New chemical tools to illuminate N-acylphosphatidylethanolamine biosynthesis

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Identification of triazole ureas as potent PLA2G4E inhibitors

Phospholipase A2ε (PLA2G4E) is a serine hydrolase that belongs to the Group IV cytosolic phosholipases. This subfamily consists of six intracellular phospholipases (PLA2G4A–F or cPLA2α–ζ) with low sequence homology that metabolize phospholipids.[1–3] PLA2G4A has an important role in the production of arachidonic acid (AA) and proinflammatory eicosanoids[4–6], but much less is known about the physiological function of PLA2G4E and the other members. In 2016, Cravatt and coworkers discovered that PLA2G4E exerted high *N*-acyltransferase activity and produced *N*-acylphosphatidylethanolamines (NAPEs) from phosphatidylcholine (PC) and phosphatidylethanolamine (PE) in a calcium-dependent manner.[7]

Two PLA2G4E isoforms, consisting of either 834 or 868 amino acids (97 or 100 kDa, respectively), have been detected in the human proteome.[8] They differ in their N-terminal sequence, but it is unknown whether they have different biological roles. PLA2G4E is mainly expressed in neurons, skeletal muscle, heart and testes.[7,9,10] The enzyme has a central catalytic lipase domain, preceded by a C2 domain, which functions as a Ca^{2+}-dependent lipid binding site.[1–3] While the translocation of PLA2G4A to intracellular membranes upon a Ca^{2+} stimulus is needed for its activity[11–13], PLA2G4E may be directly activated by Ca^{2+}

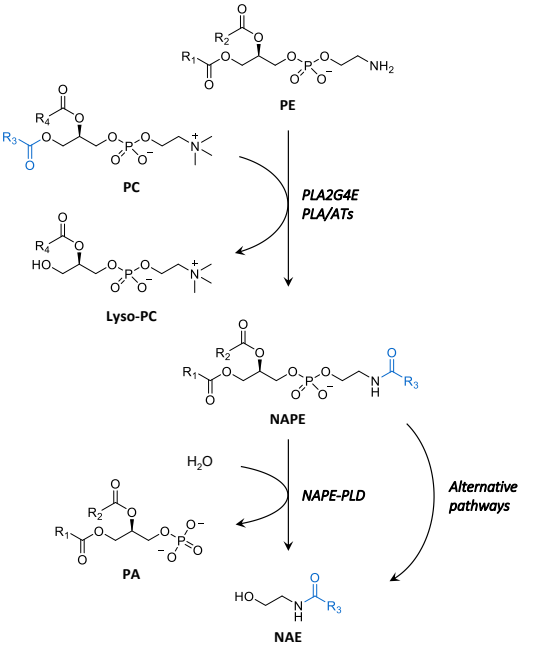


Figure 2.1. Biosynthetic pathways of NAPEs and NAEs. The *sn*-1 *O*-acyl chain of PC (blue) is transferred by PLA2G4E or PLA/ATs to PE to form NAPE. NAEs are synthesized either through direct hydrolysis by NAPE-PLD releasing phosphatidic acid (PA) or through alternative multistep pathways. R_1, R_2 and R_3 indicate saturated, mono- or poly-unsaturated fatty acid. For anandamide synthesis R_3 = arachidonyl.

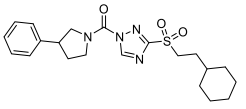
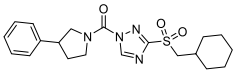
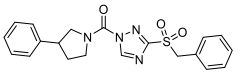
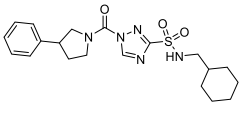
ions, independent of its translocation.[7] Instead, PLA2G4E has a KKKRLK polybasic domain at the C-terminus, that interacts with anionic lipids and is important for the subcellular localization of the enzyme to tubules and vesicles of the endocytic machinery.[8,14,15] Both the C2 and polybasic domain are necessary for catalytic activity.[14,15] PLA2G4E is an atypical serine hydrolase, because it uses a Ser-Asp catalytic dyad opposed to the canonical triad and most likely does not adopt a classical α/β-hydrolase fold.[1,2,16] It accepts various PCs as acyl donor, and has a preference for cleavage of the ester at the *sn*-1 position by the nucleophilic serine.[7] The acyl chain is subsequently transferred to the free amine of PE, thereby producing NAPEs and lyso-PC (Figure 2.1). However, a more detailed understanding of its *N*-acyltransferase activity mechanism is currently lacking.

NAPEs are an understudied class of bioactive lipids. They are important modulators of membrane dynamics via various mechanisms, including stabilization of membranes and lipid raft structures[17–19], induction of membrane fusion[20] and interaction with intracellular proteins.[21] Furthermore, they might regulate feeding by inhibiting food intake[22,23] and have anti-inflammatory activities.[24] Following ischemia, cellular NAPE levels are highly elevated, an effect most studied in neuronal tissue, which is suggested to represent a cytoprotective mechanism.[25–31] NAPEs also serve as substrates for NAPE-specific phospholipase D (NAPE-PLD) that generates *N*-acylethanolamines (NAEs) (Figure 2.1).[32–38] NAEs are a diverse family of signaling lipids, including the endocannabinoid anandamide (*N*-arachidonoyl-ethanolamine, AEA).[39,40] Anandamide exerts its physiological functions through activation of the cannabinoid receptors (CB) 1 and 2 and is involved in inflammation, neurotransmission, appetite and mood.[41–43]

PLA2G4E is not the only enzyme that produces NAPEs. Phospholipases $A_{1/2}$/acyltransferases (PLAAT) 1–5 synthesize NAPEs in a calcium-independent manner.[44,45] Recently, pan-PLAAT inhibitors have been developed and were shown to reduce NAE levels in cells overexpressing PLAAT 2 or 5.[46] However, Ca^{2+}-dependent *N*-acyltransferase activity is presumed to be the rate-limiting step in the on-demand biosynthesis of anandamide in the brain.[47–50] Whether PLA2G4E is the main enzyme driving NAPE and anandamide production in neuronal cells and the brain has not been established. PLA2G4E inhibitors would be valuable chemical tools to answer this question and to investigate the (patho)physiological role of PLA2G4E and NAPEs, but are currently lacking.

