observed against other bacterial species, including other ESKAPE pathogens and *E. coli*. Of note, compound **38** was generally found to be more potent against antibiotic resistant strains compared to wildtype *S. aureus*, a trend that was observed for most of the derivatives tested.

Table 3.8 | MICs of key compound **38** and clinically-used antibiotics of last resort against a panel of bacteria, including clinical isolates of *S. aureus*.

Organism		Strain	MIC (μM)			
			38	meropenem	vancomycin	daptomycin
Gram-positive						
S. aureus	**MRSA**	USA300	0.8	1.1	1.4	1.2
		NY-155	0.8	9.1	0.7	1.2
		MRSA131	1.6	2.3	0.7	1.2
		COL	1.6	293	1.4	2.4
	MSSA	ATCC 29213	1.6	≤0.1	0.7	1.2
	VISA	SA MER	1.6	0.3	2.8	4.9
		LIM3	0.8	≤2.3	2.8	2.4
		NRS126	3.1	293	2.8	2.4
	VRSA	BR-VRSA	1.6	>293	88	1.2
		VRSA-1	3.1	293	88	1.2
		VRSA-2	0.8	293	88	≤0.6
Enterococcus faecium			>50	≤0.1	0.7	1.2
Gram-negative[a]			>50	≤0.1 – 2.3	>88	>80

[a]Includes *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 29665), *Acinetobacter baumannii* (ATCC BAA747), *Pseudomonas aeruginosa* (ATCC 27853). MSSA: methicillin-susceptible *S. aureus*; VISA: vancomycin-intermediate *S. aureus;* VRSA: vancomycin-resistant *S. aureus*.

Compound **38** was able to time-dependently kill 99% of bacteria over the course of 24 hours, starting with a 10^6 CFU/mL inoculum (Figure 3.2). This indicates that this compound is able to time-dependently kill the bacteria at higher concentrations, which is advantageous because it prevents bacteria from growing after treatment halted.[15]

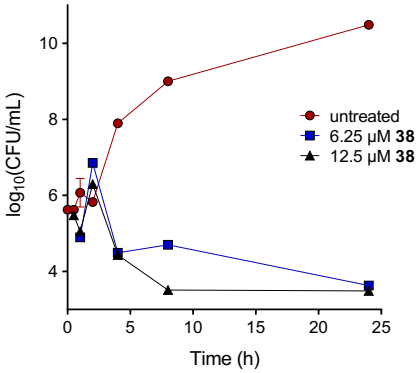
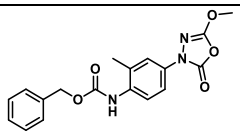
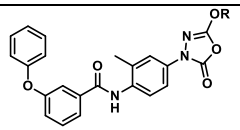


Figure 3.2 | Time-dependent killing of MRSA USA300 by compound **38** over the course of 24 h. 8× MIC, and 16× MIC concentrations are chosen.

Conclusion

In this chapter over 60 derivatives of hit **1** were synthesized, leading to compound **38** as the compound with the highest antibacterial potency. Compound **38** has favorable physicochemical properties (Table 3.9) and low human cell cytotoxicity (selectivity ratio > 10). Compound **38** time-dependently kills MRSA, and also shows strong antimicrobial activity against all clinical isolates of MRSA. To identify the mode-of-action of compound **38**, activity-based protein profiling was employed using compound **36** in Chapter 4.

Table 3.9 | Physicochemical properties of lead compound **38** compared to original hit **1**.

ID	Structure	MIC MRSA (μM)	MIC SA (μM)	MW (Da)	cLogP	PSA (Å^2)	HBA	HBD	RB
1		6.25	12.5	355	1.16	89.5	8	1	6
38		0.78	1.56	417	3.59	89.5	8	1	6

KP = *K. pneumoniae*; PSA = polar surface area; HBA = hydrogen bond acceptors; HBD = hydrogen bond donors; RB = rotatable bonds.

Acknowledgments

The following people are kindly acknowledged for their contribution to this chapter. Liza Mirenda for assisting with the synthesis and biological evaluation of new compounds. Ioli Kotsogianni for assisting with the MIC assays, as well as with the time-kill assay.

Methods

Reagents & materials. Buffers and salts were of ACS reagent grade or higher and were purchased commercially, from Carl Roth GmbH (Karlsruhe, Germany) and Sigma-Aldrich (Darmstadt, Germany), biological materials and growth media were purchased from Sigma-Aldrich, Scharlab S.L. (Barcelona, Spain) and Fisher Scientific (Landsmeer, Netherlands). Antibiotics (TRC, Combi-Blocks, Sigma-Aldrich) were dissolved in ultrapure H_2O or DMSO, stock solutions were stored in -20°C, apart from meropenem which was used fresh. All test compounds were used from 10 mM DMSO stock solutions made from freeze dried powder and stored at -20°C.

Bacterial strains. The following reagents were obtained through BEI Resources, NIAID, NIH: *Staphylococcus aureus* BR-VRSA (Strain 880, NR-49120), *S. aureus* strain MRSA131 (HM-466, as part of the Human Microbiome Project). The following *S. aureus* strains were provided by the Network on Antimicrobial Resistance in *S. aureus* (NARSA) for distribution by BEI Resources, NIAID, NIH: COL (NR-45906), NY-155 (NR-46236), USA300-0114 (NR-46070), LIM 2 (NR-45881), LIM 3 (NR-45882), NRS126 (NR-45929), NRS17 (Strain HIP06297, NR-45868), SA MER (NR-45864), VRSA-1 (Strain HIP11714, NR-46410), VRSA-2 (Strain HIP11983, NR-46411) VRSA-3a (Strain HIP13170, NR-46412). *S. aureus* USA300 (ATCC BAA1717), *S. aureus* Rosenbach (ATCC 29213) *Klebsiella pneumoniae* ATCC 29665 (NCTC 11228), *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853; *Acinetobacter baumannii* ATCC BAA747 belong to the American Type Culture Collection (ATCC). *Enterococcus faecium* E980; *E. faecium* E155; *E. faecium* E7130, were kindly provided by Dr. A.P.A. Hendrickx, National Institute for Health and Environment, Utrecht, The Netherlands, as gifts.

Minimum inhibitory concentration (MIC). From glycerol stocks, bacterial strains were cultured on blood agar plates by overnight incubation at 37°C. A single colony was transferred to TSB. In case of VRSA strains, 6 μg/mL vancomycin was supplemented to the media. The cultures were grown to exponential phase (OD600: 0.5) at 37°C. The bacterial suspensions were diluted 100-fold in CAMHB and 50 μL was added to a 2-fold serial dilution series of test compounds (50 μL per well) in polypropylene 96-well microtiter plates to reach a volume of 100 μL. The plates were sealed with breathable membranes and incubated overnight at 37°C with constant shaking (600 rpm). For Enterococci species direct colony suspension was used by immediately suspending multiple colonies from fresh blood agar plates in CAMHB to an OD600 of 0.5 and subsequent 100-fold dilution. The MIC was determined as the lowest concentration at which no visible bacterial growth was observed, as compared to the inoculum controls, from the median of a minimum of triplicates.

Mammalian cell culture. HepG2 and HEK293T cell lines (ATCC) were cultured at 37 °C and 7% CO_2 in DMEM (Sigma Aldrich, D6546) with GlutaMax, penicillin (100 μg ml−1), streptomycin (100 μg ml−1) and 10% Fetal Calf serum. Cells were passaged twice a week by first detaching using 0.05% trypsin in PBS, an then diluting to appropriate confluence.

Cytotoxicity assay (MTT). Compound cytotoxicity was evaluated against HepG2 and HEK293T human cell lines using standard (3-(4,5-dimethylthiazol-2-yl)−2,5-diphenyltetrazolium bromide (MTT) assay protocol with slight changes.[16]

HepG2 and HEK293T cells were seeded at a density of 1.5×10^4 cells per well in a clear 96-well tissue culture treated plate in a final volume of 100 μL in Dulbecco's Modified Eagle Medium (DMEM), supplemented with Fetal Bovine Serum (1%), Glutamax and Pen/Strep. Cells were incubated for 24 h at 37°C, 7% CO_2 to allow cells to attach to the plates. In addition to a single vehicle control, compounds (diluted from DMSO stock) were added into each well at eight concentrations ranging from 100 μM to 0.046 μM in three-fold dilutions (final DMSO concentration 0.5%). Incubation was done for 24 h at 37°C, 7% CO_2. After the incubation, MTT was added to each well at a final concentration of 0.40 mg/mL. The plates were then incubated for 2 h at 37°C, 7% CO_2. Medium was carefully removed via suction, and purple formazan crystals were resuspended in 100 μL DMSO.

Absorbance was read at 570 nm using a Clariostar plate reader. The data was then analysed with GraphPad Prism software. IC_{50} values were calculated using non-linear fitted curve with variable slope

settings, with values adjusted for background (plotted ABS_{SAMPLE} = (ABS_{SAMPLE} – $ABS_{BACKGROUND}$) / ($ABS_{VEHICLE}$ – $ABS_{BACKGROUND}$)). Technical triplicates for each condition were used, along with two biological replicates. The reported IC_{50} was obtained by averaging the calculated IC_{50} of both biological replicates.

Time-kill assay. From glycerol stocks, bacterial strains were cultured on blood agar plates by overnight incubation at 37°C. Subsequently, a single colony was cultured in TSB overnight at 37°C. The culture was diluted 100-fold in fresh CAMHB and grown until early exponential phase (OD600: 0.25) followed by 100-fold dilution in media (OD600: 0.0025). The culture was split in separate culture tubes containing 2 mL. Test compounds were added to the cultures at concentration 3.1 μM and 6.2 μM (corresponding to 4 and 8× MIC) and incubated at 37°C for a total of 24 h. At indicated time points (t: 0, 1/2, 1, 2, 4, 8 and 24 h) 100 μL of each culture was centrifuged for 5 min (12500 rpm). The supernatant was discarded and pellets were washed once with filter-sterilized PBS, then resuspended in an equal volume of fresh buffer and samples were 10-fold serially diluted until 10^5 dilution. 10 μL of the appropriate dilutions were inoculated on LB agar plates in technical duplicates, allowed to evaporate and incubated at 37°C for 18 h. 10 μL of the appropriate dilutions were inoculated on LB agar plates in technical duplicates, subsequently allowed to evaporate and incubated at 37°C for 18 ± 2 h. The colonies were counted and used to calculate the CFU/mL remaining in the original culture by taking the dilution factors into account. Experiment was performed in biological duplicates.

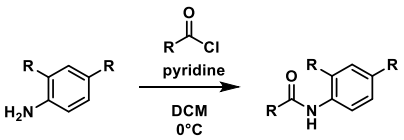
Synthetic procedures

General remarks

All chemicals (Sigma-Aldrich, Fluka, Acros, Merck, Combi-Blocks, Fluorochem, TCI) were used as received. All solvents used for reactions were of analytical grade. THF, Et_2O, DMF, ACN and DCM were dried over activated 4 Å molecular sieves, MeOH over 3 Å molecular sieves. H_2O used in synthesis procedures was of Milli-Q-grade quality. Column chromatography was performed on silica gel (Screening Devices BV, 40-63 µm, 60 Å). The eluent EtOAc was of technical grade and distilled before use. Triethylamine was distilled over KOH, and triethylamine and pyridine were stored over KOH pellets. Starting materials were coevaporated with toluene (3×) before use in water-sensitive reactions.

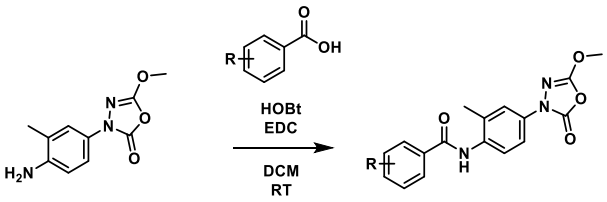
Reactions were monitored by thin layer chromatography (TLC) analysis using Merck aluminium sheets (Silica gel 60, F254). Compounds were visualized by UV-absorption (254 nm) and spraying for general compounds: $KMnO_4$ (20 g/L) and K_2CO_3 (10 g/L) in H_2O, or for amines: ninhydrin (0.75 g/L) and acetic acid (12.5 mL/L) in ethanol, followed by charring at 150°C. ^1H and ^{13}C NMR experiments were recorded on a Bruker AV-300 (300/75 MHz), Bruker AV-400 (400/101 MHz), Bruker DMX-400 (400/101 MHz), Bruker AV- 500 (500/126 MHz) and Bruker AV-600 (600/151 MHz). Chemical shifts are given in ppm (δ) relative to tetramethylsilane, as internal standard. Multiplicity: s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, quint = quintet, non = nonet m = multiplet. Coupling constants (*J*) are given in Hz. LC-MS measurements were performed on a Thermo Finnigan LCQ Advantage MAX ion-trap mass spectrometer (ESI+) coupled to a Surveyor HPLC system (Thermo Finnigan) equipped with a standard C18 (Gemini, 4.6 mm D × 50 mm L, 5 µm particle size, Phenomenex) analytical column and buffers A: H_2O, B: ACN, C: 0.1% aq. TFA. High resolution mass spectra were recorded on a LTQ Orbitrap (Thermo Finnigan) mass spectrometer or a Synapt G2-Si high-definition mass spectrometer (Waters) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 mL/min, capillary temperature 250°C) with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000) and dioctylphtalate (m/z = 391.28428) as a lock mass. Preparative HPLC was performed on a Waters Acquity Ultra Performance LC with a C18 column (Gemini, 150 × 21.2 mm, Phenomenex) using an ACN in H_2O (+0.2% TFA) gradient. All final compounds were determined to be > 95% pure by LC-UV analysis.

General Procedure A: Amide/carbamate formation from acyl chloride



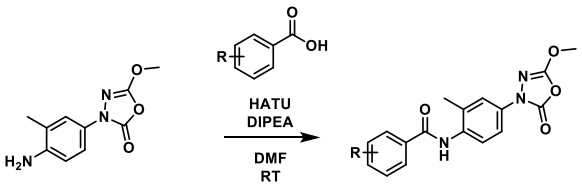
Aniline (1 equiv.) was dissolved in DCM (0.05 M) along with pyridine (1.1 equiv.) and the mixture was cooled to 0°C, after which acyl chloride (1.1 equiv.) was added. The mixture was stirred until TLC analysis indicated full conversion of the starting material. The mixture was then washed with H_2O (3×), and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to obtain the crude product.

General Procedure B: HOBt amide coupling



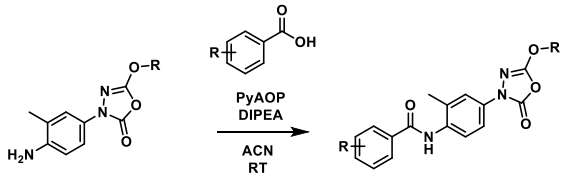
Benzoic acid (1.6 equiv.), EDC (2.7 equiv.) and HOBt (1 equiv.) were dissolved in DCM (0.2 M). The mixture was stirred for 30 min at 0°C before the substituted aniline (1 equiv.) was added and the reaction was stirred until TLC analysis showed full conversion of the aniline derivative. Additional DCM was added and the mixture was washed with 10% aq. $NaHCO_3$ (2×), dried ($MgSO_4$), filtered and concentrated *in vacuo* to obtain the crude product.

General Procedure C: HATU amide coupling



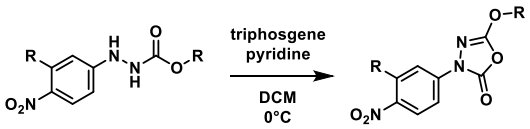
Substituted aniline (1 equiv.), benzoic acid (1.5 equiv.), HATU (2 equiv.) and DIPEA (2 equiv.) were dissolved in DMF (0.1 M), and the mixture was stirred at RT until TLC analysis indicated complete conversion of the starting material. H_2O was added and the aqueous layer was extracted with DCM (2×). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to obtain the crude product.

General Procedure D: PyAOP amide coupling



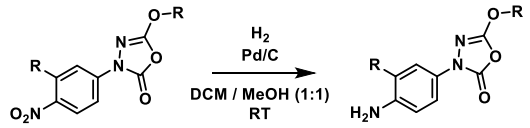
Benzoic acid (2 equiv.), PyAOP (2 equiv.) and DIPEA (4 equiv.) were dissolved in ACN (0.034 M) and the mixture was stirred for 3 min in a dry round bottom flask under nitrogen atmosphere. Substituted aniline (1 equiv.) was dissolved in ACN and this solution was added dropwise to the stirring mixture at RT. The mixture was stirred until TLC analysis indicated full conversion of the starting material. An excess of EtOAc was added and the mixture was washed with brine, sat. aq. $NaHCO_3$ (2×), 1 M aq. HCl and brine again, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to obtain the crude product.

General Procedure E: Oxadiazolone formation



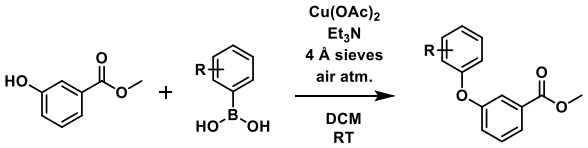
Hydrazine carboxylate (1 equiv.) and pyridine (2 equiv.) were dissolved in DCM (0.2 M), and cooled to 0°C after which a solution of triphosgene (1 equiv.) in DCM (0.5 – 1 M) was added dropwise. The mixture was stirred until TLC analysis indicated full conversion of the starting material. Then, 5% aq. NH_4OH (equal volume to DCM) was added, and the mixture was stirred for 10 min. The resulting organic layer was washed with 1 M aq. HCl, subsequently dried ($MgSO_4$), filtered and concentrated *in vacuo* to obtain the crude product.

General Procedure F: Nitrophenyl hydrogenation



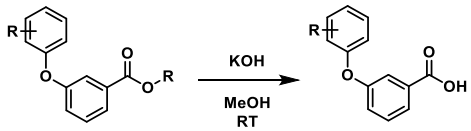
Nitrophenyl (1 equiv.) was dissolved in DCM/MeOH, and under nitrogen atmosphere Pd/C catalyst (± 0.1 equiv.) was added. The mixture was stirred, and hydrogen gas was bubbled through the solution. Once TLC analysis showed complete conversion of the starting material, the atmosphere was displaced with nitrogen, followed by filtering over Celite®, and concentration of the filtrate *in vacuo* to obtain the crude product.

General Procedure G: Chan-Lam coupling

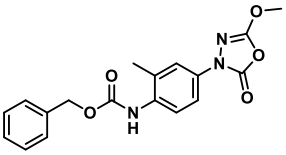


In a round-bottom flask, ethyl-3-hydroxybenzoate (**84**) (1 equiv.) and the corresponding boronic acid (1 equiv.) were dissolved in DCM (0.2 M), after which crushed 4 Å molecular sieves (1 g/mmol reactant) and $Cu(OAc)_2$ (1 equiv.) were added. Triethylamine (2.5 equiv.) was added and the mixture was stirred for 2 h under air atmosphere. The mixture was washed with 1 M aq. HCl, and sieves were filtered off. The filtrate was dried ($MgSO_4$) and filtered again, followed by concentration *in vacuo* to obtain the crude product.