Recently, a competitive activity-based protein profiling (cABPP) assay was developed using membrane preparations of PLA2G4E-overexpressing HEK293T cells to screen a focused lipase inhibitor library containing 208 compounds.[51] Compounds **1**–**4** were identified as inhibitors with apparent half-maximal inhibitory concentration (IC_{50}) values of around 1 μM (Table 2.1). In this chapter, the synthesis and testing of novel analogues based on hits **1**–**4** is described.

Table 2.1. Hits from in-house library screening. Structure, activity and physicochemical properties of the four most potent molecules on PLA2G4E identified with gel-based cABPP (N ≥ 2). [a]Molecular weight (MW) was calculated using ChemDraw Professional 16.0; [b]Partition coefficient (clogP) was calculated using DataWarrior 5.0.0; [c]HAC = number of heavy atoms; [d]Lipophilic efficiency LipE = pIC_{50} – clogP; [e]Ligand efficiency LE = 1.4pIC_{50}/HAC.

ID	Structure	pIC_{50} ± SEM	MW (Da)[a]	clogP[b]	HAC[c]	LipE[d]	LE[e]
1		6.00 ± 0.02	417	3.78	29	2.22	0.29
2		5.93 ± 0.03	403	3.33	28	2.60	0.30
3		5.66 ± 0.04	396	2.97	28	2.69	0.28
4		5.56 ± 0.03	418	3.36	29	2.20	0.27

Results

Structure activity relationship analysis of the screening hits

Hits **1**–**4** belong to the class of triazole ureas, which is a commonly used scaffold in serine hydrolase inhibitor design.[52–55] **1**–**4** have a 3-phenylpyrrolidine urea, which forms a stable carbamate adduct with the enzyme, and a lipophilic triazole sulfone that functions as a leaving group (Figure 2.2). Lipophilicity is a key parameter for binding affinity in many protein ligand interactions. Here, only a slight drop in activity was observed when the cyclohexyl group in **2** (clogP = 3.33, DataWarrior 5.0.0) was replaced by a phenyl in **3** (clogP = 2.97). This may suggest that new (electronic) interactions with the phenyl ring may compensate for the loss in lipophilicity. Sulfone **1** was more active than sulfonamide **4** (pIC_{50} = 6.0 and 5.6, respectively), which might be attributed to more favorable lipophilic

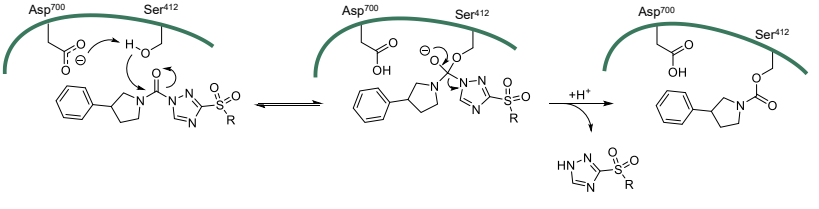
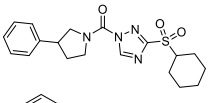
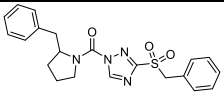
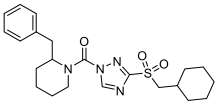
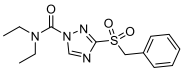


Figure 2.2. Schematic mechanism of enzyme inactivation. The nucleophilic serine of PLA2G4E, activated by Asp^{700}, attacks the carbonyl of the inhibitor (indicated as general structure of the hit molecules **1**–**4**). The triazole leaving group is expelled, leading to irreversible carbamoylation of Ser^{412}, inactivating the catalytic activity of the enzyme.

interactions of **1** or to increased reactivity of the warhead due to the stronger electron-withdrawing effect of the sulfone. No substantial difference in activity was observed between a one or two-carbon spacer between the sulfone and cyclohexane (**1**, **2**). Of interest, four close analogs of the hits (**5**–**8**) were also previously tested in the focused screen, but they did not show any significant inhibition of PLA2G4E labeling (<50% at 10 μM, Table 2.2). Compound **5** lacks the alkyl spacer between the cyclohexyl group and the sulfone, whereas compound **6**, **7** and **8** have a 2-substituted piperidine or pyrrolidine or a diethylamine substituent, respectively. This indicated that the 3-phenylpyrrolidine and the cyclohexyl group in hits **1**–**4** access specific subpockets of the active site and that the activity of the hits is not only due to reactivity of the warhead.

Table 2.2. Inactive compounds identified from in-house library screening. Structure and activity of four compounds structurally related to hits **1**–**4** that showed <50% inhibition of PLA2G4E at 10 μM, as determined with gel-based cABPP (N = 2).

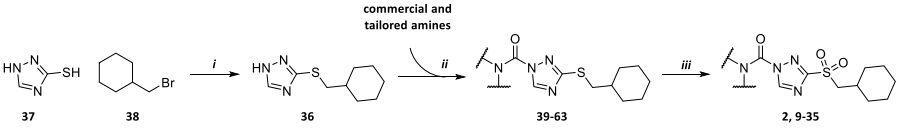
ID	Structure	Inhibition at 10 μM (%)	ID	Structure	Inhibition at 10 μM (%)
5		8	7		37
6		26	8		5

Synthesis of PLA2G4E inhibitors 9–35

The design of inhibitors **9**–**35** was based on the structure of hit **2**, because this compound had higher lipophilic efficiency (LipE) and ligand efficiency (LE) than hit **1** (Table 2.1). Different amine substituents on the triazole urea scaffold were introduced to explore the size and properties of the binding pocket. To this end, building block **36** was synthesized at large scale via alkylation of 1,2,4-triazole-3-thiol (**37**) with (cyclohexylmethyl)bromide (**38**) (88%, Scheme 2.1). A two-step reaction sequence was used to obtain the final compounds. First, the amines were coupled to building block **36** with triphosgene to afford urea compounds **39**–**63** (Scheme 2.1), which were then oxidized to the final inhibitors (**2**, **9**–**35**). Of note, for the synthesis of inhibitors **20**, **27** and **31** the sulfide in building block **36** was oxidized before the urea formation (Supplementary Scheme S2.1).

The amine substituents used in inhibitors **2**, **9**, **10** and **14**–**19** were commercially available, whereas those for compounds **11** and **13** were synthesized as previously described[56] (Table 2.3). To synthesize compound **12**, phenethylamine (**64**, Supplementary Scheme S2.2) was methylated via formation of a methyl carbamate intermediate (**65**) using methyl chloroformate (84%), followed by a reduction using $LiAlH_4$ to compound **66** (62%). The benzylpiperidine derivatives in compounds **21**–**28**, **30** and **33**–**35** were synthesized via Suzuki-Miyaura coupling (Supplementary Scheme S2.3).[57] To this end, 4-methylene-

piperidine (**67**) was hydroborated with 9-BBN, immediately followed by Pd(dppf)Cl_2-catalyzed cross-coupling to desired organohalide **68**–**78**, yielding compounds **79**–**89** (44%–quant.). Subsequent Boc deprotection afforded amines **90**–**100** (71%–quant.). Benzylation of piperazine under reflux conditions efficiently yielded benzylpiperazine **101** (85%). 4-(4-Chlorobenzyl)piperidine (**102**) was synthesized by catalytic hydrogenation of 4-(4-chlorobenzyl)pyridine over PtO_2 (87%). Suzuki coupling of 4-(4-chlorobenzyl)pyridine to phenylboronic acid provided compound **103** (58%), which was hydrogenated to afford 4-(4-phenylbenzyl)piperidine **104**. The protected building block for inhibitors **31** and **32** was synthesized as described earlier[58], which then was deprotected to yield the free amine (**105**).



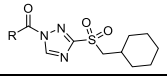
Scheme 2.1. General synthetic route for PLA2G4E inhibitors. Reagents and conditions: *i*) K_2CO_3, DMF, 6 h RT; *ii*) 1. Appropriate amine, triphosgene, DIPEA or Et_3N, THF, 3 h 0°C → RT, then 2. **36**, K_2CO_3, DMF, o/n RT; *iii*) AcOOH, DCM, 6 h 0°C → RT.

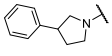
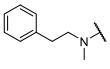
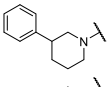
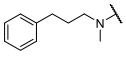
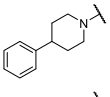
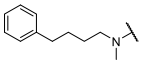
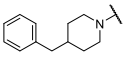
Hit confirmation and optimization of triazole urea derivatives as PLA2G4E inhibitors

First, the activity of resynthesized compound **2** was tested using a competitive, gel-based ABPP assay. This assay relies on fluorophosphonate-tetramethylrhodamine (FP-TAMRA) as a broad-spectrum activity-based probe (ABP). The fluorophosphonate moiety covalently binds to the catalytic serine of PLA2G4E and the TAMRA functions as a fluorescent reporter to visualize the enzyme activity in a biological setting.[51,59] Briefly, lysates of human embryonic kidney (HEK293T) cells that transiently expressed recombinant human PLA2G4E were treated with inhibitor or vehicle (DMSO) for 30 min at room temperature, followed by a 5-min incubation with FP-TAMRA to label residual PLA2G4E activity. Subsequently, protein resolution on molecular weight by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) and in-gel fluorescence scanning allowed quantitation of enzyme inhibition by the compounds. The activity of hit **2** was confirmed, albeit slightly lower than the compound from the screening deck (pIC_{50} = 5.70 ± 0.03, Table 2.3). To study the influence of the spacer between the urea and the phenyl on the inhibitory activity, compounds **9–13** were tested (Table 2.3). Compound **9**, in which the phenyl ring was directly coupled to the urea, was inactive, but by introducing various alkyl linkers with increasing length (**10–13**) the inhibitory activity was regained and up to 10-fold improved compared to the original hit. Compounds with propyl (**12**) and butyl (**13**) linkers showed similar activity, indicating that there was some flexibility in the binding pocket. In line with the results obtained with compound **9**, inhibitors with small fused bicyclic amines indoline (**14**) and isoindoline (**15**) displayed reduced activity. Tetrahydroquinoline **16**, however, was

10-fold more potent than hit (**2**). Compound **17** with a 3-phenylpiperidine was not active, but compound **18** with a 4-phenylpiperidine was tolerated and inhibitor **19** with a 4-benzylpiperidine moiety was the most potent compound identified so far (pIC_{50} = 6.9). These findings indicated that this subpocket of the PLA2G4E active site can accommodate rather large substituents.

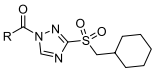
Table 2.3. Structure-activity relationships of PLA2G4E inhibitors 9–19. Potency determined with gel-based cABPP on PLA2G4E-overexpressing HEK293T membranes (N ≥ 2).

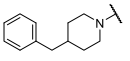
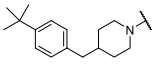
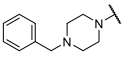
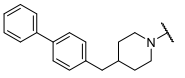
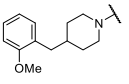
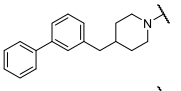
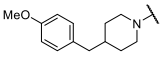
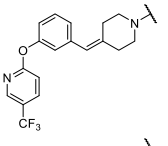
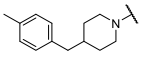
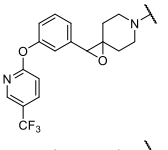
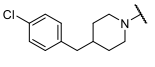
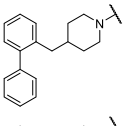
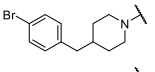
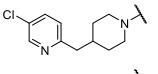
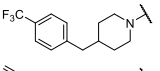
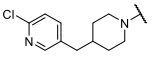
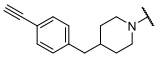


ID	R	pIC_{50} ± SEM	ID	R	pIC_{50} ± SEM
2		5.70 ± 0.03	**14**		< 5.0
9		< 5.0	**15**		< 5.0
10		6.28 ± 0.17	**16**		6.79 ± 0.15
11		< 5.0	**17**		< 5.0
12		6.70 ± 0.15	**18**		6.58 ± 0.03
13		6.73 ± 0.14	**19**		6.86 ± 0.05

Next, 13 derivatives of the 4-benzylpiperidine of compound **19** were synthesized and their potency on PLA2G4E was determined (Table 2.4). A synthetically more convenient benzylpiperazine scaffold was not active (**20**). Compound **21** with an *ortho*-methoxy had a slightly decreased potency, whereas compound **22** with a *para*-methoxy showed increased potency. This suggested that steric effects, rather than electronic, were important. Accordingly, compounds with other small *para*-substituents, both electron donating (**23**) and electron withdrawing (**24**–**26**), showed similarly improved activity (pIC_{50}'s 7.5–8.0). Of note, compound **27** with an acetylene substituent showed similar potency, but inhibitors **28** and **29** with a larger *tert*-butyl or phenyl substituent, respectively, had a reduced activity. Variants with a large substituent on the *meta* (**30**–**32**) and *ortho* (**33**) position were also less active, but they did not completely lose activity. Compound **24** with a 4-chloro substituent was the most potent compound identified in this study with pIC_{50} = 8.01 ± 0.02 (Figure 2.3, Table 2.5). Introducing an additional nitrogen in the aromatic ring decreased potency (**34**, **35**).