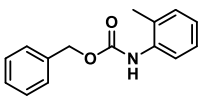
General Procedure H: Saponification



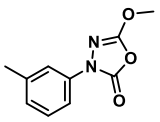
KOH (10 equiv.) was added to a stirring solution of ester (1 equiv.) in MeOH (0.3 M). When TLC indicated complete consumption of the starting ester, the mixture was concentrated *in vacuo*. The crude material was redissolved in H_2O and 50% sulfuric acid was added dropwise until precipitate was fully formed. The suspension was stirred for 30 min and was filtered, washed with H_2O and the residue was isolated and dried *in vacuo*. The resulting benzoic acid was used in the next reaction without further purification.



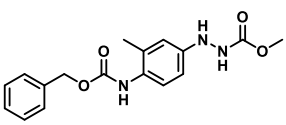
Benzyl (4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)carbamate (1). 6 (40 mg, 0.18 mmol) and benzyl chloroformate (28 µL, 0.20 mmol) were reacted following General Procedure A. The title compound was obtained as a white solid (59 mg, 0.17 mmol, 92%) without need for further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.76 (m, 1H), 7.62 – 7.54 (m, 2H), 7.44 – 7.30 (m, 5H), 6.52 (bs, 1H), 5.20 (s, 2H), 4.08 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.86, 153.69, 148.35, 136.06, 133.51, 133.47, 128.74, 128.52, 128.48, 119.89, 116.67, 67.32, 57.79, 17.96. HRMS [$C_{18}H_{17}N_3O_5$ + H]$^+$: 356.12410 calculated, 356.12409 found.



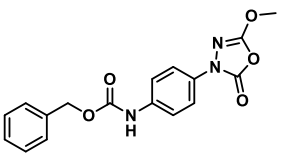
Benzyl *o*-tolylcarbamate (2). *o*-Toluidine (107 µL, 1.0 mmol) and benzyl chloroformate (165 µL, 1.1 mmol) were reacted following General Procedure A. Title compound was obtained as a white solid (242 mg, 1.0 mmol, quant.) without need for further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (bs, 1H), 7.45 – 7.27 (m, 5H), 7.25 – 7.16 (m, 1H), 7.13 (d, *J* = 7.5, 1H), 7.01 (td, *J* = 7.5, 1.3 Hz, 1H), 6.49 (bs, 1H), 5.19 (s, 2H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.78, 136.19, 135.85, 130.50, 128.82, 128.45, 126.97, 124.30, 67.18, 17.75. HRMS [$C_{15}H_{15}NO_2$ + H]$^+$: 242.11756 calculated, 242.11762 found.



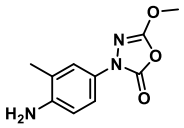
5-Methoxy-3-(*m*-tolyl)-1,3,4-oxadiazol-2(3*H*)-one (3). 70 (90 mg, 0.50 mmol) and pyridine (0.20 mL) were dissolved in dry DCM (3 mL). The mixture was cooled to 0°C, after which phosgene (20 wt% in toluene, 528 µL, 1.0 mmol) was added dropwise. After stirring for 2 h the mixture was washed with H_2O (3×). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude material by column chromatography (5% → 10% EtOAc in pentane) afforded the desired product as a yellow oil (60 mg, 0.29 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.5, 1H), 4.09 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.87, 148.39, 139.28, 136.17, 129.03, 126.47, 117.93, 115.18, 60.02, 21.64. HRMS [$C_{10}H_{10}N_2O_3$ + Na]$^+$: 229.05836 calculated, 228.96498 found.



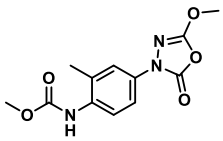
Methyl 2-(4-(((benzyloxy)carbonyl)amino)-3-methylphenyl)hydrazine-1-carboxylate (4). 71 (23 mg, 0.12 mmol) and benzyl chloroformate (18 µL, 0.13 mmol) were reacted following General Procedure A. Purification of the crude material by column chromatography (0% → 1% MeOH in DCM) yielded the title compound as a white powder (17 mg, 52 µmol, 45%). ^{1}H NMR (500 MHz, DMSO) δ 9.02 (s, 1H), 8.70 (s, 1H), 7.64 – 7.27 (m, 6H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.60 – 6.31 (m, 2H), 5.09 (s, 2H), 3.59 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 157.40, 154.83, 147.15, 137.12, 128.40, 127.85, 127.78 127.31, 127.30, 113.20, 109.57, 65.45, 51.73, 18.01. HRMS [$C_{17}H_{19}N_3O_4$ + Na]$^+$: 352.12678 calculated, 352.12661 found.



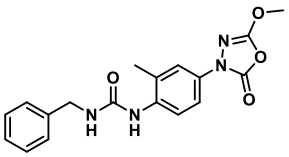
Benzyl (4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)phenyl)carbamate (5). 67b (35 mg, 0.17 mmol) and benzyl chloroformate (27 µL, 0.19 mmol) were reacted following General Procedure A. The title compound was obtained as a yellow solid (58 mg, 0.15 mmol, 90%) without further need for purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.39 – 7.27 (m, 5H), 6.91 (bs, 1H), 5.19 (s, 2H), 4.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.88, 153.43, 148.37, 136.02, 135.52, 131.78, 128.72, 128.48, 128.37, 125.95, 118.89, 67.19, 57.80. HRMS [$C_{17}H_{15}N_3O_5$ + H]$^+$: 342.10845 calculated, 342.10844 found.



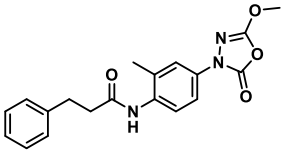
3-(4-Amino-3-methylphenyl)-5-methoxy-1,3,4-oxadiazol-2(3*H*)-one (6). 66a (470 mg, 1.87 mmol) was dissolved in DCM (25 mL) and MeOH (15 mL), and was reacted with Pd/C catalyst (10 wt%, 150 mg, 0.14 mmol) following General Procedure F. This yielded the title compound as an off-white solid (408 mg, 1.84 mmol, 99%) without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 2.5 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 4.05 (m, 3H), 3.65 (bs, 2H), 2.19 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.65, 148.65, 143.03, 127.28, 122.90, 121.33, 118.08, 114.94, 57.59, 17.51. HRMS $[C_{10}H_{11}N_3O_3 + H]^+$: 222.08732 calculated, 222.08730 found.



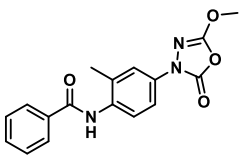
Methyl (4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)carbamate (7). 6 (40 mg, 0.18 mmol) and methyl chloroformate (15 µL, 0.20 mmol) were reacted following General Procedure A. The title compound was obtained as a white solid (50 mg, 0.18 mmol, 99%) without need for further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (bs, 1H), 7.61 (d, *J* = 2.6, Hz, 1H), 7.59 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.45 (bs, 1H), 4.10 (s, 3H), 3.78 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.89, 154.46, 148.38, 133.52, 132.30, 132.16, 119.91, 116.70, 57.81, 52.61, 17.95. HRMS $[C_{12}H_{13}N_3O_5 + H]^+$: 280.09280 calculated, 280.09272 found.



1-Benzyl-3-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)urea (8). 6 (40 mg, 0.18 mmol) and triethylamine (25 µL, 0.18 mmol) were dissolved in DCM (2 mL). The mixture was cooled to 0°C, after which a solution of triphosgene (32 mg, 0.11 mmol) in DCM (2 mL) was added dropwise. After stirring for 15 min, a solution of benzylamine (58 mg, 0.54 mmol) in DCM (2 mL) was added. 3 h later more triethylamine was added (51 µL, 0.36 mmol), and 2 h hereafter the reaction mixture was washed with 1 M aq. HCl and 5% aq. NH_4OH. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by preparative HPLC was performed to give the final product as a white solid (12 mg, 34 µmol, 19%). ^{1}H NMR (400 MHz, DMSO) δ 7.94 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.83 (s, 1H), 7.51 – 7.21 (m, 6H), 7.04 (t, *J* = 5.8 Hz, 1H), 6.68 (bs, 1H), 4.31 (d, *J* = 5.8 Hz, 2H), 4.06 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 171.50, 155.34, 148.06, 140.18, 135.96, 130.05, 128.40, 127.75, 127.29, 126.85, 120.81, 119.84, 116.19, 58.08, 42.91, 18.09. HRMS $[C_{18}H_{18}N_4O_4 + H]^+$: 355.14008 calculated, 355.13990 found.

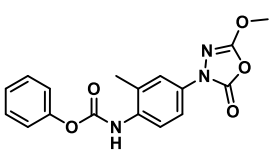


***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-phenylpropanamide (9). 6** (40 mg, 0.18 mmol) and hydrocinnamoyl chloride (30 µL, 0.20 mmol) were reacted following General Procedure A. Purification of the crude material by column chromatography (0% → 0.25% MeOH in DCM) yielded the title compound as a white powder (39 mg, 0.11 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.7 Hz, 1H), 7.55 (d, *J* = 2.5 Hz, 1H), 7.52 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.34 – 7.17 (m, 5H), 7.02 (s, 1H), 4.09 (s, 3H), 3.05 (t, *J* = 7.5 Hz, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.69, 155.88, 148.32, 140.61, 133.12, 133.08, 130.69, 128.80, 128.53, 126.58, 124.20, 119.71, 116.33, 57.84, 39.23, 31.80, 17.85. HRMS $[C_{19}H_{19}N_3O_4 + H]^+$: 354.14483 calculated, 354.14464 found.

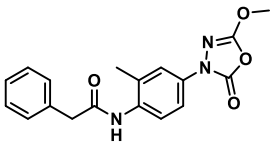


***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (10). 6** (40 mg, 0.18 mmol) was reacted with benzoyl chloride (23 µL, 0.20 mmol) following General Procedure A. The resulting crude material was purified by column chromatography (DCM) to obtain **10** as a white solid. (35 mg, 0.11 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.9 Hz, 1H), 7.93 – 7.86 (m, 2H), 7.72 – 7.62 (m, 2H), 7.62 – 7.55 (m, 1H), 7.55 – 7.47 (m, 2H), 4.12 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 165.68,

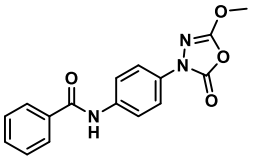
155.96, 148.39, 134.89, 133.44, 133.23, 132.16, 130.44, 129.04, 127.18, 123.86, 119.91, 116.65, 57.87, 18.21. HRMS $[C_{17}H_{15}N_3O_4 + H]^+$: 326.11353 calculated, 326.11306 found.



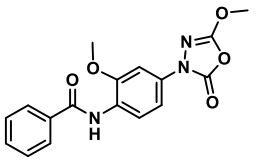
Phenyl (4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)carbamate (11). 6 (40 mg, 0.18 mmol) and phenyl carbonochloridate (25 µL, 0.20 mmol) were reacted following General Procedure A. The resulting crude material was purified by column chromatography (DCM). The product was additionally redissolved in DCM, washed with 1 M aq. HCl, dried ($MgSO_4$) and concentrated *in vacuo* to obtain **16** as a white solid (28 mg, 82 µmol, 45%). ^{1}H NMR (400 MHz, DMSO) δ 9.57 (s, 1H), 7.60 – 7.52 (m, 3H), 7.47 – 7.39 (m, 2H), 7.30 – 7.20 (m, 3H), 4.08 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 155.42, 152.76, 150.78, 148.03, 133.26, 132.88, 129.43, 125.38, 121.92, 119.44, 115.73, 58.15, 18.07. HRMS $[C_{17}H_{17}N_3O_5 + H]^+$: 342.10845 calculated, 342.10835 found.



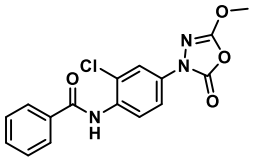
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-2-phenylacetamide (12). 6** (40 mg, 0.18 mmol) was reacted with 2-phenylacetyl chloride (26 µL, 0.20 mmol) according to General Procedure A. The resulting crude material was purified by column chromatography (0% → 0.5% MeOH in DCM). The purified compound was redissolved in DCM, washed with sat aq. $NaHCO_3$ (2×), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to obtain **12** as a white solid (43 mg, 0.13 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.89 (m, 1H), 7.56 (m, 2H), 7.47 – 7.32 (m, 5H), 6.97 (s, 1H), 4.09 (s, 3H), 3.79 (s, 2H), 1.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.14, 155.77, 148.21, 134.51, 133.10, 132.76, 130.46, 129.70, 129.35, 127.94, 123.38, 119.57, 116.37, 57.73, 44.82, 16.95. HRMS $[C_{18}H_{17}N_3O_4 + H]^+$: 340.12918 calculated, 340.12908 found.



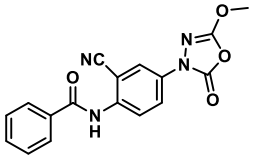
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)phenyl)benzamide (13). 67b** (11 mg, 84 µmol) was reacted with benzoyl chloride (6 µL, 53 µmol) using solely pyridine (0.7 mL) as solvent following General Procedure A. Purification of the crude material by column chromatography (0% → 2% MeOH in DCM) gave the final compound as a yellow solid (11 mg, 35 µmol, 67%). ^{1}H NMR (400 MHz, DMSO) δ 10.39 (s, 1H), 7.99 – 7.95 (m, 2H), 7.92 – 7.86 (m, 2H), 7.71 – 7.66 (m, 2H), 7.63 – 7.57 (m, 1H), 7.56 – 7.49 (m, 2H), 4.08 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 165.52, 155.42, 148.02, 136.65, 134.76, 131.68, 131.57, 128.43, 127.68, 120.98, 118.19, 58.12. HRMS $[C_{16}H_{13}N_3O_4 + H]^+$: 312.09788 calculated, 312.09768 found.



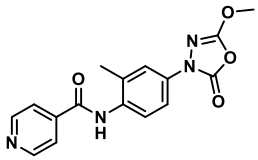
***N*-(2-Methoxy-4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)phenyl)benzamide (14). 67c** (20 mg, 84 µmol) was reacted with benzoyl chloride (11 µL, 93 µmol) according to General Procedure A. Purification of the crude material by column chromatography (0% → 2% MeOH in DCM) gave the title compound as a yellow solid (25 mg, 73 µmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.9 Hz, 1H), 8.51 (s, 1H), 7.93 – 7.84 (m, 2H), 7.63 – 7.45 (m, 4H), 7.37 (dd, *J* = 8.9, 2.4 Hz, 1H), 4.11 (s, 3H), 3.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.27, 155.85, 148.52, 148.32, 135.12, 132.23, 131.94, 128.90, 127.13, 125.45, 120.07, 110.44, 100.68, 57.90, 56.24. HRMS $[C_{17}H_{15}N_3O_5 + H]^+$: 342.10845 calculated, 342.10832 found.



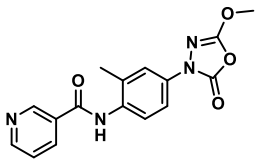
***N*-(2-Chloro-4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)phenyl)benzamide (15). 67d** (19 mg, 79 µmol) was reacted with benzoyl chloride (10 µL, 86 µmol) following General Procedure A using solely pyridine (0.7 mL) as solvent. Purification of the crude material by column chromatography (0% → 2% MeOH in DCM) gave the final compound as a yellow solid (7.0 mg, 20 µmol, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 9.1 Hz, 1H), 8.46 (s, 1H), 7.98 (d, *J* = 2.5 Hz, 1H), 7.97 – 7.92 (m, 2H), 7.80 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.60 – 7.52 (m, 2H), 4.16 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.29, 156.01, 148.05, 134.44, 132.46, 132.40, 132.24, 129.07, 127.15, 123.53, 121.88, 118.34, 117.21, 57.94. HRMS $[C_{16}H_{12}ClN_3O_4 + H]^+$: 346.05891 calculated, 346.05886 found.



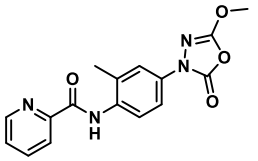
***N*-(2-Cyano-4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)phenyl)benzamide (16). 67e** (6.0 mg, 26 µmol) and benzoyl chloride (6.6 µL, 57 µmol) were reacted following General Procedure A, with the addition that a catalytic amount of DMAP was used. Purification of the crude material by column chromatography (0% → 0.25% MeOH in DCM) gave the final compound as a white solid (6.8 mg, 20 µmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 – 8.65 (m, 1H), 8.41 (s, 1H), 8.15 – 8.06 (m, 2H), 7.98 – 7.89 (m, 2H), 7.67 – 7.59 (m, 1H), 7.59 – 7.47 (m, 2H), 4.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.47, 156.18, 147.95, 137.89, 133.53, 132.87, 132.34, 129.22, 127.27, 123.31, 122.12, 120.63, 115.81, 102.80, 58.08. HRMS $[C_{17}H_{12}N_4O_4 + H]^+$: 337.09313 calculated, 337.09304 found.



***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)isonicotinamide (17).** Isonicotinic acid (18.6 mg, 0.151 mmol) and **6** (20 mg, 90 µmol) were reacted following General Procedure B. The resulting crude material was purified by column chromatography (0.1% → 0.5% MeOH in DCM) to obtain **17** as a yellow solid (5.0 mg, 15 µmol, 17%). ^{1}H NMR (400 MHz, DMSO) δ 10.23 (s, 1H), 8.82 – 8.76 (m, 2H), 7.91 – 7.86 (m, 2H), 7.66 – 7.56 (m, 2H), 7.47 (d, *J* = 8.6 Hz, 1H), 4.09 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 163.99, 155.45, 150.38, 148.49, 141.36, 135.00, 134.01, 133.01, 127.45, 121.60, 119.73, 115.53, 58.17, 18.11. HRMS $[C_{16}H_{14}N_4O_4 + H]^+$: 327.10878 calculated, 327.10850 found.

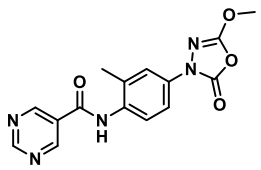


***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)nicotinamide (18). 6** (20 mg, 90 µmol) and nicotinic acid (16.7 mg, 0.136 mmol) were reacted following General Procedure C. The resulting crude material was purified by column chromatography (0.1% → 0.5% MeOH in DCM) to obtain **18** as a yellow solid (13 mg, 0.40 mmol, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 – 9.07 (m, 1H), 8.77 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.22 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.92 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 2.5 Hz, 1H), 7.64 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.44 (dd, *J* = 8.0, 4.9 Hz, 1H), 4.11 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.07, 155.97, 152.81, 148.35, 148.03, 135.56, 133.77, 132.77, 131.47, 130.54, 125.15, 123.89, 119.92, 116.49, 57.91, 18.23. HRMS $[C_{16}H_{14}N_4O_4 + H]^+$: 327.10878 calculated, 327.10855 found.