Table 2.4. Structure-activity relationships of PLA2G4E inhibitors 20–35. Potency determined with gel-based cABPP on PLA2G4E-overexpressing HEK293T membranes (N ≥ 2).



ID	R	pIC_{50} ± SEM	ID	R	pIC_{50} ± SEM
19		6.86 ± 0.05	28		6.83 ± 0.06
20		< 5.0	29		6.60 ± 0.06
21		6.33 ± 0.08	30		6.41 ± 0.12
22		7.50 ± 0.11	31		7.30 ± 0.09
23		7.46 ± 0.17	32		6.58 ± 0.03
24 (WEN091)		8.01 ± 0.02	33		6.86 ± 0.05
25		7.00 ± 0.07	34		6.62 ± 0.19
26		7.53 ± 0.39	35		7.42 ± 0.10
27		7.36 ± 0.03			

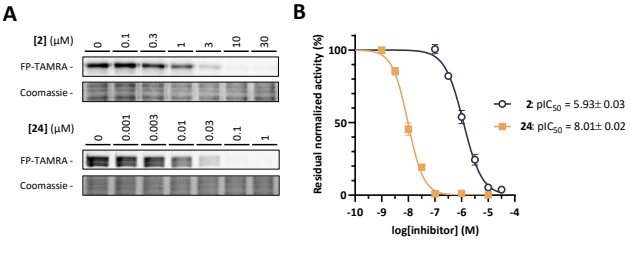


Figure 2.3. Activity of compounds 2 and 24 on PLA2G4E. A) Representative gel excerpts of cABPP experiments with **2** and **24** on PLA2G4E overexpression lysates. B) Corresponding inhibition curves and pIC_{50} values. Data presented as mean ± SEM (N ≥ 2).

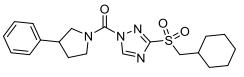
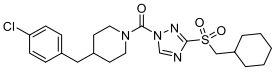
Discussion and conclusion

The PLA2G4 proteins have previously been exploited for the discovery and development of molecular therapeutics. Several classes of *in vivo* active inhibitors have been reported.[60–66] For example, PLA2G4A inhibitor WAY-196025 was able to fully protect mice from developing clinical symptoms of multiple sclerosis in the experimental autoimmune encephalomyelitis (EAE) model.[67] Ecopladib, ZPL-5212372 and giripladib have even advanced into phase I and phase II clinical trials for the treatment of atopic dermatitis or rheumatoid arthritis.[68,69] To date, no potent inhibitors for PLA2G4E have been described. These inhibitors are required to further our understanding of the biological role of PLA2G4E and may help the development of drugs for the treatment of neurodegeneration, metabolic syndrome or inflammatory pain.[41,70–73]

Here, the identification and ABPP-guided optimization of the first potent inhibitors of PLA2G4E is reported. Compound **24** ((4-(4-chlorobenzyl)piperidin-1-yl)(3-((cyclohexyl-methyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)methanone, **WEN091**) is a covalent, irreversible potent inhibitor of PLA2G4E with an IC_{50} of 10 nM, which is 100-fold more potent than the original hit (**2**). Of note, the IC_{50} of an irreversible inhibitor is dependent on its incubation time with the enzyme. The values reported in this thesis, therefore, are apparent IC_{50} values that only apply to the assay conditions described here. These values can only be reliably compared between compounds tested under identical conditions. Both LipE and LE of **24** were increased compared to **2** (Table 2.5) and with MW < 500 Da, HBA < 10, HBD < 5, RB < 10, clogP < 5 and tPSA < 90 $Å^2$, **24** has favorable physicochemical properties for a lead compound in the development of a CNS-active enzyme inhibitor, according to Lipinski's and Veber's rules for druglikeness.[74,75]

Triazole urea-based inhibitors have been previously applied as valuable tool compounds to study the biology of serine hydrolases.[54,76] ABPP assays, substrate-based assays and lipid analysis platforms have been set up to measure their activity and selectivity in complex proteomes.[77–79] In addition, they have shown efficacy in both cellular and *in vivo* systems, demonstrating good brain penetration and low toxicity.[52–54,80] The identification of triazole ureas as inhibitors of PLA2G4E therefore holds promise for the development of valuable tool compounds with therapeutic potential. The activity of compound **24** in biological systems and its selectivity over other PLA2G4 family members, ECS-related enzymes and other serine hydrolases will be described in the next chapter.

Table 2.5. Physicochemical properties of hit 2 and most potent molecule 24. Potency on PLA2G4E determined using gel-based cABPP (N ≥ 2) [a]Molecular weight (MW) and topological polar surface area (tPSA) calculated using ChemDraw Professional 16.0; [b]Partition coefficient (clogP) using DataWarrior 5.0.0; [c]HAC = number of heavy atoms; [d]HBA = number of hydrogen bond acceptors; [e]HBD = number of hydrogen bond donors; [f]RB = number of rotatable bonds; [g]Lipophilic efficiency LipE = pIC_{50} – clogP; [h]Ligand efficiency LE = 1.4pIC_{50}/HAC.

ID	Structure	pIC_{50} ± SEM	MW (Da)[a]	tPSA (Å^2)[a]	clogP[b]	HAC[c]	HBA[d]	HBD[e]	RB[f]	LipE[g]	LE[h]
2		5.93 ± 0.03	403	82.4	3.33	28	7	0	5	2.60	0.30
24		8.01 ± 0.02	465	82.4	4.24	31	7	0	6	3.77	0.36

Acknowledgements

Paul ten Bras is kindly acknowledged for performing organic synthesis and cABPP, Francisca Schutter and Juan Zhou for cABPP on the hits, Hans van den Elst for HRMS analysis. Hans den Dulk and Tom van der Wel are acknowledged for plasmid cloning and purification.