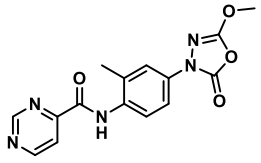


***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)picolinamide (19). 6** (20 mg, 90 µmol) and picolinic acid (18.6 mg, 0.151 mmol) were reacted following General Procedure B. The resulting crude material was purified by column chromatography (0.1% → 2% MeOH in DCM) to obtain **23** as a yellow solid (12 mg, 38 µmol, 42%). ^{1}H NMR (300 MHz, DMSO) δ 10.33 (s, 1H), 8.75 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.8, 1.2 Hz, 1H), 8.08 (td, *J* = 7.6, 1.7 Hz, 1H),

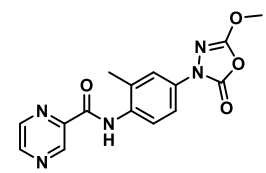
7.90 (d, *J* = 8.6 Hz, 1H), 7.70 (ddd, *J* = 7.5, 4.8, 1.4 Hz, 1H), 7.63 – 7.54 (m, 2H), 4.08 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 162.15, 154.73, 149.55, 148.63, 147.36, 138.29, 133.41, 132.81, 131.93, 127.11, 124.19, 122.25, 119.49, 115.81, 58.15, 17.81. HRMS [$C_{16}H_{14}N_4O_4$ + H]$^+$: 327.10878 calculated, 327.10853 found.



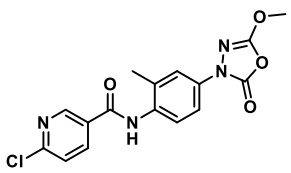
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)pyrimidine-5-carboxamide (20). 6** (20 mg, 90 µmol) and pyrazine-2-carbonyl chloride (14 mg, 99 µmol) were reacted following General Procedure A. The resulting crude material was purified by column chromatography (1% → 10% MeOH in DCM) to obtain **20** as a yellow solid (18 mg, 55 µmol, 61%). ^{1}H NMR (400 MHz, DMSO) δ 10.27 (s, 1H), 9.36 (s, 1H), 9.27 (s, 2H), 7.64 – 7.54 (m, 2H), 7.49 (d, *J* = 8.6 Hz, 1H), 4.07 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 162.32, 159.95, 156.29, 155.45, 148.04, 134.77, 133.98, 132.82, 128.07, 127.17, 119.33, 115.53, 58.17, 18.16. HRMS [$C_{15}H_{13}N_5O_4$ + H]$^+$: 328.10403 calculated, 328.10399 found.



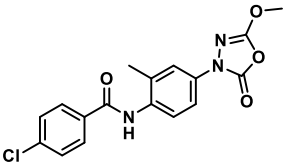
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)pyrimidine-4-carboxamide (21). 6** (20 mg, 90 µmol) and pyrimidine-4-carboxylic acid (18.7 mg, 0.151 mmol) were reacted following General Procedure B. The resulting crude material was purified by column chromatography (0.1% → 0.5% MeOH in DCM) to obtain **5** as a yellow solid (4.9 mg, 15 µmol, 17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 9.33 (d, *J* = 1.4 Hz, 1H), 9.06 (d, *J* = 5.0 Hz, 1H), 8.34 (d, *J* = 8.9 Hz, 1H), 8.24 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.74 (d, *J* = 2.5 Hz, 1H), 7.69 (dd, *J* = 8.9, 2.6 Hz, 1H), 4.12 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.24, 159.81, 157.91, 156.49, 155.99, 148.38, 133.09, 132.83, 129.37, 122.11, 119.97, 118.74, 116.73, 57.89, 18.01. HRMS [$C_{15}H_{13}N_5O_4$ + H]$^+$: 328.10403 calculated, 328.10384 found.



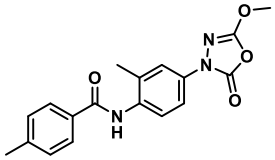
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)pyrazine-2-carboxamide (22).** Pyrazinoic acid (18.6 mg, 0.151 mmol) and **6** (20 mg, 90 µmol) were reacted following General Procedure B. The resulting crude material was purified by column chromatography (0.1% → 0.5% MeOH in DCM) to obtain **25** as a yellow solid (18 mg, 55 µmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 9.33 (d, *J* = 1.4 Hz, 1H), 9.06 (d, *J* = 5.0 Hz, 1H), 8.34 (d, *J* = 8.9 Hz, 1H), 8.24 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.74 (d, *J* = 2.6 Hz, 1H), 7.69 (dd, *J* = 8.9, 2.6 Hz, 1H), 4.12 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.24, 159.81, 157.91, 156.49, 155.99, 148.38, 133.09, 132.83, 129.37, 122.11, 119.97, 118.74, 116.73, 57.89, 18.01. HRMS [$C_{19}H_{15}N_3O_4$ + H]$^+$: 328.10403 calculated, 328.10380 found.



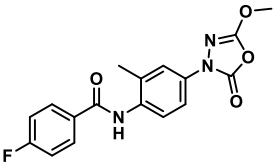
6-Chloro-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)nicotinamide (23). 6 (20 mg, 90 µmol) and 6-chloronicotinoyl chloride (14 mg, 99 µmol) were reacted following General Procedure A. The resulting crude material was purified by column chromatography (1% → 10% MeOH in DCM) to obtain **23** as a yellow solid (11 mg, 30 µmol, 33%). ^{1}H NMR (400 MHz, DMSO) δ 10.20 (s, 1H), 8.97 (d, *J* = 2.6 Hz, 1H), 8.36 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.72 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.65 – 7.55 (m, 2H), 7.51 – 7.44 (m, 1H), 4.08 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 163.00, 155.44, 152.89, 149.34, 148.03, 139.06, 134.89, 133.94, 133.03, 129.43, 127.34, 124.26, 119.30, 115.52, 58.16, 18.15. HRMS [$C_{16}H_{13}ClN_4O_4$ + H]$^+$: 361.06981 calculated, 361.06955 found.



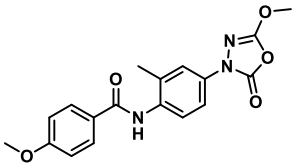
4-Chloro-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (24). 6 (20 mg, 90 µmol) was reacted with 4-chlorobenzoyl chloride (13 µL, 99 µmol) according to General Procedure A. Purification of the crude material by column chromatography (0% → 2% MeOH in DCM) gave the final compound (29 mg, 81 µmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 4H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.60 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 4.12 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.93, 155.93, 148.33, 138.34, 133.51, 133.05, 133.03, 131.32, 129.16, 128.68, 124.44, 119.82, 116.40, 57.89, 18.18. HRMS $[C_{17}H_{14}ClN_3O_4 + H]^+$: 360.07456 calculated, 360.07431 found.



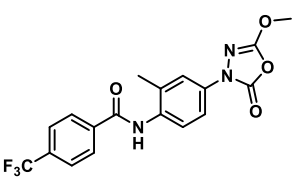
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-4-methylbenzamide (25). 6** (20 mg, 90 µmol) was reacted with 4-methylbenzoyl chloride (13 µL, 99 µmol) according to General Procedure A. Purification of the crude material by column chromatography (0% → 2% MeOH in DCM) gave the title compound (27 mg, 80 µmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.9 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.74 (s, 1H), 7.68 (d, *J* = 2.6 Hz, 1H), 7.62 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 4.11 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.78, 155.91, 148.35, 142.66, 133.52, 133.09, 131.94, 130.59, 129.62, 127.20, 123.94, 119.83, 116.50, 57.86, 21.64, 18.17. HRMS $[C_{18}H_{17}N_3O_4 + H]^+$: 340.12918 calculated, 340.12896 found.



4-Fluoro-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (26). 6 (20 mg, 90 µmol) was reacted with 4-fluorobenzoyl chloride (12 µL, 99 µmol) according to General Procedure A. Purification of the crude material by column chromatography (0% → 2% MeOH in DCM) gave the title compound (24 mg, 70 µmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.86 (m, 3H), 7.71 (d, *J* = 2.7 Hz, 1H), 7.65 (dd, *J* = 8.8, 2.6 Hz, 2H), 7.23 – 7.13 (m, 2H), 4.12 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.14 (d, *J* = 253 Hz), 164.80, 155.97, 148.38, 133.41, 133.23, 130.99, 130.78, 129.60 (d, *J* = 9.2 Hz), 124.12, 119.92, 116.61, 116.11 (d, *J* = 22.2 Hz), 57.88, 18.21. HRMS $[C_{17}H_{14}FN_3O_4 + H]^+$: 344.10411 calculated, 344.10395 found.

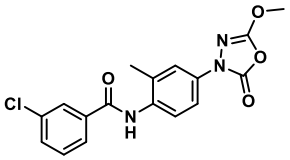


4-Methoxy-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (27). 6 (20 mg, 90 µmol) was reacted with 4-methoxybenzoyl chloride (17 mg, 99 µmol) according to General Procedure A. Purification of the crude material by column chromatography (0% → 2% MeOH in DCM) gave the title compound (26 mg, 73 µmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.8 Hz, 1H), 7.85 (dd, *J* = 9.0, 2.3 Hz, 2H), 7.76 – 7.65 (m, 2H), 7.62 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.03 – 6.94 (m, 2H), 4.11 (s, 3H), 3.88 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.35, 162.69, 155.91, 148.37, 133.62, 133.04, 130.57, 129.07, 126.97, 123.95, 119.84, 116.53, 114.14, 57.86, 55.62, 18.19. HRMS $[C_{18}H_{17}N_3O_5 + H]^+$: 356.12410 calculated, 356.12390 found.

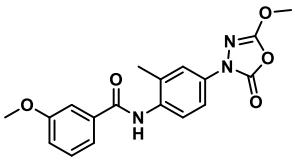


***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-4-(trifluoromethyl)benzamide. (28) 6** (20 mg, 90 µmol) was reacted with 4-(trifluoromethyl)benzoyl chloride (15 µL, 99 µmol) according to General Procedure A. Purification of the crude material by column chromatography (0% → 2% MeOH in DCM) gave the title compound (28 mg, 71 µmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.89 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 2.6 Hz, 1H), 7.62 (dd, *J* = 8.8, 2.6 Hz, 1H), 4.12 (s, 3H), 2.34

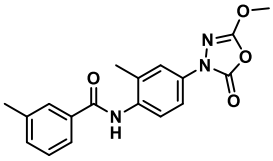
(s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.72, 155.97, 148.35, 138.00, 133.74 (t, *J* = 15.1 Hz), 132.80, 131.46, 127.75, 125.98 (q, *J* = 3.6 Hz), 125.06, 124.53, 122.35, 119.87, 116.44, 57.91, 18.18. HRMS [$C_{18}H_{14}F_3N_3O_4$ + H]$^+$: 394.10092 calculated, 394.10077 found.



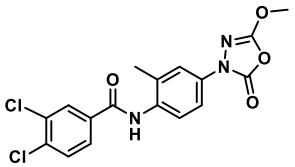
3-Chloro-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (29). 6 (20 mg, 90 µmol) was reacted with 3-chlorobenzoyl chloride (13 µL, 99 µmol) according to General Procedure A. Purification of the crude material by column chromatography (0% → 2% MeOH in DCM) gave the title compound (30 mg, 83 µmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.83 (m, 2H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.74 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.60 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.55 – 7.49 (m, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 4.12 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.69, 155.93, 148.33, 136.48, 135.12, 133.61, 132.88, 132.10, 131.52, 130.23, 127.67, 125.25, 124.56, 119.82, 116.38, 57.90, 18.21. HRMS [$C_{17}H_{14}ClN_3O_4$ + H]$^+$: 360.07456 calculated, 360.07426 found.



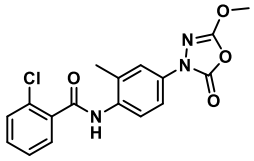
3-Methoxy-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (30). 6 (20 mg, 90 µmol) and 3-methoxybenzoic acid (27.5 mg, 0.181 mmol), were reacted following General Procedure D using DMF (2.5 mL) instead of ACN as solvent. The resulting crude material was purified by column chromatography (DCM → 25% EtOAc in pentane) to obtain **30** as white solid (14.4 mg, 41 µmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 2.4 Hz, 1H), 7.68 – 7.57 (m, 2H), 7.54 – 7.46 (m, 2H), 7.45 – 7.37 (m, 1H), 7.17 – 7.08 (m, 1H), 4.14 (s, 3H), 3.88 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.84, 159.70, 155.77, 148.43, 135.59, 133.72, 133.56, 133.05, 129.61, 125.82, 119.77, 119.21, 117.84, 116.04, 112.62, 57.68, 55.23, 17.85. HRMS [$C_{18}H_{17}N_3O_5$ + H]$^+$: 356.12410 calculated, 356.12423 found.



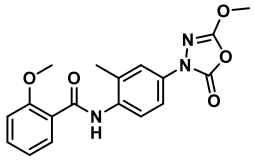
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-methylbenzamide (31). 6** (20.0 mg, 90.0 µmol) and 3-methylbenzoic acid (18.5 mg, 0.136 mmol) were reacted following General Procedure C. The resulting crude material was purified by column chromatography (20% → 25% EtOAc in pentane) to obtain **33** as a white solid (10.9 mg, 32.0 µmol, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9.0 Hz, 1H), 7.73 – 7.68 (m, 3H), 7.68 – 7.62 (m, 2H), 7.40 – 7.35 (m, 2H), 4.11 (s, 3H), 2.44 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.02, 155.94, 148.38, 138.97, 134.86, 133.47, 133.19, 132.87, 130.57, 128.86, 128.00, 124.06, 123.94, 119.88, 116.59, 57.87, 21.56, 18.23. HRMS [$C_{18}H_{17}N_3O_4$ + H]$^+$: 340.12918 calculated, 340.12912 found.



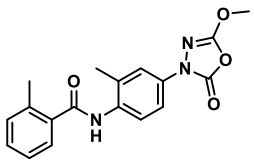
3,4-Dichloro-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (32). 6 (20 mg, 90 µmol) was reacted with 3,4-dichlorobenzoyl chloride (21 mg, 99 µmol) according to General Procedure A. Purification of the crude material by column chromatography (0% → 2% MeOH in DCM) gave the title compound (23 mg, 58 µmol, 65%). ^{1}H NMR (400 MHz, DMSO) δ 10.13 (s, 1H), 8.22 (d, *J* = 2.1 Hz, 1H), 7.95 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.62 (d, *J* = 2.6 Hz, 1H), 7.57 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 4.08 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 163.28, 155.46, 148.06, 135.03, 134.70, 134.48, 133.94, 133.23, 131.41, 130.88, 129.68, 128.02, 127.48, 119.32, 115.55, 58.18, 18.16. HRMS [$C_{17}H_{13}Cl_2N_3O_4$ + H]$^+$: 394.03559 calculated, 394.03551 found.



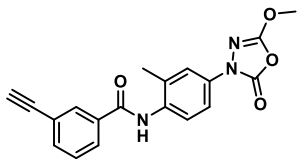
2-Chloro-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (33). 6 (20 mg, 90 µmol) was reacted with 2-chlorobenzoic acid (28.3 mg, 0.181 mmol) following General Procedure D, using DMF (2.5 mL) as solvent. The resulting crude material was purified by column chromatography (10% EtOAc in pentane → DCM) to obtain **33** as a white solid (7.0 mg, 19 µmol, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 1H), 7.90 – 7.80 (m, 2H), 7.72 (d, *J* = 2.6 Hz, 1H), 7.67 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.51 – 7.37 (m, 3H), 4.12 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.53, 155.96, 148.37, 134.92, 133.41, 133.13, 132.04, 131.04, 130.63, 130.60, 130.56, 127.58, 123.90, 119.92, 116.55, 57.88, 18.49. HRMS $[C_{17}H_{14}ClN_3O_4 + H]^+$: 360.07456 calculated, 360.07449 found.



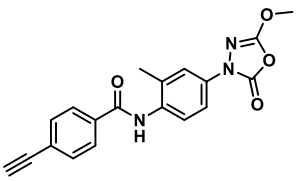
2-Methoxy-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (34). 6 (20.0 mg, 90.0 µmol) and 2-methoxybenzoic acid (20.6 mg, 0.136 mmol), were reacted following General Procedure C. The resulting crude material was purified by column chromatography (0.5% → 1% MeOH in DCM) to obtain **34** as a white solid (7.00 mg, 20.0 µmol, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.41 (d, *J* = 8.9 Hz, 1H), 8.33 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.70 (d, *J* = 2.6 Hz, 1H), 7.63 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.52 (ddd, *J* = 8.3, 7.3, 1.9 Hz, 1H), 7.16 (ddd, *J* = 8.1, 7.4, 1.1 Hz, 1H), 7.06 (dd, *J* = 8.5, 1.0 Hz, 1H), 4.11 (s, 3H), 4.08 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.18, 157.31, 155.91, 148.43, 134.77, 133.46, 132.83, 132.13, 128.42, 122.53, 121.89, 121.79, 119.77, 116.72, 111.56, 57.84, 56.34, 18.40. HRMS $[C_{18}H_{17}N_3O_5 + H]^+$: 356.12412 calculated, 356.12410.



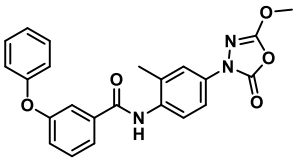
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-2-methylbenzamide (35). 6** (20 mg, 90 µmol) was reacted with 2-methylbenzoic acid (25 mg, 0.181 mmol) following General Procedure D using DMF (2.5 mL) instead of ACN as solvent. The resulting crude material was purified by column chromatography (DCM → 25% EtOAc in pentane) to obtain **37** as a white solid (6.0 mg, 18 µmol, 20%). ^{1}H NMR (400 MHz, MeOD) δ 7.70 (d, *J* = 2.3 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.57 – 7.50 (m, 1H), 7.41 – 7.32 (m, 1H), 7.28 (d, *J* = 7.5 Hz, 2H), 4.14 (s, 3H), 2.51 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 169.86, 155.71, 148.36, 135.91, 135.78, 133.73, 133.49, 132.78, 130.72, 129.95, 126.69, 125.82, 125.52, 119.69, 115.87, 57.54, 19.22, 17.80. HRMS $[C_{18}H_{17}N_3O_4 + H]^+$: 340.12918 calculated, 340.12904 found.