Experimental procedures

General remarks

All chemicals and reagents for biochemical experiments were purchased from Thermo Fisher Scientific or Bio-Rad, unless noted otherwise. Inhibitors were synthesized in-house as described below.

Plasmids

The full-length wild-type human PLA2G4E cDNA was obtained from GenScript Biotech and cloned into a pcDNA3.1(+) expression vector in-frame with a C-terminal FLAG tag. Plasmids were isolated from transformed *Escherichia coli* XL-10 using a Qiagen Plasmid Midi kit and stored at 4°C in TE buffer (10 mM Tris, 0.1 mM EDTA, pH 8.0). The sequence was determined (Macrogen) and verified using CLC Main Workbench.

Cell culture

HEK293T (human embryonic kidney, ATCC) cells were cultured in DMEM (Sigma-Aldrich, D6546) with additional heat-inactivated new-born calf serum (10% (v/v), Avantor Seradigm), L-Ala-L-Gln (2 mM, Sigma-Aldrich), penicillin and streptomycin (both 200 µg/mL, Duchefa Biochemie) at 37°C, 7% CO_2. Medium was refreshed every 2–3 days and cells were passaged twice a week at 70–80% confluence by aspirating the medium, thorough pipetting in fresh medium and seeding to appropiate density. Cell cultures were regularly tested for mycoplasma and discarded after 2–3 months.

Transient transfection

One day prior to transfection, 10^7 HEK293T cells were seeded to a 15 cm dish. Upon transfection, medium was aspirated and replaced by 13 mL fresh medium. Plasmid DNA (20 µg per 15 cm dish) and PEI (60 µg per 15 cm dish) were separately dissolved in 1 mL DMEM without serum, mixed, incubated for 15 min and added dropwise to the cells. 24 h p.t. medium was replaced by 25 mL fresh medium. 72 h p.t. medium was aspirated and the cells were washed with RT Dulbecco's PBS, harvested in PBS and centrifuged (3000 × *g*, 15 min, RT). Cell pellets were flash-frozen in liquid N_2 and stored at −80°C until use.

HEK293T membrane preparation

HEK293T cell pellets were thawed on ice and homogenized in 2 mL ice-cold lysis buffer (50 mM Tris-HCl, 2 mM DTT, 3 mM $CaCl_2$, 1 mM $MgCl_2$, 5 U/mL Benzonase® (Santa Cruz Biotechnology, Inc.), pH 8.0) per 15 cm cell culture dish using a Sonics® Vibra-Cell VCX 130 probe sonicator equipped with a 2 mm microtip (3 × 10 s on/10 s off, 20% amplitude). After incubation on ice for 30 min, the insoluble ("membrane") fraction was separated from the soluble ("cytosol") fraction by ultracentrifugation (10^5 × *g*, 35 min, 4°C, Beckman-Coulter ultracentrifuge, Ti70.1 rotor). The pellet was resuspended in 1 mL ice-cold storage buffer (50 mM Tris-HCl, 2 mM DTT, pH 8.0) per 15 cm plate and homogenized by passing through an insulin needle. After determination of the protein concentration using a Quick Start™ Bradford Protein Assay (Bio-Rad), the samples were diluted to 1.0 mg/mL in ice-cold storage buffer, aliquoted to single-use volumes, flash-frozen in liquid N_2 and stored at −80°C until further use.

Activity-based protein profiling

Membrane preparations were thawed on ice. 19.5 µL lysate was incubated with 0.5 µL inhibitor in DMSO (30 min, RT), followed by 0.5 µL FP-TAMRA in DMSO (50 nM, 5 min, RT, final DMSO concentration 5%). The reactions were quenched by addition of 7 µL 4× Laemmli buffer (240 mM Tris, 8% (w/v) SDS, 40% (v/v) glycerol, 5% (v/v) β-mercaptoethanol (Sigma-Aldrich), 0.04% bromophenol

blue). 10 µL sample was resolved on 8% acrylamide SDS-PAGE gel (180 V, 70 min) and afterwards imaged on a Bio-Rad Chemidoc MP using Cy3/TAMRA settings (ex. 532/12 nm, em. 602/50 nm). Coomassie Brilliant Blue R250 staining was used for total protein loading correction. Images were analyzed using Bio-Rad Image Lab 6. IC_{50} calculations were performed in GraphPad Prism 8.

Organic synthesis

General remarks

All reagents were purchased from Sigma-Aldrich, Fluorochem, Fisher Scientific, Combi-Blocks or Alfa Aesar and used without further purification. Solvents were purchased from Sigma-Aldrich, VWR Chemicals or Honeywell Riedel-de Haën, common salts from Sigma-Aldrich or Chem-Lab and used without further purification. Moisture-sensitive reactions were carried out in solvents dried over heat-activated molecular sieves (4 Å, Sigma-Aldrich), using flame-dried glassware under an atmosphere of N_2. TLC analysis was performed on Merck silica gel 60 F_{254} aluminum TLC plates, on which compounds were visualized under 254 or 366 nm UV light and using $KMnO_4$ (30 mM $KMnO_4$, 180 mM K_2CO_3 in water) or ninhydrin (7.5 mM ninhydrin, 10% (v/v) AcOH in EtOH) stain. Flash column chromatography was performed using SiO_2 (Macherey-Nagel, 60 M) as stationary phase.

NMR spectra were recorded on a Bruker AV-400 MHz or AV-500 MHz spectrometer at 400 MHz (^{1}H) and 101 MHz (^{13}C) or 500 MHz (^{1}H) and 126 MHz (^{13}C) respectively, using $CDCl_3$ or MeOD (Eurisotop) as solvent. Chemical shifts are reported in ppm with TMS (^{1}H $CHCl_3$, δ 0.00) or solvent resonance (^{1}H MeOD, δ 3.31; ^{13}C MeOD, δ 49.00; ^{13}C $CHCl_3$, δ 77.16) as internal standard. Data are reported as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, p = pentet, dd = doublet of doublets, td = triplet of doublets, qd = quartet of doublets, dt = doublet of triplets, bs = broad singlet (^{1}H), br = broad (^{13}C), m = multiplet), coupling constants *J* (Hz) and integration. HPLC-MS analysis was performed on a Finnigan Surveyor HPLC system equipped with a Macherey-Nagel NUCLEODUR C_{18} Gravity, 5 µm, 50 × 4.6 mm column followed by a Thermo Scientific LTQ Orbitrap XL spectrometer, using H_2O/CH_3CN + 1% TFA as mobile phase. All compounds used for biological experiments were ≥ 95% pure based on LC-MS UV absorbance.

General procedure A

Triazole urea thioether or sulfoxide (1 eq) was dissolved in dry DCM (40–50 mL/mmol) and cooled on ice. Peracetic acid (5–10 eq, 36–40% solution in AcOH) was added dropwise, after which the mixture was allowed to warm to RT and stirred for at least 6 h. When full conversion was confirmed using TLC analysis, the mixture was washed once with water, dried over $MgSO_4$, filtrated and concentrated *in vacuo*.

General procedure B

N-Boc 4-methylenepiperidine (1 eq) was dissolved in dry THF (7 mL/mmol) which had been degassed by three cycles of reduced pressure and N_2 purging. The solution was cooled on ice before 9-BBN (1.5 eq, 0.5 M in THF) was added dropwise. The ice bath was removed and the reaction mixture was stirred for 6 h. In the meantime, desired halobenzene (1.5 eq) and K_2CO_3 (1.5 eq) were added to a three-neck flask equipped with a reflux cooler which was then flushed with N_2. DMF (7 mL/mmol) and water (0.7 mL/mmol) were degassed, added to the flask and purged with N_2. When full consumption of *N*-Boc 4-methylenepiperidine was confirmed using TLC analysis, the reaction mixture was added to the three-neck flask and purging was continued. $Pd(dppf)Cl_2$ (1 mol%) was added and the mixture was heated to 60°C and stirred overnight. The mixture was cooled to RT, diluted with Et_2O and washed with 1 M aq. NaOH. The pH of the aqueous layer was set to 7 with 12 M HCl, after which the aqueous

layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated *in vacuo*.

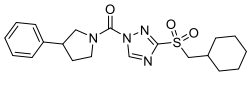
General procedure C

Desired amine intermediate (1 eq) was dissolved in dry THF (10–15 mL/mmol of amine intermediate) and added dropwise (< 0.5 mL/min) to an ice-cold solution of triphosgene (3 eq) and Et_3N or DIPEA (3 eq) in dry THF (10–15 mL/mmol of amine intermediate). The cloudy mixture was stirred on ice for 1 h, followed by 2 h at RT. When full conversion was confirmed using TLC analysis, the mixture was diluted with EtOAc and washed with 1 M aqueous HCl and brine, dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Water was removed by co-evaporation with toluene, after which the oily residue was dissolved in dry DMF (5–10 mL/mmol of amine intermediate). Desired triazole or pyrazole intermediate (1 eq) and K_2CO_3 (3 eq) were added and the mixture was stirred overnight. The mixture was diluted with EtOAc and washed with water and brine, dried over $MgSO_4$, filtrated and concentrated *in vacuo*.

General procedure D

Triazole urea thioether (1 eq) was dissolved in dry DCM (5 mL) and cooled on ice. Peracetic acid (1–3 eq, 36–40% solution in AcOH) was added dropwise, after which the mixture was allowed to warm to RT and stirred for at least 6 h. When full conversion was confirmed using TLC analysis, the mixture was washed once with water, dried over $MgSO_4$, filtrated and concentrated *in vacuo*.

(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(3-phenylpyrrolidin-1-yl)methanone (2)



39 (51 mg, 0.138 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 30% EtOAc in pentane) afforded the title compound (55 mg, 0.137 mmol, quant.). HPLC showed presence of a single product (rt = 8.15 min). NMR showed two products which are probably conformationally restricted isomers (ratio ~1:1), as reported before for similar compounds (data not published).

Conformer 1:

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.41 – 7.32 (m, 2H), 7.32 – 7.21 (m, 3H), 4.42 (dd, *J* = 11.8, 7.6 Hz, 1H), 4.24 (ddd, *J* = 11.3, 8.1, 2.8 Hz, 1H), 4.13 – 4.04 (m, 1H), 3.92 (dd, *J* = 11.8, 9.8 Hz, 1H), 3.56 – 3.43 (m, 1H), 3.32 (d, *J* = 6.4 Hz, 2H), 2.50 – 2.33 (m, 1H), 2.23 – 2.10 (m, 1H), 2.12 – 1.97 (m, 1H), 1.96 – 1.82 (m, 2H), 1.75 – 1.51 (m, 2H), 1.38 – 1.00 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.73, 147.66, 146.11, 139.70, 128.94, 127.49, 127.17, 60.68, 55.86, 50.00, 45.04, 33.73, 32.98, 32.53, 25.71, 25.66.

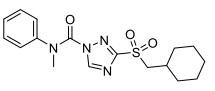
Conformer 2:

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.41 – 7.32 (m, 2H), 7.32 – 7.21 (m, 3H), 4.17 (dd, *J* = 12.0, 7.6 Hz, 1H), 3.99 (ddd, *J* = 11.3, 8.3, 2.6 Hz, 1H), 3.79 (ddd, *J* = 12.1, 10.2, 6.8 Hz, 1H), 3.71 (dd, *J* = 12.0, 9.6 Hz, 1H), 3.56 – 3.43 (m, 1H), 3.28 (d, *J* = 6.4 Hz, 2H), 2.50 – 2.33 (m, 1H), 2.23 – 2.10 (m, 1H), 2.12 – 1.97 (m, 1H), 1.96 – 1.82 (m, 2H), 1.75 – 1.51 (m, 2H), 1.38 – 1.00 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.70, 147.59, 146.11, 139.34, 128.92, 127.37, 127.02, 60.68, 54.85, 49.07, 42.06, 32.93, 32.50, 31.11, 25.69, 25.66.

HRMS: $[M+H]^+$ calculated for $C_{20}H_{26}N_4O_3S+H^+$ 403.17984, found 403.17950.