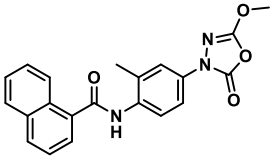
3-Ethynyl-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (36). 3-Ethynylbenzoic acid (66 mg, 0.452 mmol) was reacted with **6** (50 mg, 0.226 mmol) following General Procedure D. The crude product was purified with column chromatography (0% → 10% MeOH in DCM) to obtain title compound **36** as a white solid (40 mg, 0.114 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.94 – 7.81 (m, 2H), 7.76 – 7.58 (m, 4H), 7.46 (t, *J* = 7.8 Hz, 1H), 4.11 (s, 3H), 3.16 (s, 1H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.98, 155.95, 148.36, 135.48, 135.12, 133.50, 133.07, 131.04, 130.69, 129.13, 127.65, 124.27, 123.11, 119.89, 116.54, 82.60, 78.74, 57.89, 18.24. HRMS $[C_{19}H_{15}N_3O_4 + H]^+$: 350.11353 calculated, 350.11321 found.



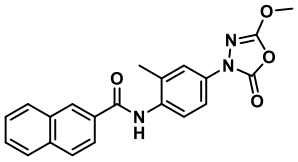
4-Ethynyl-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (37). 6 (20 mg, 90 µmol) and 4-ethynylbenzoic acid (22.0 mg, 0.151 mmol) were reacted following General Procedure B. Due to accidental addition of DMF (1 mL) work-up was slightly modified: brine was added and the mixture was extracted with Et_2O (3×). The organic layers were combined and washed with 10% aq. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (5% → 40% EtOAc in pentane) to obtain **37** as a yellow solid (7.1 mg, 20 µmol, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.80 (m, 4H), 7.69 (d, *J* = 2.5 Hz, 1H), 7.63 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.61 – 7.56 (m, 2H), 4.11 (s, 3H), 3.23 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.04, 155.97, 148.37, 134.74, 133.43, 133.16, 132.69, 130.74, 127.19, 126.05, 124.07, 119.92, 116.61, 82.71, 80.09, 57.88, 18.21. HRMS [$C_{19}H_{15}N_3O_4$ + H]$^+$: 350.11353 calculated, 350.11332 found.



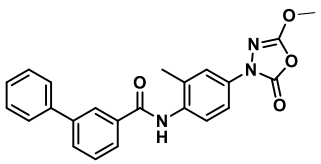
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-phenoxybenzamide (38).** 3-Phenoxybenzoic acid (194 mg, 0.904 mmol) was reacted with **6** (100 mg, 0.452 mmol) following General Procedure D. The crude product was purified with column chromatography (20% → 30% EtOAc in pentane) to obtain **38** as a white powder (60 mg, 0.144 mmol, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.9 Hz, 1H), 7.71 (s, 1H), 7.68 – 7.60 (m, 2H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.51 (s, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.22 – 7.13 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 4.11 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.15, 158.27, 156.47, 155.96, 148.38, 136.74, 133.29, 133.27, 130.43, 130.16, 124.22, 123.82, 122.04, 121.40, 119.90, 119.56, 117.26, 116.62, 57.87, 18.17. HRMS [$C_{23}H_{19}N_3O_5$ + H]$^+$: 418.13975 calculated, 418.13967.



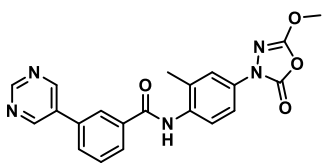
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-1-naphthamide (39). 6** (20 mg, 90 µmol) and 1-naphthoic acid (23.4 mg, 0.136 mmol) were reacted following General Procedure C. The crude product was purified with preparative HPLC to obtain **39** as a white solid (19.6 mg, 52.0 µmol, 58%). ^{1}H NMR (400 MHz, DMSO) δ 10.12 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 8.05 – 7.98 (m, 1H), 7.83 (d, *J* = 7.0 Hz, 1H), 7.66 – 7.56 (m, 6H), 4.09 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.47, 167.63, 155.50, 148.12, 134.52, 133.67, 133.27, 130.24, 129.89, 129.73, 128.41, 127.18, 127.05, 126.44, 125.67, 125.29, 125.14, 119.45, 115.63, 58.22, 18.37. HRMS [$C_{21}H_{17}N_3O_4$ + H]$^+$: 376.12918 calculated, 376.12926.



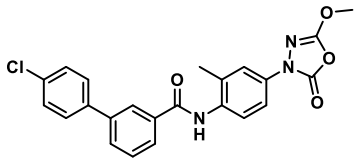
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-2-naphthamide (40). 6** (20 mg, 90 µmol) and 2-naphthoic acid (23.4 mg, 0.136 mmol were reacted following General Procedure C. The resulting crude material was purified by column chromatography (10% → 15% EtOAc in pentane) to obtain **40** as a white solid (10 mg, 27 µmol, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.98 – 7.83 (m, 5H), 7.72 (dd, *J* = 2.5, Hz, 1H), 7.66 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.63 – 7.53 (m, 2H), 4.12 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.93, 155.95, 148.38, 135.05, 133.47, 133.29, 132.76, 132.03, 130.72, 129.15, 128.98, 128.13, 127.97, 127.82, 127.15, 124.07, 123.61, 119.91, 116.60, 57.87, 18.28. HRMS [$C_{21}H_{17}N_3O_4$ + H]$^+$: 376.12918 calculated, 376.12938 found.



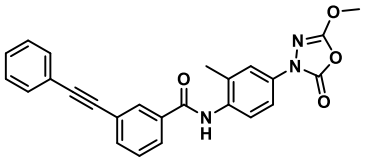
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-[1,1'-biphenyl]-3-carboxamide (41).** In a microwave tube, **73** (20 mg, 49 µmol), phenylboronic acid (7.24 mg, 32 µmol) and K_2CO_3 (27.4 mg, 0.198 mmol) were dissolved in 1,4-dioxane (0.4 mL) and H_2O (0.133 mL). The mixture was flushed with nitrogen gas using a sonicator, followed by addition of $Pd(PPh_3)_4$ (0.86 mg, 0.74 µmol). Subsequently the tube was capped and the mixture was stirred at 40°C for 28 h, after which the reaction mixture was filtered over Celite®, flushed with EtOAc and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (15% → 30% EtOAc in pentane) to obtain **41** as a white solid (13 mg, 32 µmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (t, *J* = 1.8 Hz, 1H), 8.01 (d, *J* = 8.9 Hz, 1H), 7.84 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.79 (ddd, *J* = 7.7, 1.9, 1.1 Hz, 1H), 7.76 (s, 1H), 7.73 – 7.70 (m, 1H), 7.69 – 7.61 (m, 3H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.43 – 7.37 (m, 1H), 4.12 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.84, 155.97, 148.39, 142.23, 140.19, 135.50, 133.39, 133.32, 130.82, 130.68, 129.46, 129.13, 128.07, 127.36, 126.17, 125.74, 124.03, 119.92, 116.62, 57.87, 18.26. HRMS $[C_{23}H_{19}N_3O_4 + H]^+$: 402.14483 calculated, 402.14497 found.



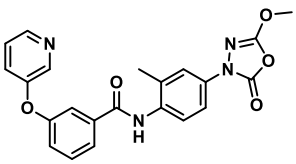
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-(pyrimidin-5-yl)benzamide (42).** In a microwave tube, **73** (60 mg, 0.15 mmol), pyrimidin-5-ylboronic acid (31 mg, 0.25 mmol) and K_2CO_3 (82 mg, 0.59 mmol) were dissolved in 1,4-dioxane (1.2 mL) and H_2O (0.40 mL). The mixture was flushed with nitrogen gas using a sonicator, followed by addition of $Pd(PPh_3)_4$ (2.6 mg, 2.2 µmol). Subsequently the tube was capped and the reaction mixture was stirred at 45°C overnight. Additional pyrimidin-5-ylboronic acid (16 mg, 0.10 mmol) and $Pd(PPh_3)_4$ (1.3 mg, 1.1 µmol) were added and the reaction mixture was stirred at 45°C for over the weekend. The reaction mixture was filtered over a glass filter, flushed with EtOAc, and the filtrate was concentrated *in vacuo*. The resulting crude material was purified by column chromatography (0% → 3% MeOH in DCM) to obtain **42** as a white solid (15 mg, 38 µmol, 26%). ^{1}H NMR (400 MHz, MeOD) δ 9.18 (s, 1H), 9.07 (s, 2H), 8.26 (t, *J* = 1.9 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.72 – 7.61 (m, 3H), 7.53 – 7.47 (m, 2H), 4.14 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 166.66, 157.08, 155.95, 155.05, 148.57, 135.55, 134.92, 134.32, 134.23, 134.05, 133.05, 130.22, 129.85, 128.27, 126.86, 126.39, 119.88, 116.02, 57.81, 18.01. HRMS $[C_{21}H_{17}N_5O_4 + H]^+$: 404.13533 calculated, 404.13516 found.



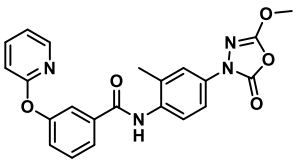
4'-Chloro-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-[1,1'-biphenyl]-3-carboxamide (43). In a microwave tube, **73** (60.0 mg, 0.148 mmol), (4-chlorophenyl)boronic acid (27.9 mg, 0.178 mmol) and K_2CO_3 (82.0 mg, 0.594 mmol) were dissolved in 1,4-dioxane (0.4 mL) and H_2O (0.13 mL). The mixture was flushed with nitrogen gas using a sonicator, followed by addition of $Pd(PPh_3)_4$ (2.57 mg, 2.23 µmol). Subsequently the tube was capped and the reaction mixture was stirred at 45°C over the weekend, after which it was filtered over a glass filter, flushed with EtOAc and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (10% → 30% EtOAc in pentane) to obtain **43** as a white solid (39.7 mg, 91.0 µmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (t, *J* = 1.8 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.83 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.77 – 7.73 (m, 2H), 7.72 (d, *J* = 2.6 Hz, 1H), 7.66 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.60 – 7.53 (m, 3H), 7.47 – 7.41 (m, 2H), 4.12 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.68, 155.97, 148.38, 141.02, 138.60, 135.61, 134.26, 133.40, 133.28, 130.76, 130.59, 129.55, 129.29, 128.59, 126.17, 125.86, 124.09, 119.92, 116.62, 57.88, 18.26. HRMS $[C_{23}H_{18}ClN_3O_4 + H]^+$: 436.10586 calculated, 436.10587 found.



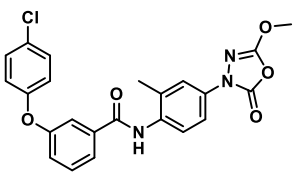
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-(phenylethynyl)benzamide (44).** 3-(Phenylethynyl)benzoic acid (**77**) (75 mg, 0.34 mmol) was reacted with **6** (38 mg, 0.17 mmol) following General Procedure D. The resulting crude material was purified by column chromatography (20% → 30% EtOAc in pentane) to obtain **44** as a white solid (51 mg, 0.12 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (t, *J* = 1.7 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.80 – 7.68 (m, 3H), 7.65 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.41 – 7.33 (m, 3H), 4.11 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.18, 155.94, 148.36, 135.11, 134.94, 133.47, 133.14, 131.82, 131.06, 130.13, 129.15, 128.82, 128.73, 128.58, 127.06, 124.29, 122.83, 119.89, 116.54, 90.83, 88.33, 57.87, 18.28. HRMS $[C_{25}H_{19}N_3O_4 + H]^+$: 426.14483 calculated, 426.14495 found.



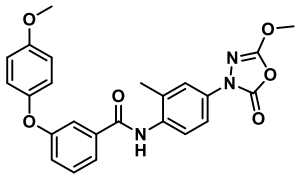
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-(pyridin-3-yloxy)benzamide (45). 80** (58 mg, 0.27 mmol) was reacted with **6** (30 mg, 0.135 mmol) following General Procedure D using 5 equivalents of DIPEA. The resulting crude material was purified by column chromatography (0.1% → 1.2% MeOH in DCM) to obtain **45** as a white solid (5.0 mg, 12 µmol, 9%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 – 8.37 (m, 2H), 7.90 – 7.84 (m, 2H), 7.73 – 7.61 (m, 3H), 7.56 (m, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.39 – 7.28 (m, 2H), 7.21 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 4.12 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.05, 157.26, 155.95, 153.31, 148.37, 145.17, 141.81, 136.94, 133.55, 133.10, 131.30, 130.68, 126.24, 124.48, 124.40, 122.24, 122.20, 119.93, 117.79, 116.51, 57.91, 18.18. HRMS $[C_{22}H_{18}N_4O_5 + H]^+$: 419.13500 calculated, 419.13459 found.



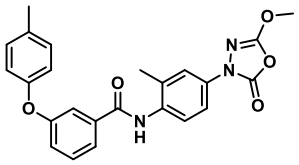
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-(pyridin-2-yloxy)benzamide (46). 83** (58 mg, 0.27 mmol) was reacted with **6** (30 mg, 0.135 mmol) following General Procedure D using 5 equivalents of DIPEA. The resulting crude material was purified by column chromatography (0.5% → 1% MeOH in DCM) to obtain **46** as a yellow solid (6.0 mg, 14 µmol, 11%). ^{1}H NMR (400 MHz, MeOD) δ 8.16 (ddd, *J* = 5.1, 2.0, 0.8 Hz, 1H), 7.93 – 7.82 (m, 2H), 7.73 (d, *J* = 2.4 Hz, 2H), 7.67 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.35 (ddd, *J* = 8.2, 2.4, 1.0 Hz, 1H), 7.18 – 7.13 (m, 1H), 7.04 (d, *J* = 8.3, 1H), 4.13 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 168.22, 164.72, 157.54, 155.99, 149.95, 148.44, 141.77, 137.35, 136.80, 136.21, 134.35, 131.22, 128.52, 125.67, 124.91, 121.37, 120.82, 120.54, 116.98, 113.19, 58.63, 18.46. HRMS $[C_{22}H_{18}N_4O_5 + H]^+$: 419.13500 calculated, 419.13481 found.



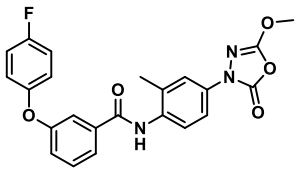
3-(4-Chlorophenoxy)-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (47). 86b (67 mg, 0.27 mmol) was reacted with **6** (30 mg, 0.135 mmol) following General Procedure D. The resulting crude material was purified by column chromatography (10% → 50% Et_2O in pentane) to obtain **47** as a yellow solid (35 mg, 77 µmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 2.5 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.54 – 7.48 (m, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.15 – 7.10 (m, 1H), 7.00 – 6.91 (m, 2H), 4.09 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.10, 157.69, 155.87, 155.17, 148.28, 136.70, 133.40, 133.06, 130.39, 130.06, 129.12, 128.31, 125.38, 122.00, 121.80, 120.61, 117.60, 116.31, 57.86, 18.13. HRMS $[C_{23}H_{18}ClN_3O_5 + H]^+$: 452.10077 calculated, 452.10059 found.



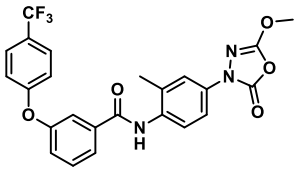
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-(4-methoxyphenoxy)benzamide (48). 86d** (67 mg, 0.27 mmol) was reacted with **6** (30 mg, 0.135 mmol) following General Procedure D. The crude product was purified by column chromatography (10% → 50% Et_2O in pentane) to obtain **48** as a white solid (11 mg, 23 µmol, 17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 9.0 Hz, 1H), 7.70 (d, *J* = 2.6 Hz, 1H), 7.64 (dd, *J* = 8.8, 2.6 Hz, 2H), 7.51 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.48 – 7.37 (m, 2H), 7.13 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 7.07 – 6.97 (m, 2H), 6.96 – 6.87 (m, 2H), 4.11 (s, 3H), 3.82 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.30, 159.34, 156.48, 155.90, 149.33, 148.32, 136.52, 133.25, 130.72, 130.21, 123.96, 121.31, 121.26, 120.81, 120.66, 119.79, 116.44, 116.12, 115.18, 57.86, 55.77, 18.12. HRMS $[C_{24}H_{21}N_3O_6 + H]^+$: 448.15031 calculated, 448.15003 found.



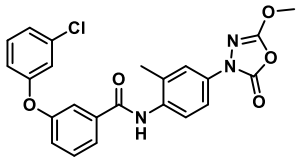
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-(p-tolyloxy)benzamide (49). 86c** (62 mg, 0.27 mmol) was reacted with **6** (30 mg, 0.135 mmol) following General Procedure D. The resulting crude material was purified by column chromatography (10% → 50% Et_2O in pentane) to obtain **49** as a white solid (34 mg, 79 µmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.86 (m, 1H), 7.78 – 7.71 (m, 1H), 7.68 – 7.65 (m, 1H), 7.61 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.53 (d, *J* = 7.8, 1H), 7.47 (t, *J* = 2.1 Hz, 1H), 7.40 (td, *J* = 7.9, 1.4 Hz, 1H), 7.20 – 7.11 (m, 3H), 6.97 – 6.91 (m, 2H), 4.10 (s, 3H), 2.34 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.30, 158.71, 155.90, 153.92, 148.32, 136.54, 133.91, 133.27, 133.23, 130.79, 130.61, 130.52, 130.25, 124.02, 121.46, 121.03, 119.79, 119.68, 116.76, 116.43, 57.85, 20.86, 18.12. HRMS $[C_{24}H_{21}N_3O_5 + H]^+$: 432.15540 calculated, 432.15520 found.



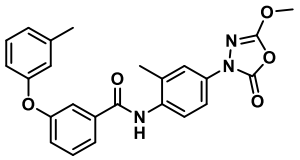
3-(4-Fluorophenoxy)-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (50). 86e (63 mg, 0.27 mmol) was reacted with **6** (30 mg, 0.135 mmol) following General Procedure D. The crude product was purified by column chromatography (0% → 0.5% MeOH in DCM) to obtain **50** as a white solid (18 mg, 41 µmol, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 1H), 7.74 (s, 1H), 7.70 – 7.65 (m, 1H), 7.62 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.55 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.48 (t, *J* = 2.1 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.14 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 7.11 – 6.97 (m, 4H), 4.11 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.14, 159.34 (d, *J* = 243 Hz), 158.56, 155.92, 152.12 (d, *J* = 2.6 Hz), 148.33, 136.71, 133.34, 133.17, 130.78, 130.39, 124.03, 121.42, 121.24, 121.19 (d, *J* = 8.2 Hz), 119.83, 116.88, 116.73 (d, *J* = 23 Hz), 116.47, 57.87, 18.15. HRMS $[C_{23}H_{18}FN_3O_5 + H]^+$: 436.13033 calculated, 436.13014 found.