3-((Cyclohexylmethyl)sulfonyl)-*N*-methyl-*N*-phenyl-1*H*-1,2,4-triazole-1-carboxamide (9)



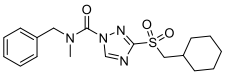
107 (24 mg, 0.069 mmol) was oxidized according General procedure A. Flash column chromatography (25 → 35% EtOAc in pentane) afforded the title compound (yield not determined).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.43 – 7.29 (m, 3H), 7.19 – 7.12 (m, 2H), 3.56 (s, 3H), 2.97 – 2.93 (m, 2H), 2.02 – 1.87 (m, 1H), 1.83 – 1.75 (m, 2H), 1.72 – 1.59 (m, 4H), 1.36 – 1.08 (m, 2H), 0.99 (qd, *J* = 11.6, 3.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.38, 147.65, 142.43, 129.91, 128.46, 126.28, 60.45, 40.91, 32.94, 32.16, 25.78, 25.68.

HRMS: $[M+H]^+$ calculated for $C_{17}H_{22}N_4O_3S+H^+$ 363.14854, found 363.14808.

***N*-Benzyl-3-((cyclohexylmethyl)sulfonyl)-*N*-methyl-1*H*-1,2,4-triazole-1-carboxamide (10)**



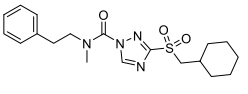
41 (37 mg, 0.107 mmol) was oxidized according General procedure A. Flash column chromatography (15 → 30% EtOAc in pentane) afforded the title compound as blue-grayish oil (25 mg, 0.066 mmol, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.43 – 7.29 (m, 5H), 5.02 – 4.66 (m, 2H), 3.36 – 3.09 (m, 5H), 2.13 – 1.99 (m, 1H), 1.96 – 1.78 (m, 2H), 1.72 – 1.60 (m, 4H), 1.34 – 1.20 (m, 2H), 1.19 – 1.01 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.45, 148.36, 134.94, 129.12, 128.50, 60.75, 54.74, 37.26, 33.04, 32.52, 29.82, 25.77, 25.74.

HRMS: $[M+Na]^+$ calculated for $C_{18}H_{24}N_4O_3S+Na^+$ 399.14613, found 399.14614.

3-((Cyclohexylmethyl)sulfonyl)-*N*-methyl-*N*-phenethyl-1*H*-1,2,4-triazole-1-carboxamide (11)



42 (17 mg, 0.047 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 30% EtOAc in pentane) afforded the title compound as white crystalline solid (16 mg, 0.040 mmol, 84%). HPLC showed presence of a single product (rt = 4.64 min). NMR showed two products which are probably conformationally restricted isomers (ratio ~1:2), as reported before for similar compounds (data not published).

Conformer 1:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.44 – 7.03 (m, 5H), 3.81 – 3.68 (m, 2H), 3.35 – 3.17 (m, 5H), 3.05 – 2.94 (m, 2H), 2.14 – 2.02 (m, 1H), 1.95 – 1.85 (m, 2H), 1.74 – 1.59 (m, 3H), 1.35 – 1.14 (m, 3H), 1.18 – 1.03 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.69, 137.32, 128.93, 127.09, 60.81, 53.04, 34.44, 33.03, 32.53, 25.76, 25.74.

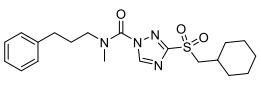
Conformer 2:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.44 – 7.03 (m, 5H), 4.01 – 3.87 (m, 2H), 3.35 – 3.17 (m, 5H), 3.05 – 2.94 (m, 2H), 2.14 – 2.02 (m, 1H), 1.95 – 1.85 (m, 2H), 1.74 – 1.59 (m, 3H), 1.35 – 1.14 (m, 3H), 1.18 – 1.03 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.69, 137.32, 128.93, 127.09, 60.81, 53.36, 34.44, 33.03, 32.53, 25.76, 25.74.

HRMS: $[M+Na]^+$ calculated for $C_{19}H_{26}N_4O_3S+Na^+$ 413.16178, found 413.16131.

3-((Cyclohexylmethyl)sulfonyl)-*N*-methyl-*N*-(3-phenylpropyl)-1*H*-1,2,4-triazole-1-carboxamide (12)



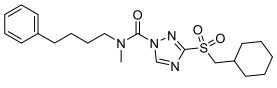
43 (9.8 mg, 0.026 mmol) was oxidized according General procedure A. Flash column chromatography (15 → 25% EtOAc in pentane) afforded the title compound (7.4 mg, 0.018 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.34 – 7.26 (m, 2H), 7.24 – 7.15 (m, 3H), 3.69 – 3.52 (m, 2H), 3.33 – 3.26 (m, 4H), 3.15 (s, 1H), 2.76 – 2.63 (m, 2H), 2.16 – 2.00 (m, 3H), 1.96 – 1.86 (m, 2H), 1.75 – 1.59 (m, 3H), 1.36 – 1.21 (m, 3H), 1.18 – 1.03 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.54, 128.71, 128.38, 126.39, 60.83, 51.31, 33.07, 32.55, 29.84, 25.79, 25.77.

HRMS: $[M+H]^+$ calculated for $C_{20}H_{28}N_4O_3S+H^+$ 405.19549, found 405.19542.

3-((Cyclohexylmethyl)sulfonyl)-*N*-methyl-*N*-(4-phenylbutyl)-1*H*-1,2,4-triazole-1-carboxamide (13)



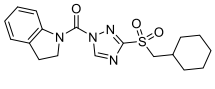
44 (17 mg, 0.044 mmol) was oxidized according General procedure A. Flash column chromatography (15 → 30% EtOAc in pentane) afforded the title compound as white crystalline solid (17 mg, 0.041 mmol, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.32 – 7.25 (m, 2H), 7.23 – 7.11 (m, 3H), 3.72 – 3.49 (m, 2H), 3.32 – 3.08 (m, 5H), 2.71 – 2.60 (m, 2H), 2.14 – 2.03 (m, 1H), 1.94 – 1.86 (m, 2H), 1.80 – 1.56 (m, 6H), 1.35 – 1.21 (m, 2H), 1.21 – 1.05 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.28, 148.17, 141.76, 128.56, 128.51, 126.11, 60.82, 51.47, 37.69, 36.76, 35.55, 33.06, 32.55, 29.83, 29.79, 28.45, 25.79, 25.76.