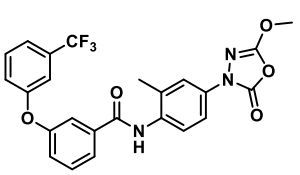
***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-(4-(trifluoromethyl)phenoxy)benzamide (51). 86a** (77 mg, 0.27 mmol) was reacted with **6** (30 mg, 0.135 mmol) following General Procedure D. The resulting crude material was purified by column chromatography (10% → 50% Et_2O in pentane) to obtain **51** as a white solid (38 mg, 78 µmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 2H), 7.67 – 7.64 (m, 2H), 7.63 – 7.55 (m, 4H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.22 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 4.11 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.98, 159.77, 156.61, 155.92, 148.32, 136.93, 133.50, 133.01, 131.24, 130.63, 127.43 (q, *J* = 3.8 Hz), 125.70 (32 Hz), 124.34, 124.14 (q, *J* = 273 Hz), 123.07, 122.63, 119.81, 118.69, 118.54, 116.39, 57.87, 19.43. HRMS $[C_{24}H_{18}F_3N_3O_5 + H]^+$: 486.12713 calculated, 486.12723 found.



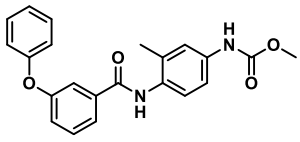
3-(3-Chlorophenoxy)-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (52). 86f (67 mg, 0.27 mmol) was reacted with **6** (30 mg, 0.135 mmol) following General Procedure D. The crude product was purified by preparative HPLC to obtain **52** as a yellow oil (18 mg, 41 µmol, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.8 Hz, 1H), 7.75 (s, 1H), 7.69 (dd, *J* = 2.6, 0.8 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.53 (s, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.28 (t, *J* = 8.1 Hz, 1H), 7.20 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 7.12 (ddd, *J* = 8.0, 2.0, 0.9 Hz, 1H), 7.02 (t, *J* = 2.2 Hz, 1H), 6.92 (ddd, *J* = 8.2, 2.4, 0.9 Hz, 1H), 4.11 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.61, 157.51, 157.33, 155.95, 148.37, 136.71, 135.40, 133.56, 132.97, 131.04, 130.89, 130.61, 124.24, 124.20, 122.64, 122.16, 119.88, 119.53, 118.00, 117.34, 116.53, 57.89, 18.18. HRMS $[C_{23}H_{18}ClN_3O_5 + H]^+$: 452.10077 calculated, 452.10045 found.



***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-(m-tolyloxy)benzamide (53). 86g** (62 mg, 0.271 mmol) was reacted with **6** (30 mg, 0.135 mmol) following General Procedure D. The crude product was purified by column chromatography (0% → 1% MeOH in DCM) to obtain **53** as a yellow oil (21 mg, 41 µmol, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 6.5 Hz, 1H), 7.66 (d, *J* = 2.4 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.50 (t, *J* = 2.0 Hz, 1H), 7.45 – 7.36 (m, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.16 (dt, *J* = 8.2, 1.6 Hz, 1H), 6.96 (ddt, *J* = 7.5, 1.7, 0.8 Hz, 1H), 6.87 – 6.79 (m, 2H), 4.10 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.27, 158.22, 156.37, 155.86, 148.28, 140.31, 136.53, 133.21 (d, *J* = 10.9 Hz), 130.25, 129.75, 124.93, 123.87 (d, *J* = 33.0 Hz), 121.91, 121.32, 120.12, 119.75, 117.24, 116.41 (d, *J* = 4.8 Hz), 57.82, 21.47, 18.09. HRMS $[C_{24}H_{21}N_3O_5 + H]^+$: 432.15540 calculated, 432.15524 found.

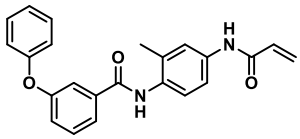


***N*-(4-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-(3-(trifluoromethyl)phenoxy)benzamide (54). 86h** (77 mg, 0.27 mmol) was reacted with **6** (30 mg, 0.135 mmol) following General Procedure D. The crude product was purified by preparative HPLC to obtain **54** as a yellow oil (40 mg, 82 µmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.86 (m, 1H), 7.79 (s, 1H), 7.69 – 7.58 (m, 3H), 7.56 (t, *J* = 2.1 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.41 – 7.37 (m, 1H), 7.27 (t, *J* = 2.0 Hz, 1H), 7.22 – 7.17 (m, 2H), 4.10 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.98, 157.13, 157.10, 155.93, 148.33, 136.96, 133.44, 133.07, 132.56 (q, *J* = 32 Hz), 131.01, 130.71, 130.63, 124.19, 123.71 (q, *J* = 273 Hz), 122.55, 122.32, 122.22, 120.55 (q, *J* = 3.8 Hz) 119.82, 118.15, 116.44, 115.97 (q, *J* = 3.8 Hz), 57.87, 18.14. HRMS $[C_{24}H_{18}F_3N_3O_5 + H]^+$: 486.12713 calculated, 486.12672 found.

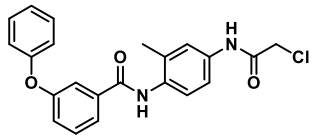


Methyl (3-methyl-4-(3-phenoxybenzamido)phenyl)carbamate (55). 89 (20 mg, 63 µmol) was co-evaporated with toluene and dissolved in DCM (1 mL). Pyridine (10 µL, 0.126 mmol) was added, and the mixture was cooled down to 0°C. Methyl chloroformate (5.3 µL, 69 µmol) was added and the reaction was stirred for 4 h at RT. The mixture was resuspended in excessive amounts of EtOAc and 1 M aq. HCl. The organic layer was washed with brine and subsequently dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (70% Et_2O in pentane) to obtain title compound **55** as a white solid (13 mg, 35 µmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 2.1 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.40 – 7.31 (m, 3H), 7.30 – 7.26 (m, 1H), 7.24 – 7.09 (m, 3H), 7.03 (d, *J* = 8.2 Hz, 2H), 3.73 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.22,

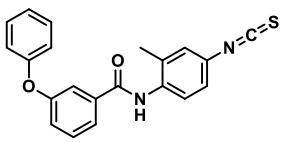
158.81, 157.68, 156.23, 138.41, 137.16, 135.94, 131.43, 130.85, 130.76, 127.99, 124.67, 122.90, 122.64, 121.42, 119.99, 118.60, 117.50, 52.49, 18.38. HRMS $[C_{22}H_{20}N_2O_4 + H]^+$: 377.14958 calculated, 377.14952 found.



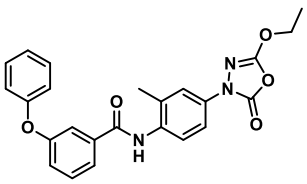
***N*-(4-Acrylamido-2-methylphenyl)-3-phenoxybenzamide (56). 89** (20 mg, 63 µmol) was co-evaporated with toluene and dissolved in DCM (1 mL). Pyridine (10 µL, 0.126 mmol) was added, and the mixture was cooled down to 0°C. Acryloyl chloride (5.3 µL, 69 µmol) was added and the reaction was stirred for 4 h at RT. The mixture was resuspended in excessive amounts of EtOAc and 1 M aq. HCl. The organic layer was washed with brine and subsequently dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (80% Et_2O in pentane) to obtain title compound **56** as a clear oil (10 mg, 27 µmol, 43%). ^{1}H NMR (300 MHz, MeOD) δ 7.67 – 7.60 (m, 1H), 7.55 (dd, *J* = 8.1, 2.3 Hz, 2H), 7.45 – 7.27 (m, 5H), 7.18 – 7.06 (m, 2H), 7.04 – 6.97 (m, 2H), 6.35 (d, *J* = 5.9 Hz, 2H), 5.71 (t, *J* = 5.9 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, MeOD) δ 167.25, 165.23, 158.21, 157.01, 137.03, 136.64, 134.48, 132.03, 131.54, 130.42, 130.31, 127.57, 126.75, 125.78, 124.25, 122.62, 122.34, 122.23, 119.58, 118.68, 118.12, 18.21. HRMS $[C_{23}H_{20}N_2O_3 + H]^+$: 373.1547 calculated, 373.1545 found.



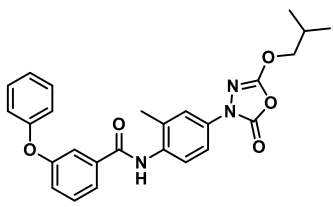
***N*-(4-(2-Chloroacetamido)-2-methylphenyl)-3-phenoxybenzamide (57). 89** (30 mg, 94 µmol) was co-evaporated with toluene and dissolved in DCM (1 mL). K_2CO_3 (13 mg, 94 µmol) was added and the mixture was cooled down to 0°C. Chloroacetyl chloride (7.5 µL, 94 µmol) was added dropwise and the reaction was stirred overnight at RT. H_2O (2 mL) was added and mixture was washed with 1 M aq. HCl. The organic layer was separated and dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (20% → 50% EtOAc in pentane) to obtain title compound **57** as a white solid (9.0 mg, 24 µmol, 25%). ^{1}H NMR (400 MHz, DMSO) δ 10.29 (s, 1H), 9.90 (s, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.60 - 7.57 (m, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.46 – 7.40 (m, 3H), 7.28 – 7.15 (m, 3H), 7.10 – 7.04 (m, 2H), 4.25 (s, 2H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 170.40, 164.57, 156.92, 156.28, 136.40, 136.38, 134.46, 132.03, 130.24, 127.25, 123.93, 122.52, 121.59, 121.06, 119.01, 117.50, 117.19, 43.61, 18.15. HRMS $[C_{22}H_{19}ClN_2O_3 + H]^+$: 395.11570 calculated, 395.11573 found.



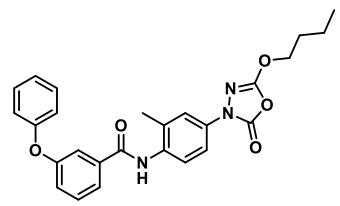
***N*-(4-Isothiocyanato-2-methylphenyl)-3-phenoxybenzamide (58). 89** (20 mg, 63 µmol) was co-evaporated with toluene and dissolved in H_2O and DCM (0.5 mL, 1:1). $NaHCO_3$ (18 mg, 0.22 mmol) was added and the mixture was cooled down to 0°C. Thiophosgene (6.0 µL, 94 µmol) was dissolved in H_2O and DCM (0.5 mL, 1:1) and this solution was added dropwise to the stirred reaction mixture, which was then stirred for 30 min. The layers were separated and the aqueous layer was extracted with DCM (3×). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*, which yielded the title compound **58** as a white solid (10 mg, 28 µmol, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 1H), 7.64 (s, 1H), 7.55 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.42 – 7.32 (m, 2H), 7.23 – 7.00 (m, 6H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.02, 158.33, 156. 37, 136.50, 135.15, 135.03, 130.49, 130.22, 130.18, 127.76, 127.65, 124.40, 124.29, 123.56, 122.15, 121.32, 119.58, 117.17, 17.79. HRMS $[C_{21}H_{17}N_3O_2 + H]^+$: 361.15467 calculated, 361.15428 found.



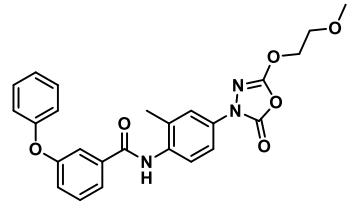
***N*-(4-(5-Ethoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-phenoxybenzamide (59).** 3-Phenoxybenzoic acid (73 mg, 0.34 mmol) was reacted with **67f** (40 mg, 0.17 mmol) following General Procedure D. The crude product was purified by column chromatography (1% MeOH in DCM) to obtain the title compound as a clear oil (34 mg, 67 µmol, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.90 (m, 1H), 7.71 – 7.68 (m, 1H), 7.66 (bs, 1H), 7.63 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.57 (d, *J* = 7.6, 1H), 7.52 – 7.49 (m, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.21 – 7.13 (m, 2H), 7.07 – 7.03 (m, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 2.34 (s, 3H), 1.50 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.83, 158.26, 156.51, 155.28, 148.39, 136.77, 133.41, 133.21, 130.54, 130.40, 130.15, 124.20, 123.91, 122.02, 121.42, 119.89, 119.54, 117.31, 116.59, 67.91, 18.15, 14.25. HRMS [$C_{24}H_{21}N_3O_5$ + H]$^+$: 432.15540 calculated, 432.15526 found.



***N*-(4-(5-Isobutoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-phenoxybenzamide (60).** 3-Phenoxybenzoic acid (68 mg, 0.32 mmol) was reacted with **67g** (42 mg, 0.16 mmol) following General Procedure D. The crude product was purified by column chromatography (1% MeOH in DCM) to obtain the title compound as a clear oil (77 mg, 0.15 mmol, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 1H), 7.72 (s, 1H), 7.69 – 7.64 (m, 1H), 7.61 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.57 (d, *J* = 7.9, 1H), 7.52 – 7.49 (m, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.20 – 7.11 (m, 2H), 7.07 – 6.97 (m, 2H), 4.17 (d, *J* = 6.6 Hz, 2H), 2.32 (s, 3H), 2.16 (non, *J* = 6.8 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.18, 158.20, 156.51, 155.51, 148.37, 136.73, 133.42, 133.17, 130.74, 130.35, 130.12, 124.15, 124.02, 121.99, 121.45, 119.85, 119.51, 117.34, 116.52, 77.55, 27.88, 18.81, 18.13. HRMS [$C_{26}H_{25}N_3O_5$ + H]$^+$: 460.18670 calculated, 460.18640 found.

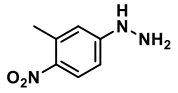


***N*-(4-(5-Butoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-phenoxybenzamide (61).** 3-Phenoxybenzoic acid (81 mg, 0.38 mmol) was reacted with **67h** (50 mg, 0.19 mmol) following General Procedure D. The crude product was purified by column chromatography (1% MeOH in DCM) to obtain the title compound as a clear oil (82 mg, 0.16 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.62 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.20 – 7.12 (m, 2H), 7.07 – 6.99 (m, 2H), 4.40 (t, *J* = 6.5 Hz, 2H), 2.33 (s, 3H), 1.85 – 1.78 (m, 2H), 1.49 (sext, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.16, 158.23, 156.51, 155.44, 148.39, 136.76, 133.42, 133.19, 130.61, 130.37, 130.13, 124.18, 123.95, 122.00, 121.43, 119.87, 119.53, 117.32, 116.56, 71.66, 30.52, 18.88, 18.14, 13.69. HRMS [$C_{26}H_{25}N_3O_5$ + H]$^+$: 460.18670 calculated, 460.18651 found.

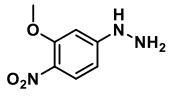


***N*-(4-(5-(2-Methoxyethoxy)-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)-3-phenoxybenzamide (62).** 3-Phenoxybenzoic acid (84 mg, 0.39 mmol) was reacted with **67i** (52 mg, 0.20 mmol) following General Procedure D. The crude product was purified by column chromatography (1% MeOH in DCM) to obtain the title compound as a clear oil (71 mg, 0.14 mmol, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.61 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.52 – 7.49 (m, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.41 – 7.31 (m, 2H), 7.21 – 7.10 (m, 2H), 7.09 – 6.99 (m, 2H), 4.59 – 4.48 (m, 2H),

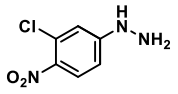
3.81 – 3.72 (m, 2H), 3.44 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.16, 158.24, 156.51, 155.34, 148.29, 136.74, 133.32, 133.27, 130.61, 130.39, 130.14, 124.19, 123.93, 122.01, 121.43, 119.90, 119.53, 117.31, 116.58, 70.57, 69.71, 59.33, 18.14. HRMS $[C_{25}H_{23}N_3O_6 + H]^+$: 462.16596 calculated, 462.16577 found.



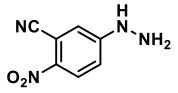
(3-Methyl-4-nitrophenyl)hydrazine (64a). 4-Fluoro-2-methyl-1-nitrobenzene (10.0 g, 64.5 mmol) was suspended in ethanol (100 mL), after which hydrazine monohydrate (10.0 mL, 191 mmol) was added dropwise. The mixture was heated to 80°C, and stirred for 16 h. The mixture was then transferred to a beaker and cooled to 0°C, which formed an orange precipitate. The mixture was filtered, and washed on the filter with ice cold EtOH (100 mL). The residue was collected and concentrated *in vacuo* to give the title compound as an orange powder (8.60 g, 51.4 mmol, 80%). ^{1}H NMR (400 MHz, DMSO) δ 8.17 (s, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 6.67 – 6.61 (m, 2H), 4.41 (s, 2H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 156.21, 137.16, 136.03, 128.02, 112.12, 108.19, 22.46.



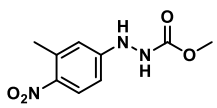
(3-Methoxy-4-nitrophenyl)hydrazine (64c). 4-Fluoro-2-methoxy-1-nitrobenzene (1.00 g, 5.84 mmol) was dissolved in NMP (1 mL), after which hydrazine hydrate (700 µL, 13.4 mmol) was added dropwise. The mixture was heated to 65°C and stirred for 75 min, after which the mixture was cooled to RT and H_2O (10 mL) was added. The precipitate was put over a filter, and subsequently the precipitate was recrystallized from isopropanol to give the title compound as a yellow solid (790 mg, 4.31 mmol, 74%). ^{1}H NMR (400 MHz, DMSO) δ 8.26 (s, 1H), 7.84 (d, *J* = 9.3 Hz, 1H), 6.50 (s, 1H), 6.32 (d, *J* = 9.3 Hz, 1H), 4.47 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 158.15, 157.00, 128.72, 126.40, 102.96, 92.48, 55.91.



(3-Chloro-4-nitrophenyl)hydrazine (64d). 2-Chloro-4-fluoro-1-nitrobenzene (1.00 g, 5.70 mmol) was dissolved in NMP (1 mL), after which hydrazine hydrate (700 µL, 13.4 mmol) was added dropwise. The mixture was heated to 65°C and stirred for 45 min, after which the mixture was cooled to RT and H_2O (10 mL) was added. The precipitate was put over a filter, and subsequently the precipitate was recrystallized from isopropanol to give the title compound as orange crystals (817 mg, 4.36 mmol, 76%). ^{1}H NMR (400 MHz, DMSO) δ 8.47 (s, 1H), 7.98 (d, *J* = 9.3 Hz, 1H), 6.88 (s, 1H), 6.70 (d, *J* = 9.6 Hz, 1H), 4.55 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 156.85, 133.85, 129.98, 129.62, 111.58, 109.28.

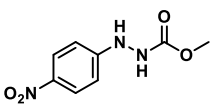


5-Hydrazineyl-2-nitrobenzonitrile (64e). 5-Fluoro-2-benzonitrile (500 mg, 3.01 mmol) was dissolved in NMP (5 mL), after which the mixture was cooled to 0°C, followed by dropwise addition of hydrazine hydrate (250 µL, 4.78 mmol). After stirring for 4 h, H_2O (45 mL) was added to the mixture, and the precipitate was put over a filter. The residue was recrystallized from MeOH to give the title compound as a yellow solid (415 mg, 2.33 mmol, 77%). ^{1}H NMR (400 MHz, DMSO) δ 8.85 (s, 1H), 8.13 (d, *J* = 9.4 Hz, 1H), 7.33 – 6.82 (m, 2H), 4.70 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 156.05, 134.26, 128.33, 116.66, 115.58, 112.56, 109.20.

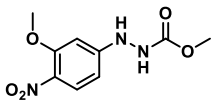


Methyl 2-(3-methyl-4-nitrophenyl)hydrazine-1-carboxylate (65a). 64a (203 mg, 1.21 mmol) and NMP (104 µL, 1.09 mmol) were dissolved in pyridine (1.2 mL). The mixture was cooled to 0°C, after which methyl chloroformate (0.141 mL, 1.80 mmol) was added dropwise. The reaction mixture was stirred for 90 min, after which the mixture was resuspended in excessive amounts of EtOAc and 1 M aq. HCl. The organic layer was washed with brine, and subsequently dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the crude material by column chromatography (10% → 50% EtOAc in pentane) yielded the title compound as a yellow oil (246 mg, 1.09 mmol, 90%). ^{1}H NMR (400 MHz, DMSO) δ 9.38 (bs, 1H), 8.80 (s, 1H), 7.99 (d, *J* = 9.1 Hz, 1H), 6.60 (dd, *J* = 9.1,

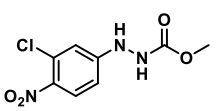
2.6 Hz, 1H), 6.58 – 6.50 (m, 1H), 3.63 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 157.02, 153.78, 138.71, 136.78, 127.81, 113.15, 108.87, 52.17, 21.77.



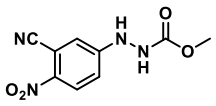
Methyl 2-(4-nitrophenyl)hydrazine-1-carboxylate (65b). 1-Fluoro-4-nitrobenzene (**63b**) (706 mg, 5.0 mmol) was suspended in ethanol (10 mL), after which hydrazine monohydrate (0.78 mL, 15 mmol) was added dropwise. The mixture was heated to 80°C, and stirred for 3 h. The mixture was then transferred cooled to 0°C, which formed an orange precipitate. The mixture was filtered, and washed on the filter with ice cold EtOH (50 mL). The remaining residue was collected and concentrated *in vacuo* to give the hydrazine intermediate as orange crystals (146 mg, 0.95 mmol, 19%). The crystals and NMP (83 µL, 0.86 mmol) were dissolved in pyridine (3 mL). The mixture was cooled to 0°C, after which methyl chloroformate (81 µL, 1.05 mmol) was added dropwise. The reaction mixture was stirred for 16 h, after which the mixture was resuspended in EtOAc and 1 M aq. HCl, followed by extraction with EtOAc (2×). The organic layers were washed with brine, and subsequently dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title compound (122 mg, 0.58 mmol, 61%). ^{1}H NMR (400 MHz, DMSO) δ 9.46 (s, 1H), 9.01 (s, 1H), 8.11 – 8.06 (m, 2H), 6.78 – 6.72 (m, 2H), 3.65 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 162.93, 154.49, 138.08, 126.01, 110.33, 52.18.



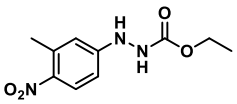
Methyl 2-(3-methoxy-4-nitrophenyl)hydrazine-1-carboxylate (65c). 64c (172 mg, 0.94 mmol) and NMP (81 µL, 0.85 mmol) were dissolved in pyridine (3 mL). The mixture was cooled to 0°C, after which methyl chloroformate (80 µL, 1.03 mmol) was added dropwise. The reaction mixture was stirred for 90 min, after which the mixture was resuspended in excessive amounts of EtOAc and 1 M aq. HCl. The organic layer was washed with brine, and subsequently dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title compound (103 mg, 0.43 mmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.0 Hz, 1H), 7.80 (s, 1H), 7.27 (s, 1H), 6.40 (d, *J* = 2.2 Hz, 1H), 6.35 (dd, *J* = 9.0, 2.2 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.61, 156.26, 154.75, 130.78, 128.78, 103.36, 95.38, 56.22, 53.04.



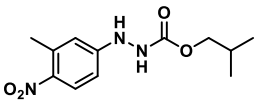
Methyl 2-(3-chloro-4-nitrophenyl)hydrazine-1-carboxylate (65d). 64d (180 mg, 0.960 mmol) and pyridine (155 µL, 1.92 mmol) were dissolved in DCM (5 mL). The mixture was cooled to 0°C, after which methyl chloroformate (82.0 µL, 1.06 mmol) was added dropwise. After stirring for 16 h 1 M aq. HCl was added, the layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the title compound as a yellow oil (220 mg, 0.90 mmol, 93%). ^{1}H NMR (400 MHz, DMSO) δ 9.49 (s, 1H), 9.07 (s, 1H), 8.04 (d, *J* = 9.1 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.72 (dd, *J* = 9.1, 2.6 Hz, 1H), 3.64 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 156.90, 156.30, 154.11, 136.50, 129.11, 112.11, 109.65, 52.35.



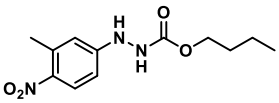
Methyl 2-(3-cyano-4-nitrophenyl)hydrazine-1-carboxylate (65e). 64e (190 mg, 1.07 mmol) was dissolved in pyridine (5 mL). The mixture was cooled to 0°C, after which methyl chloroformate (91 µL, 1.17 mmol) was added dropwise. After stirring for 20 min 1 M aq. HCl was added, the layers were separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the title compound as an off-white solid (232 mg, 0.98 mmol, 92%). ^{1}H NMR (400 MHz, DMSO) δ 9.39 (d, *J* = 3.3 Hz, 1H), 8.24 (d, *J* = 9.3, 1H), 7.14 (s, 1H), 7.01 (d, *J* = 9.3, 1H), 3.65 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 156.71, 154.16, 137.57, 128.42, 113.77, 109.08, 52.42.



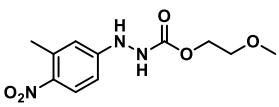
Ethyl 2-(3-methyl-4-nitrophenyl)hydrazine-1-carboxylate (65f). 64a (502 mg, 3.00 mmol) and pyridine (485 µL, 6.00 mmol) were dissolved in DCM (20 mL). The mixture was cooled to 0°C, after which ethyl chloroformate (325 µL, 3.30 mmol) was added dropwise. The reaction mixture was stirred for 15 min and was then warmed up to RT to stir for 30 additional min. The mixture was resuspended in excessive amounts of EtOAc and 1 M aq. HCl. The organic layer was washed with brine, and subsequently dried ($MgSO_4$), filtered and concentrated *in vacuo* without any further purification to yield the title compound as a yellow oil (500 mg, 2.09 mmol, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9.0 Hz, 1H), 6.84 (s, 1H), 6.63 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.59 (d, *J* = 2.6 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.54 (s, 3H), 1.40 – 1.20 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.10, 152.29, 141.35, 137.26, 127.71, 114.91, 109.75, 62.53, 22.01, 14.54.



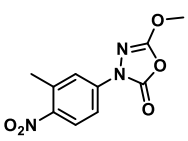
Isobutyl 2-(3-methyl-4-nitrophenyl)hydrazine-1-carboxylate (65g). 64a (502 mg, 3.00 mmol) and pyridine (485 µL, 6.00 mmol) were dissolved in DCM (20 mL). The mixture was cooled to 0°C, after which isobutyl chloroformate (437 µL, 3.30 mmol) was added dropwise. The reaction mixture was stirred for 15 min and was then warmed up to RT to stir for 30 additional min. The mixture was resuspended in excessive amounts of EtOAc and 1 M aq. HCl. The organic layer was washed with brine, and subsequently dried ($MgSO_4$), filtered and concentrated *in vacuo* without any further purification to yield the title compound as a yellow oil (732 mg, 2.74 mmol, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9.0 Hz, 1H), 6.86 (s, 1H), 6.64 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 3.95 (d, *J* = 6.7 Hz, 2H), 2.54 (s, 3H), 1.97 (m, 1H), 1.10 – 0.33 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.24, 152.33, 141.34, 137.26, 127.72, 114.92, 109.74, 72.43, 28.01, 22.02, 18.93.



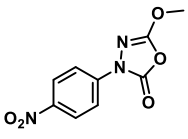
Butyl 2-(3-methyl-4-nitrophenyl)hydrazine-1-carboxylate (65h). 64a (502 mg, 3.00 mmol) and pyridine (485 µL, 6.00 mmol) were dissolved in DCM (20 mL). The mixture was cooled to 0°C, after which butyl chloroformate (428 µL, 3.30 mmol) was added dropwise. The reaction mixture was stirred for 15 min and was then warmed up to RT to stir for 30 additional min. The mixture was resuspended in excessive amounts of EtOAc and 1 M aq. HCl. The organic layer was washed with brine, and subsequently dried ($MgSO_4$), filtered and concentrated *in vacuo* without any further purification to yield the title compound as a yellow oil (684 mg, 2.56 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 9.0 Hz, 1H), 6.96 (bs, 1H), 6.83 (bs, 1H), 6.61 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.56 (d, *J* = 2.6 Hz, 1H), 4.16 (t, *J* = 6.7 Hz, 2H), 2.51 (s, 3H), 1.83 – 1.51 (m, 2H), 1.51 – 1.11 (m, 2H), 1.11 – 0.49 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.30, 152.38, 141.07, 137.21, 127.65, 114.78, 109.62, 66.28, 30.85, 21.96, 18.94, 13.67.



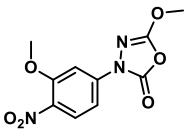
2-Methoxyethyl 2-(3-methyl-4-nitrophenyl)hydrazine-1-carboxylate (65i). 64a (502 mg, 3.00 mmol) and pyridine (485 µL, 6.00 mmol) were dissolved in DCM (20 mL). The mixture was cooled to 0°C, after which 2-methoxyethyl chloroformate (384 µL, 3.30 mmol) was added dropwise. The reaction mixture was stirred for 15 min and was then warmed up to RT to stir for 30 additional min. The mixture was resuspended in excessive amounts of EtOAc and 1 M aq. HCl. The organic layer was washed with brine, and subsequently dried ($MgSO_4$), filtered and concentrated *in vacuo* without any further purification to yield the title compound as a yellow oil (750 mg, 2.79 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.9 Hz, 1H), 6.97 (s, 1H), 6.66 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.64 – 6.60 (m, 1H), 6.49 (s, 1H), 4.33 (t, *J* = 4.5 Hz, 2H), 3.68 – 3.57 (m, 2H), 3.48 – 3.32 (m, 3H), 2.57 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.84, 152.11, 141.57, 137.29, 127.75, 115.00, 109.89, 70.58, 65.24, 59.06, 22.05.



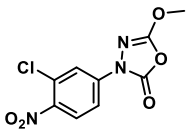
5-Methoxy-3-(3-methyl-4-nitrophenyl)-1,3,4-oxadiazol-2(3*H*)-one (66a). 65a (500 mg, 2.22 mmol) was reacted according to General Procedure E. Purification of the crude material by column chromatography (5% → 10% EtOAc in pentane) yielded the desired product as an off-white solid (484 mg, 1.93 mmol, 87%). ^{1}H NMR (400 MHz, DMSO) δ 8.16 (d, *J* = 8.9 Hz, 1H), 7.74 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.71 (d, *J* = 2.5 Hz, 1H), 4.11 (s, 3H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 155.78, 147.85, 144.79, 139.52, 135.37, 126.64, 119.86, 115.16, 58.43, 20.47.



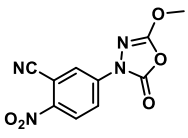
5-Methoxy-3-(4-nitrophenyl)-1,3,4-oxadiazol-2(3*H*)-one (66b). 65b (122 mg, 0.58 mmol) was reacted according to General Procedure E. Purification of the crude material by column chromatography (10% → 50% EtOAc in pentane) yielded the desired product as an off-white solid (50 mg, 0.21 mmol, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.9 Hz, 2H), 4.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.47, 141.16, 125.16, 117.64, 58.22.



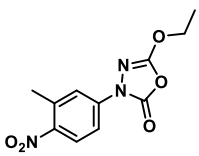
5-Methoxy-3-(3-methoxy-4-nitrophenyl)-1,3,4-oxadiazol-2(3H)-one (66c). 65c (106 mg, 0.44 mmol) was reacted according to General Procedure E. Purification of the crude material by column chromatography (DCM) yielded the desired product as an off-white solid (23 mg, 86 µmol, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 2.2 Hz, 1H), 7.46 (dd, *J* = 9.0, 2.2 Hz, 1H), 4.16 (s, 3H), 4.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.27, 154.60, 147.98, 141.11, 135.94, 127.62, 108.85, 102.25, 58.25, 56.88.



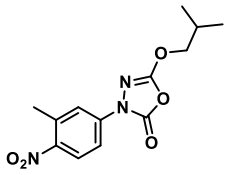
3-(3-Chloro-4-nitrophenyl)-5-methoxy-1,3,4-oxadiazol-2(3*H*)-one (66d). 65d (103 mg, 0.42 mmol) was reacted according to General Procedure E. Purification of the crude material by column chromatography (DCM) yielded the desired product as an off-white solid (48 mg, 0.18 mmol, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.01 (m, 2H), 7.91 (dd, *J* = 9.1, 2.3 Hz, 1H), 4.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.46, 147.74, 143.94, 139.76, 129.10, 127.18, 120.05, 115.79, 58.38.



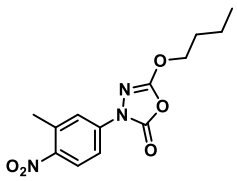
5-(5-Methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-nitrobenzonitrile (66e). 65e (140 mg, 0.59 mmol) was reacted according to General Procedure E. Purification of the crude material by column chromatography (DCM) yielded the desired product as a yellow solid (26 mg, 99 µmol, 17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 9.2 Hz, 1H), 8.36 (d, *J* = 2.3 Hz, 1H), 8.32 (t, *J* = 2.3 Hz, 1H), 4.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.75, 153.29, 147.61, 140.78, 129.93, 127.33, 123.38, 114.64, 109.67, 58.63.



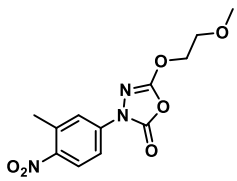
5-Ethoxy-3-(3-methyl-4-nitrophenyl)-1,3,4-oxadiazol-2(3*H*)-one (66f). 65f (500 mg, 2.09 mmol) was reacted according to General Procedure E. Purification of the crude material by column chromatography (6% EtOAc in pentane) yielded the desired product as a yellow solid (420 mg, 1.58 mmol, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 – 7.93 (m, 1H), 7.77 – 7.62 (m, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 3H), 1.51 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.46, 147.80, 145.19, 139.55, 135.89, 126.32, 120.42, 115.19, 68.35, 21.16, 14.04.



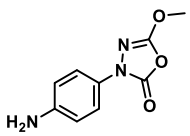
5-Isobutoxy-3-(3-methyl-4-nitrophenyl)-1,3,4-oxadiazol-2(3*H*)-one (66g). 65g (732 mg, 2.74 mmol) was reacted according to General Procedure E. Purification of the crude material by column chromatography (5% EtOAc in pentane) yielded the desired product as a yellow solid (673 mg, 2.29 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.92 (m, 1H), 7.70 – 7.62 (m, 2H), 4.17 (d, *J* = 6.6 Hz, 2H), 2.56 (s, 3H), 2.14 (nonet, *J* = 6.7 Hz, 1H), 1.02 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.63, 147.68, 145.03, 139.46, 135.75, 126.18, 120.27, 115.05, 77.77, 27.64, 21.04, 18.52.



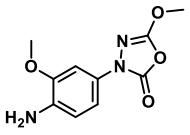
5-Butoxy-3-(3-methyl-4-nitrophenyl)-1,3,4-oxadiazol-2(3*H*)-one (66h). 65h (684 mg, 2.56 mmol) was reacted according to General Procedure E. Purification of the crude material by column chromatography (5% EtOAc in pentane) yielded the desired product as a yellow oil (565 mg, 1.93 mmol, 75%). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.62, 147.81, 145.18, 139.56, 135.88, 126.32, 120.42, 115.20, 72.02, 30.28, 21.15, 18.70, 13.52.



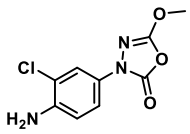
5-(2-Methoxyethoxy)-3-(3-methyl-4-nitrophenyl)-1,3,4-oxadiazol-2(3*H*)-one (66i). 65i (750 mg, 2.79 mmol) was reacted according to General Procedure E. Purification of the crude material by column chromatography (10% EtOAc in pentane) yielded the desired product as an off-white solid (538 mg, 1.82 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.83 – 7.76 (m, 2H), 4.61 – 4.55 (m, 2H), 3.82 – 3.77 (m, 2H), 3.45 (s, 3H), 2.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.72, 147.91, 145.56, 139.63, 136.13, 126.59, 120.75, 115.51, 70.96, 69.58, 59.35, 21.37.



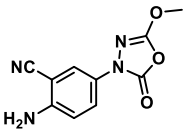
3-(4-Aminophenyl)-5-methoxy-1,3,4-oxadiazol-2(3*H*)-one (67b). 66b (50 mg, 0.21 mmol) was dissolved in DCM (3 mL) and MeOH (3 mL), and was reacted with Pd/C catalyst (10 wt%, 150 mg, 0.14 mmol) following General Procedure F. The filtrate was concentrated to give the title compound as an orange solid (35 mg, 0.17 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 2H), 4.07 (s, 3H), 3.80 (bs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.76, 148.66, 144.72, 127.60, 120.39, 115.33, 57.66, 29.79.



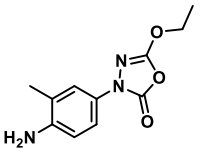
3-(4-Amino-3-methoxyphenyl)-5-methoxy-1,3,4-oxadiazol-2(3*H*)-one (67c). 66c (23 mg, 86 µmol) was dissolved in DCM (3 mL) and MeOH (3 mL) was reacted with Pd/C catalyst (10 wt%, 10 mg, 9.4 µmol) following General Procedure F. The title compound was obtained as an off-white solid (19 mg, 80 µmol, 93%) without further need for purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 2.3 Hz, 1H), 7.14 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 4.08 (s, 3H), 3.89 (s, 3H), 3.83 (bs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.64, 148.54, 147.23, 134.36, 127.54, 114.47, 111.68, 102.32, 57.62, 55.70.



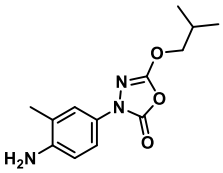
3-(4-Amino-3-chlorophenyl)-5-methoxy-1,3,4-oxadiazol-2(3*H*)-one (67d). A solution of **66d** (24 mg, 88 µmol) in dioxane (2 mL) was stirred with Raney nickel (±5 mg, 50% slurry in H_2O) under hydrogen atmosphere at room pressure for 2 h. Afterwards the reaction mixture flushed with nitrogen and was then filtered through a Celite® filter. The filtrate was concentrated *in vacuo* to give the title compound as a red solid (19 mg, 79 µmol, 92%). ^{1}H NMR (400 MHz, MeOD) δ 7.58 (d, *J* = 2.5 Hz, 1H), 7.42 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 4.09 (s, 3H), 3.66 (s, 2H). ^{13}C NMR (101 MHz, MeOD) δ 157.39, 150.09, 143.84, 128.23, 121.01, 119.78, 119.48, 116.73, 58.54.



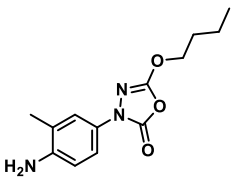
2-Amino-5-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)benzonitrile (67e). 66e (26 mg, 99 µmol) was dissolved in DCM (3 mL) and MeOH (3 mL), and was reacted with Pd/C catalyst (10 wt%, 8.0 mg, 7.5 µmol) following General Procedure F. Purification of the crude material by column chromatography (0% → 0.25% MeOH in DCM) gave the title compound as a clear white solid (6.0 mg, 26 µmol, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.80 (d, *J* = 2.6 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 1H), 4.47 (bs, 2H), 4.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.03, 148.27, 147.50, 127.36, 124.66, 121.87, 116.88, 115.95, 96.25, 57.93.



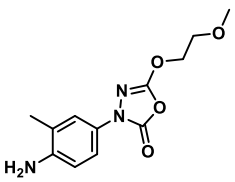
3-(4-Amino-3-methylphenyl)-5-ethoxy-1,3,4-oxadiazol-2(3*H*)-one (67f). 66f (420 mg, 1.58 mmol) was dissolved in DCM (25 mL) and MeOH (15 mL), and reacted with Pd/C catalyst (20 wt%, 150 mg, 0.28 mmol) following General Procedure F. The title compound was obtained as an off-white solid (223 mg, 0.950 mmol, 60%) without further need for purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 2.6 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.65 (s, 2H), 2.17 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.02, 148.69, 142.95, 127.44, 122.94, 121.35, 118.10, 115.00, 67.56, 17.57, 14.19.



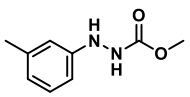
3-(4-Amino-3-methylphenyl)-5-isobutoxy-1,3,4-oxadiazol-2(3*H*)-one (67g). 66g (673 mg, 2.30 mmol) was dissolved in DCM (25 mL) and MeOH (15 mL), and was reacted with Pd/C catalyst (20 wt%, 70.0 mg, 0.13 mmol) following General Procedure F. The title compound was obtained as an off-white solid (105 mg, 0.400 mmol, 17%) without further need for purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.6 Hz, 1H), 7.38 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 4.13 (d, *J* = 6.6 Hz, 2H), 3.65 (s, 2H), 2.19 (s, 3H), 2.17 – 2.08 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.34, 148.73, 142.93, 127.55, 123.00, 121.43, 118.18, 115.07, 77.26, 27.84, 18.81, 17.62.



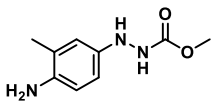
3-(4-Amino-3-methylphenyl)-5-butoxy-1,3,4-oxadiazol-2(3*H*)-one (67h). 66h (565 mg, 1.93 mmol) was dissolved in DCM (25 mL) and MeOH (15 mL), and reacted with Pd/C catalyst (5 wt%, 210 mg, 99 µmol) following General Procedure F. The title compound was obtained as an off-white solid (163 mg, 0.620 mmol, 32%) without further need for purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 2.6 Hz, 1H), 7.37 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 4.36 (t, *J* = 6.5 Hz, 2H), 3.65 (s, 2H), 2.18 (s, 3H), 1.80 (quint, *J* = 6.5 Hz, 2H), 1.48 (sext, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.22, 148.72, 142.93, 127.50, 122.97, 121.39, 118.14, 115.03, 71.33, 30.47, 18.84, 17.59, 13.66.



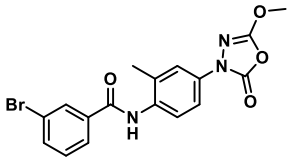
3-(4-Amino-3-methylphenyl)-5-(2-methoxyethoxy)-1,3,4-oxadiazol-2(3*H*)-one (67i). 66i (500 mg, 1.69 mmol) was dissolved in DCM (15 mL) and MeOH (15 mL), and reacted with Pd/C catalyst (5 wt%, 360 mg, 0.17 mmol) following General Procedure F. The title compound was obtained as an off-white solid (440 mg, 1.66 mmol, 98%) without further need for purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 2.5, 1H), 7.37 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 4.53 – 4.46 (m, 2H), 3.86 – 3.64 (m, 4H), 3.43 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.08, 148.60, 142.68, 127.53, 123.14, 121.37, 118.10, 115.17, 70.27, 69.66, 59.24, 17.58.



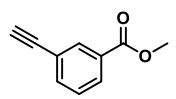
Methyl 2-(*m*-tolyl)hydrazine-1-carboxylate (70). *m*-Tolylhydrazine hydrochloride (801 mg, 5.05 mmol) and pyridine (2.00 mL, 25.0 mmol) and were dissolved in dry DCM (20 mL). The mixture was cooled to 0°C, after which methyl chloroformate (430 µL, 5.55 mmol) was added dropwise. The mixture was stirred for 2 h, after which the reaction mixture was diluted with H_2O (20 mL), and subsequently extracted with Et_2O (100 mL). The organic layer was concentrated to about 10 mL, and subsequently cooled at to 0°C, forming crystals. Using filtration, crystals were collected yielding the title compound as a yellow solid (546 mg, 3.03 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (t, 1H, *J* = 7.5 Hz), 6.72 (bs, 1H), 6.70 (d, *J* = 7.5 Hz, 1H), 6.64 – 6.56 (m, 2H), 5.21 (bs, 1H), 3.73 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.78, 147.96, 139.18, 129.14, 121.97, 113.82, 110.27, 52.93, 21.62.



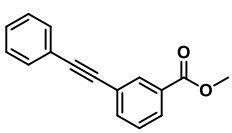
Methyl 2-(4-amino-3-methylphenyl)hydrazine-1-carboxylate (71). 65a (100 mg, 0.44 mmol) was dissolved in DCM (5 mL) and MeOH (5 mL), and was reacted with Pd/C catalyst (10 wt%, 50 mg, 47 µmol) following General Procedure F. Purification of the crude material by column chromatography (0% → 2% MeOH in DCM) was performed to give the title compound as a yellowish solid (54 mg, 0.28 mmol, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (bs, 1H), 6.58 – 6.46 (m, 3H), 5.55 (bs, 1H), 3.71 (s, 3H), 3.28 (bs, 2H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.37, 138.93, 123.84, 116.54, 116.08, 112.73, 52.73, 17.62.



3-Bromo-*N*-(4-(5-methoxy-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl)-2-methylphenyl)benzamide (73). 2-Bromobenzoic acid (182 mg, 0.90 mmol) was reacted with **6** (100 mg, 0.45 mmol) following General Procedure D. The crude product was purified with column chromatography (0% → 2% MeOH in DCM) to obtain title compound **73** as a yellow solid (78 mg, 0.45 mmol, 43%). ^{1}H NMR (400 MHz, DMSO) δ 10.08 (s, 1H), 8.16 (t, *J* = 1.9 Hz, 1H), 7.98 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.81 (ddd, *J* = 8.0, 2.1, 1.0 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 4.08 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 163.98, 155.43, 148.03, 136.54, 135.00, 134.38, 133.84, 133.39, 130.75, 130.34, 127.47, 126.82, 121.77, 119.28, 115.51, 58.15, 18.16.

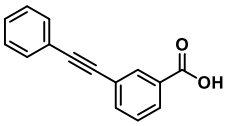


Methyl 3-ethynylbenzoate (75). 3-Ethynyl benzoic acid (200 mg, 1.37 mmol) and K_2CO_3 (567 mg, 4.11 mmol) were dissolved in DMF (10 mL) followed by cooling on ice. Methyl iodide (0.171 mL, 2.74 mmol) was then added dropwise, and the mixture was stirred overnight. The reaction mixture was diluted with EtOAc and washed with H_2O (3×), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield the title compound as a yellow oil (210 mg, 1.37 mmol, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (t, *J* = 1.7 Hz, 1H), 8.01 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.66 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 3.92 (s, 3H), 3.13 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.31, 136.31, 133.32, 130.53, 129.87, 128.56, 122.65, 82.64, 78.28, 52.39.

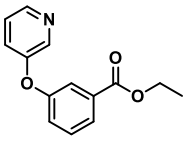


Methyl 3-(phenylethynyl)benzoate (76). One flask was was charged with methyl 3-ethynylbenzoate (**75**) (100 mg, 0.624 mmol), iodobenzene (0.139 mL, 1.25 mmol), and triethylamine (1 mL), and a second flask was charged with CuI (23.8 mg, 0.125 mmol), PPh_3 (16.4 mg, 62.0 µmol), $Pd(PPh_3)_2Cl_2$ (43.8 mg, 62.0 µmol), and triethylamine (4 mL). Both mixtures were purged with argon while sonicating for 15 min, followed by addition of the second mixture to the first. The reaction mixture was warmed to 40°C and was stirred overnight, after which the solvent was evaporated under nitrogen flow. The residue was resuspended in 1 M aq. HCl and EtOAc, and the resulting aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude material by column chromatography (5% EtOAc in pentane) yielded the title compound (107 mg, 0.451 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20

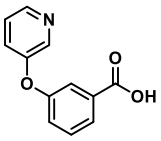
(t, *J* = 1.7 Hz, 1H), 7.98 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.68 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.36 – 7.30 (m, 3H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.43, 135.72, 132.78, 131.72, 130.47, 129.25, 128.61, 128.55, 128.46, 123.79, 122.90, 90.36, 88.38, 52.31.



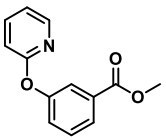
3-(Phenylethynyl)benzoic acid (77). 76 (107 mg, 0.451 mmol) was dissolved in MeOH (5 mL) and THF (5 mL) in a 250 mL round-bottom flask, after which KOH (275 mg, 4.90 mmol) was added. The mixture was stirred overnight, after which it was diluted with H_2O (100 mL). Carefully, 50% aq. H_2SO_4 (30 mL) was added, followed by additional stirring (30 min). The precipitate was filtered, washed with H_2O and dried *in vacuo*. Purification by column chromatography afforded **77** as an off-white solid (75.0 mg, 0.337 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (bs, 1H), 8.29 (t, *J* = 1.7 Hz, 1H), 8.07 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.75 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.55 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.39 – 7.32 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.47, 136.64, 133.42, 131.77, 129.84, 129.64, 128.72, 128.69, 128.49, 124.05, 122.84, 90.59, 88.16.



Ethyl 3-(pyridin-3-yloxy)benzoate (79). A flask containing pyridin-3-ol (114 mg, 1.2 mmol), picolinic acid (25 mg, 0.20 mmol), K_3PO_4 (425 mg, 2.0 mmol), and CuI (19 mg, 0.10 mmol) was purged with argon and subsequently DMSO (2 mL) and ethyl 3-iodobenzoate (168 µL, 1.0 mmol) were added. The solution was purged with argon while sonicating for 15 min, after which the reaction mixture was stirred vigorously at 110°C overnight. EtOAc (10 mL) and H_2O (1 mL) were added and the mixture was stirred for 3 min. The aqueous layer was extracted with EtOAc (2×), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (10% → 30% EtOAc in pentane) to obtain **79** as a yellow oil (88 mg, 0.36 mmol, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 2.6, 1.0 Hz, 1H), 8.41 – 8.38 (m, 1H), 7.85 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1H), 7.69 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.44 (t, *J* = 8.2 Hz, 1H), 7.31 – 7.28 (m, 2H), 7.23 (ddd, *J* = 8.2, 2.6, 1.1 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.76, 156.50, 153.49, 144.86, 141.56, 132.63, 130.07, 125.68, 125.20, 124.25, 123.37, 119.78, 61.32, 14.31.

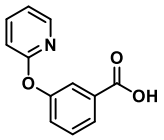


3-(Pyridin-3-yloxy)benzoic acid (80). 79 (88 mg, 0.36 mmol) was dissolved in 6 M aq. HCl (4 mL) and was stirred overnight at 110°C in a capped microwave vial. The mixture was washed with EtOAc (2×), and the aqueous layer was concentrated *in vacuo* to obtain the hydrochloride salt of **80** as a white powder (81 mg, 0.32 mmol, 89%). ^{1}H NMR (400 MHz, MeOD) δ 8.78 – 8.67 (m, 2H), 8.27 (dd, *J* = 8.8, 2.5 Hz, 1H), 8.14 (dd, *J* = 8.8, 5.5 Hz, 1H), 8.00 – 7.93 (m, 1H), 7.82 (t, *J* = 1.8 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 1H), 7.52 (dd, *J* = 8.1, 2.5 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 168.06, 158.20, 155.39, 137.36, 135.84, 134.75, 133.32, 132.19, 129.97, 128.46, 125.73, 122.10.

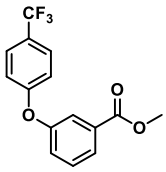


Methyl 3-(pyridin-2-yloxy)benzoate (82). A flask containing 2-bromopyridine (1.9 mL, 20 mmol), picolinic acid (0.49 g, 4.0 mmol), K_3PO_4 (8.5 g, 40 mmol), and CuI (0.38 g, 2.0 mmol) was purged with argon and subsequently DMSO (40 mL) and methyl 3-hydroxybenzoate (3.7 g, 24 mmol) were added. The solution was purged with argon while sonicating for 15 min, and the reaction mixture was stirred vigorously at 110°C overnight. After the reaction was completed, 2 mL of the mixture (5%, 1.0 mmol max.) was taken for further purification. EtOAc (10 mL) and H_2O (1 mL) were added and the aqueous layer was extracted with EtOAc (2×), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (0% → 2% MeOH in DCM) to obtain **82** as a yellow oil (65 mg, 0.28 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.06 (m, 1H), 7.86 – 7.74 (m, 2H), 7.67 – 7.55 (m, 1H), 7.54 – 7.25 (m, 2H), 6.97 – 6.83

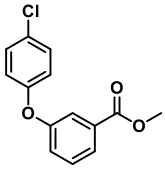
(m, 2H), 3.81 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.07, 162.98, 153.92, 147.27, 139.48, 131.49, 129.41, 125.68, 125.50, 122.05, 118.67, 111.55, 51.93.



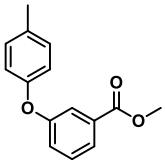
3-(Pyridin-2-yloxy)benzoic acid (83). 82 (65 mg, 0.28 mmol) was dissolved in 6 M aq. HCl (6 mL) and was stirred overnight at 110°C in a capped microwave vial. The mixture was washed with EtOAc (2×), and the aqueous layer was concentrated *in vacuo* to obtain the hydrochloride salt of **83** (81 mg, 0.32 mmol, 89%) as a white solid. ^{1}H NMR (300 MHz, MeOD) δ 8.59 (d, *J* = 5.6 Hz, 1H), 8.51 (t, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 7.3 Hz, 1H), 7.82 (s, 1H), 7.78 – 7.57 (m, 3H), 7.16 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.21, 160.46, 152.52, 150.42, 141.08, 133.99, 132.44, 129.56, 126.64, 122.59, 121.65, 113.26.



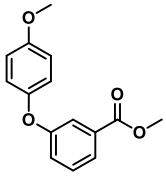
Methyl 3-(4-(trifluoromethyl)phenoxy)benzoate (85a). (4-(Trifluoromethyl)phenyl)boronic acid (380 mg, 2.0 mmol) was subjected to General Procedure G to obtain **85a** as a yellow oil (193 mg, 0.65 mmol, 33%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.60 – 7.56 (m, 2H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.25 (ddd, *J* = 8.2, 2.6, 1.1 Hz, 1H), 7.07 – 7.01 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.30, 160.07, 156.03, 132.40, 130.21, 127.38 (q, *J* = 3.8 Hz), 125.63, 125.49 (q, *J* = 32 Hz), 124.41, 124.20 (q, *J* = 273 Hz) 120.74, 118.23, 52.37.



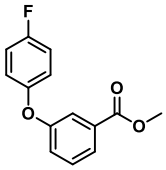
Methyl 3-(4-chlorophenoxy)benzoate (85b). (4-Chlorophenyl)boronic acid (313 mg, 2.0 mmol) was subjected to General Procedure G to obtain **85b** as a clear oil (164 mg, 0.62 mmol, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.63 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.19 (ddd, *J* = 8.2, 2.6, 1.1 Hz, 1H), 6.98 – 6.89 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.38, 157.12, 155.40, 132.07, 132.06 129.96, 128.83, 124.73, 123.38, 120.36, 119.55, 52.33.



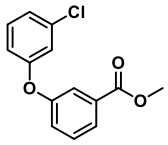
Methyl 3-(*p*-tolyloxy)benzoate (85c). *p*-Tolylboronic acid (272 mg, 2.0 mmol) was subjected to General Procedure G to obtain **85c** as a clear oil (165 mg, 0.68 mmol, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.63 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.19 – 7.10 (m, 3H), 6.93 – 6.88 (m, 2H), 3.86 (s, 3H), 2.32 (s, 3H).



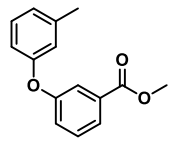
Methyl 3-(4-methoxyphenoxy)benzoate (85d). (4-Methoxyphenyl)boronic acid (304 mg, 2.0 mmol) was subjected to General Procedure G to obtain **85d** as a yellow oil (138 mg, 0.53 mmol, 27%). ^{1}H NMR (300 MHz, DMSO) δ 7.71 (ddd, *J* = 7.7, 1.6, 1.1 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.35 (t, *J* = 8.1 Hz, 1H), 7.14 (ddd, *J* = 8.2, 2.6, 1.1 Hz, 1H), 7.05 – 6.79 (m, 4H), 3.87 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.68, 158.76, 156.28, 149.62, 131.81, 129.71, 123.63, 122.18, 121.06, 118.24, 115.08, 55.69, 52.28.



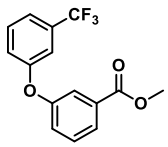
Methyl 3-(4-fluorophenoxy)benzoate (85e). (4-Fluorophenyl)boronic acid (280 mg, 2.0 mmol) was subjected to General Procedure G to obtain **85e** as a clear oil (133 mg, 0.54 mmol, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.60 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.16 (ddd, *J* = 8.2, 2.6, 1.1 Hz, 1H), 7.09 – 6.93 (m, 4H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.49, 159.13 (d, *J* = 243 Hz), 157.92, 152.37 (d, *J* = 2.6 Hz), 131.99, 129.87, 124.27, 122.76, 120.87 (d, *J* = 8.2 Hz), 118.89, 116.59 (d, *J* = 23 Hz), 52.31.



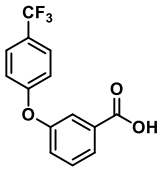
Methyl 3-(3-chlorophenoxy)benzoate (85f). (3-Chlorophenyl)boronic acid (313 mg, 2.0 mmol) was subjected to General Procedure G to obtain **85f** as a clear oil (150 mg, 0.57 mmol, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.67 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.32 – 7.15 (m, 2H), 7.08 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 6.98 (t, *J* = 2.2 Hz, 1H), 6.87 (ddd, *J* = 8.3, 2.4, 0.9 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.26, 157.76, 156.55, 135.20, 132.13, 130.68, 129.98, 125.07, 123.79, 123.75, 120.12, 119.09, 116.91, 52.28.



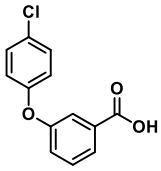
Methyl 3-(*m*-tolyloxy)benzoate (85g). *m*-Tolylboronic acid (272 mg, 2.0 mmol) was subjected to General Procedure G to obtain **85g** as a clear oil (120 mg, 0.50 mmol, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.65 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.24 – 7.15 (m, 2H), 7.24 – 7.16 (m, 1H), 6.85 – 6.77 (m, 2H), 3.86 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.56, 157.63, 156.69, 140.16, 131.90, 129.74, 129.66, 124.62, 124.21, 123.30, 119.83, 119.56, 116.14, 52.23, 21.41.



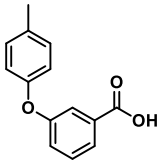
Methyl 3-(3-(trifluoromethyl)phenoxy)benzoate (85h). (3-(Trifluoromethyl)phenyl)boronic acid (380 mg, 2.0 mmol) was subjected to General Procedure G to obtain **85h** as a yellow oil (193 mg, 0.65 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (ddd, *J* = 7.7, 1.5, 1.0 Hz, 1H), 7.70 – 7.68 (m, 1H), 7.48 – 7.42 (m, 2H), 7.39 – 7.35 (m, 1H), 7.27 – 7.20 (m, 2H), 7.18 – 7.14 (m, 1H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.00, 157.45, 156.49, 132.50 (*J* = 32 Hz), 132.36, 130.60, 130.20, 125.38, 123.95, 123.72 (q, *J* = 273 Hz) 121.88, 120.30, 120.27 (q, *J* = 3.8 Hz), 115.70 (q, *J* = 3.8 Hz), 52.42.



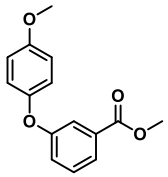
3-(4-(Trifluoromethyl)phenoxy)benzoic acid (86a). 85a (193 mg, 0.65 mmol) was subjected to General Procedure H to obtain **86a** as a white solid (164 mg, 0.65 mmol, 89%). ^{1}H NMR (400 MHz, MeOD) δ 7.85 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.68 – 7.61 (m, 3H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.10 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 168.78, 161.59, 157.35, 134.18, 131.38, 128.42 (q, *J* = 3.8 Hz), 126.74, 126.36 (q, *J* = 32 Hz), 125.63 (q, *J* = 273 Hz), 125.31, 121.60, 119.40.



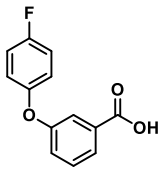
3-(4-Chlorophenoxy)benzoic acid (86b). 85b (164 mg, 0.63 mmol) was subjected to General Procedure H to obtain **86b** as a white solid (143 mg, 0.58 mmol, 92%). ^{1}H NMR (400 MHz, MeOD) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.58 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.40 – 7.31 (m, 2H), 7.29 – 7.25 (m, 1H), 7.03 – 6.95 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 168.83, 160.36, 155.36, 133.07, 131.16, 131.02, 129.34, 125.85, 124.24, 121.57, 120.40.



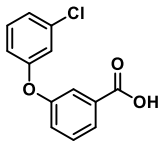
3-(*p*-Tolyloxy)benzoic acid (86c). 85c (193 mg, 0.80 mmol) was subjected to General Procedure H to obtain **86c** as a white solid (151 mg, 0.66 mmol, 83%). ^{1}H NMR (400 MHz, MeOD) δ 7.72 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.52 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.22 – 7.13 (m, 3H), 6.94 – 6.86 (m, 2H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 169.16, 159.65, 155.48, 134.90, 133.64, 131.51, 130.88, 124.97, 123.55, 120.51, 119.59, 20.76.



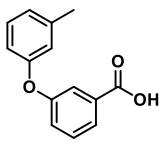
3-(4-Methoxyphenoxy)benzoic acid (86d). 85d (138 mg, 0.53 mmol) was subjected to General Procedure H to obtain **86d** as a white solid (108 mg, 0.44 mmol, 83%). ^{1}H NMR (400 MHz, MeOD) δ 7.69 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.49 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.13 (ddd, *J* = 8.2, 2.7, 1.1 Hz, 1H), 7.00 – 6.90 (m, 4H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 169.22, 160.27, 157.87, 150.79, 133.54, 130.82, 124.63, 122.90, 122.12, 118.91, 116.10, 56.04.



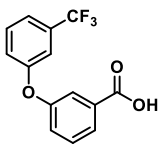
3-(4-Fluorophenoxy)benzoic acid (86e). 85e (133 mg, 0.54 mmol) was subjected to General Procedure H, with heating to 55°C. **86e** was obtained as a white solid (115 mg, 0.50 mmol, 92%). ^{1}H NMR (400 MHz, MeOD) δ 7.73 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.53 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.16 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 7.13 – 6.96 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 169.02, 160.5 (d, *J* = 243 Hz), 159.32, 153.76 (d, *J* = 2.6 Hz), 133.72, 131.00, 125.33, 123.55, 122.11 (d, *J* = 8.2 Hz), 119.65, 117.47 (d, *J* = 23 Hz).



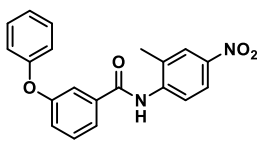
3-(3-Chlorophenoxy)benzoic acid (86f). 85f (150 mg, 0.57 mmol) was subjected to General Procedure H with heating to 55°C. **86f** was obtained as a white solid (126 mg, 0.51 mmol, 89%). ^{1}H NMR (400 MHz, MeOD) δ 7.80 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.60 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.30 (t, *J* = 8.2 Hz, 1H), 7.21 (ddd, *J* = 8.2, 2.6, 1.1 Hz, 1H), 7.11 (ddd, *J* = 8.0, 2.0, 0.9 Hz, 1H), 6.99 (t, *J* = 2.2 Hz, 1H), 6.89 (ddd, *J* = 8.3, 2.4, 0.9 Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 168.85, 159.14, 158.00, 136.23, 133.95, 132.04, 131.17, 126.19, 124.78, 124.59, 120.86, 120.07, 118.09.



3-(*m*-Tolyloxy)benzoic acid (86g). 85g (120 mg, 0.50 mmol) was subjected to General Procedure H, with heating to 55°C. **86g** was obtained as a white solid (101 mg, 0.44 mmol, 89%). ^{1}H NMR (400 MHz, MeOD) δ 7.73 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.55 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.24 – 7.12 (m, 2H), 6.94 (ddt, *J* = 7.5, 1.6, 0.8 Hz, 1H), 6.82 – 6.79 (m, 1H), 6.78 – 6.74 (m, 1H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 169.12, 159.15, 157.84, 141.40, 133.60, 130.88, 130.73, 125.73, 125.20, 123.93, 120.90, 120.07, 117.28, 21.39.

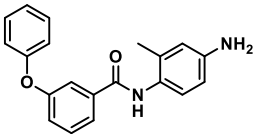


3-(3-(Trifluoromethyl)phenoxy)benzoic acid (86h). 85h (120 mg, 0.41 mmol) was subjected to General Procedure H with heating to 55°C. **86h** was obtained as white solid (105 mg, 0.37 mmol, 92%). ^{1}H NMR (400 MHz, MeOD) δ 7.82 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.62 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.55 – 7.36 (m, 3H), 7.28 – 7.15 (m, 3H). ^{13}C NMR (101 MHz, MeOD) δ 168.81, 158.79, 157.80, 134.09, 133.33 (q, *J* = 32 Hz), 132.01, 131.29, 126.44, 125.08 (q, *J* = 273 Hz) 124.72, 123.13, 121.17 (q, *J* = 3.8 Hz), 121.03, 116.45 (q, *J* = 3.8 Hz).



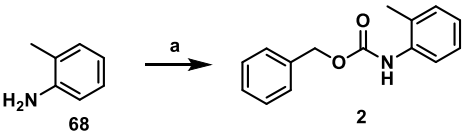
***N*-(2-Methyl-4-nitrophenyl)-3-phenoxybenzamide (88).** 3-Phenoxybenzoic acid (2.0 g, 9.3 mmol) was dissolved in $SOCl_2$ (27 mL) and this mixture was stirred at 60°C overnight. $SOCl_2$ was removed from the reaction mixture by nitrogen flow and the mixture was subsequently co-evaporated with toluene (3×). The crude mixture was redissolved in DCM (30 mL) and K_2CO_3 (2.1 g, 15 mmol) was added. A solution of 2-methyl-4-nitroaniline (1.1 g, 7.5 mmol) in DCM (20 mL) was added dropwise to the stirring reaction mixture. The reaction mixture was stirred for 2 weeks at RT. The mixture was washed with sat. aq. Na_2CO_3 (3×), and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (6% → 9% EtOAc in pentane) to obtain **88** as a yellow solid (405 mg, 1.2 mmol, 13%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.6 Hz, 1H), 8.13 – 8.05 (m, 2H), 7.96 (s, 1H), 7.56 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.42 – 7.33 (m, 2H), 7.25 – 7.12 (m, 2H), 7.08 – 7.00 (m, 2H),

2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.02, 158.40, 156.17, 143.71, 141.92, 136.01, 130.55, 130.16, 128.15, 125.77, 124.36, 122.96, 122.38, 121.24, 121.20, 119.58, 117.12, 17.83.

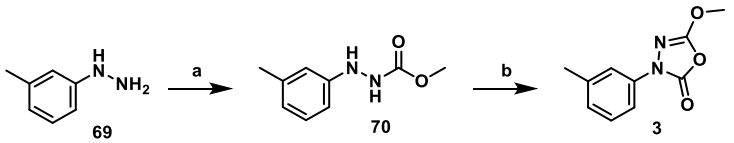


***N*-(4-Amino-2-methylphenyl)-3-phenoxybenzamide (89). 88** (405 mg, 1.2 mmol) was dissolved in MeOH and DCM (14 mL, 1:1), and was reacted with Pd/C catalyst (10 wt%, 70 mg, 66 µmol) following General Procedure F. The resulting crude material was purified by column chromatography (20% → 30% EtOAc in pentane) to obtain title compound **89** (350 mg, 1.1 mmol, 92%) as a brown solid. ^{1}H NMR (300 MHz, MeOD) δ 7.72 – 7.64 (m, 1H), 7.57 (dd, *J* = 2.5, 1.7 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.42 – 7.30 (m, 2H), 7.21 – 7.08 (m, 2H), 7.08 – 6.95 (m, 3H), 6.65 (d, *J* = 2.5 Hz, 1H), 6.58 (dd, *J* = 8.3, 2.6 Hz, 1H), 2.16 (s, 3H). ^{13}C NMR (75 MHz, MeOD) δ 168.67, 159.17, 158.12, 147.62, 137.74, 136.65, 131.12, 131.06, 128.87, 127.42, 124.92, 123.12, 122.75, 120.25, 118.73, 118.27, 114.50, 18.24.

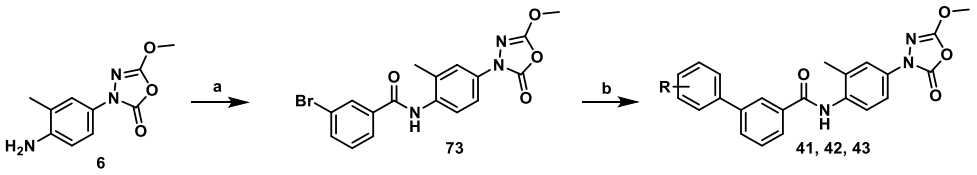
Supplementary information



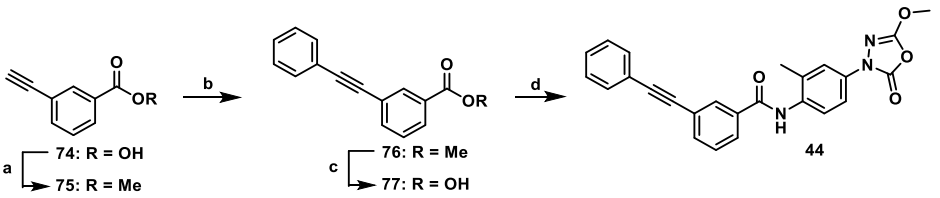
Scheme S3.1 | Synthesis of compound **2**. Reagents and conditions: a) benzyl chloroformate, pyridine, DCM, 0°C to RT, quant.



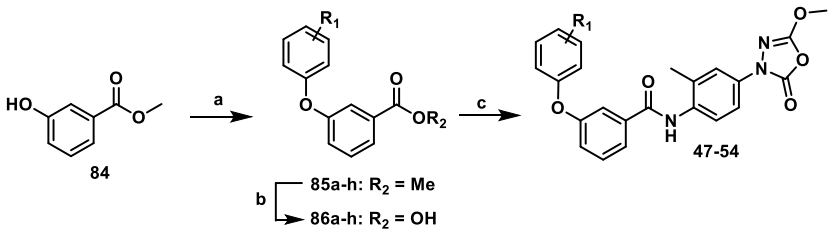
Scheme S3.2 | Synthesis of compound **3**. Reagents and conditions: a) methyl chloroformate, pyridine, DCM, 0°C to RT, 60%; b) $COCl_2$, pyridine, DCM, 0°C, 58%.



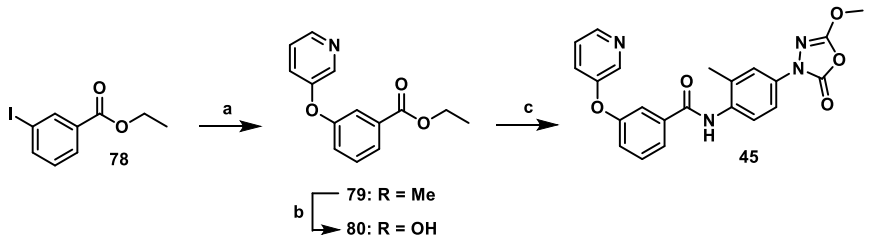
Scheme S3.3 | Synthesis of compounds **41-43**. Reagents and conditions: a) 2-bromobenzoic acid, PyAOP, DIPEA, ACN, RT, 43%; b) $RPhB(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, H_2O/dioxane, 45°C, 26% – 64%.



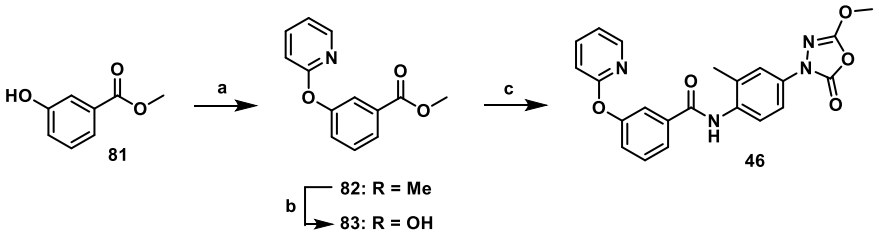
Scheme S3.4 | Synthesis of compound **44**. Reagents and conditions: a) MeI, K_2CO_3, DMF, 0°C to RT, 96%; b) iodobenzene, CuI, PPh_3, $Pd(PPh_3)_2Cl_2$, Et_3N, 40°C, 75%; c) KOH, MeOH/THF, RT, 72%; d) **6**, PyAOP, DIPEA, ACN, RT, 71%.



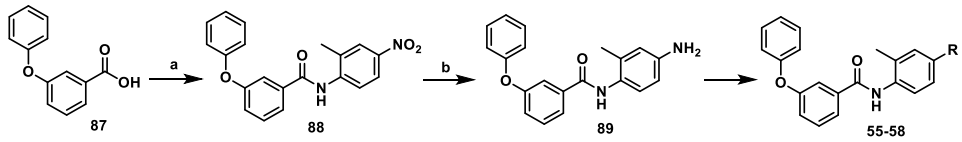
Scheme S3.5 | Synthesis of building blocks **86a-h**. Reagents and conditions: a) $RB(OH)_2$, $Cu(OAc)_2$, Et_3N, air, DCM, RT, 25% – 34%; b) KOH, MeOH, RT or 55°C, 83 – 94%.



Scheme S3.6 | Synthesis of compound **45**. Reagents and conditions: a) pyridin-3-ol, picolinic acid, K_3PO_4, CuI, DMSO, 110°C, 36%; b) 6M HCl (aq.), 110°C, 89%.



Scheme S3.7 | Synthesis of compound **46**. Reagents and conditions: a) 2-bromopyridine, picolinic acid, K_3PO_4, CuI, DMSO, 110°C, 28%; b) 6M HCl (aq.), 110°C, 89%.



Scheme S3.8 | Synthesis of compounds **55-58**. Reagents and conditions: a) *i*. $SOCl_2$, *ii*. 2-methyl-nitroaniline, DCM, RT, 13%; b) H_2, Pd/C, MeOH/DCM, RT, 92%.

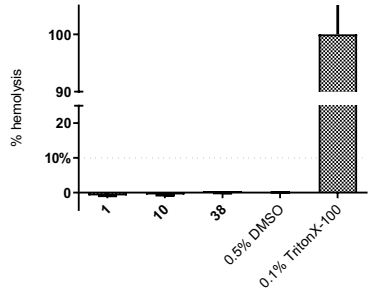


Figure S3.1 | Normalized hemolytic activity of compounds **1**, **10** and **38** at 50 µM after 20 h incubation time.

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