HRMS: $[M+Na]^+$ calculated for $C_{21}H_{30}N_4O_3S+Na^+$ 441.19308, found 441.19293.

(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(indolin-1-yl)methanone (14)



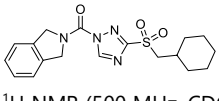
45 (50 mg, 0.146 mmol) was oxidized according General procedure A. Flash column chromatography (0 → 20% EtOAc in pentane) afforded the title compound as off-white crystalline solid (45 mg, 0.120 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.22 – 7.12 (m, 1H), 4.61 (t, *J* = 8.3 Hz, 2H), 3.33 (d, *J* = 6.4 Hz, 2H), 3.26 (t, *J* = 8.3 Hz, 2H), 2.19 – 2.02 (m, 1H), 1.98 – 1.87 (m, 2H), 1.76 – 1.60 (m, 2H), 1.36 – 1.15 (m, 4H), 1.12 (qd, *J* = 12.1, 10.6, 4.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.74, 148.09, 145.03, 141.49, 132.26, 127.89, 125.99, 125.22, 117.65, 60.74, 51.43, 33.02, 32.52, 28.62, 25.74, 25.73.

HRMS: $[M+Na]^+$ calculated for $C_{18}H_{22}N_4O_3S+Na^+$ 397.13048, found 397.13035.

(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(isoindolin-2-yl)methanone (15)



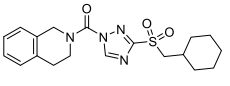
46 (61 mg, 0.178 mmol) was oxidized according General procedure A. Flash column chromatography (15 → 25% EtOAc in pentane) afforded the title compound as white crystalline solid (66 mg, 0.176 mmol, quant.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.37 – 7.30 (m, 4H), 5.38 (s, 2H), 5.08 (s, 2H), 3.35 (d, *J* = 6.4 Hz, 2H), 2.18 – 2.06 (m, 1H), 1.98 – 1.89 (m, 2H), 1.75 – 1.61 (m, 2H), 1.40 – 1.23 (m, 4H), 1.13 (qd, *J* = 12.1, 3.6 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.03, 147.79, 146.28, 135.95, 133.75, 128.26, 128.19, 122.85, 122.63, 60.73, 55.61, 55.28, 33.00, 32.57, 25.74, 25.68.

HRMS: $[M+H]^+$ calculated for $C_{18}H_{22}N_4O_3S+H^+$ 375.14845, found 375.14828.

(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(3,4-dihydroisoquinolin-2(1*H*)-yl)methanone (16)



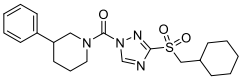
47 (58 mg, 0.163 mmol) was oxidized according General procedure A. Flash column chromatography (15 → 30% EtOAc in pentane) afforded the title compound (46 mg, 0.12 mmol, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.28 – 7.14 (m, 4H), 5.09 – 4.79 (m, 2H), 4.13 – 3.89 (m, 2H), 3.32 (d, *J* = 6.3 Hz, 2H), 3.06 (t, *J* = 5.9 Hz, 2H), 2.15 – 2.05 (m, 1H), 1.95 – 1.88 (m, 2H), 1.76 – 1.61 (m, 2H), 1.35 – 1.23 (m, 2H), 1.22 – 1.06 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.68, 148.23, 147.67, 133.91, 131.57, 128.79, 127.47, 126.93, 126.43, 60.74, 49.29, 47.79, 45.79, 44.11, 33.00, 32.54, 29.10, 25.74, 25.72.

HRMS: $[M+Na]^+$ calculated for $C_{19}H_{24}N_4O_3S+Na^+$ 411.14613, found 411.14584.

(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(3-phenylpiperidin-1-yl)methanone (17)



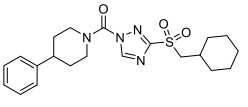
48 (50 mg, 0.130 mmol) was oxidized according General procedure A. Flash column chromatography (0 → 30% EtOAc in pentane) afforded the title compound as colorless oil (22 mg, 0.053 mmol, 41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.44 – 7.36 (m, 2H), 7.34 – 7.27 (m, 3H), 5.87 – 5.72 (m, 1H), 4.33 – 4.23 (m, 1H), 3.27 (d, *J* = 6.4 Hz, 2H), 3.15 (td, *J* = 13.2, 12.4, 3.4 Hz, 1H), 2.55 – 2.45 (m, 1H), 2.17 – 1.99 (m, 2H), 1.93 – 1.85 (m, 2H), 1.84 – 1.59 (m, 6H), 1.35 – 1.20 (m, 4H), 1.20 – 1.01 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.62, 148.59, 148.32, 137.63, 129.17, 127.52, 126.56, 60.64, 56.42 (br), 44.19, 33.03, 32.52, 30.42, 29.81, 25.78, 25.76, 19.20.

HRMS: $[M+Na]^+$ calculated for $C_{21}H_{28}N_4O_3S+Na^+$ 439.17743, found 439.17742.

(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(4-phenylpiperidin-1-yl)methanone (18)



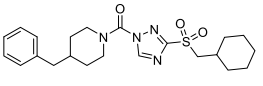
108 (19 mg, 0.047 mmol) was oxidized according General procedure A. Flash column chromatography (25 → 35% EtOAc in pentane) afforded the title compound (12 mg, 0.029 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.38 – 7.30 (m, 2H), 7.26 – 7.19 (m, 3H), 4.72 – 4.48 (m, 2H), 3.32 (d, *J* = 6.3 Hz, 2H), 3.40 – 3.04 (m, 2H), 2.85 (tt, *J* = 12.2, 3.8 Hz, 1H), 2.20 – 2.02 (m, 1H), 1.97 – 1.75 (m, 4H), 1.75 – 1.53 (m, 4H), 1.42 – 1.13 (m, 4H), 1.11 (qd, *J* = 12.2, 3.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.61, 148.28, 147.37, 144.35, 128.85, 126.96, 126.82, 60.77, 48.09 (br), 47.05 (br), 42.37, 33.07, 32.57, 29.83, 25.78.

HRMS: $[M+H]^+$ calculated for $C_{21}H_{28}N_4O_2S+H^+$ 401.20057, found 401.20033.

(4-Benzylpiperidin-1-yl)(3-((cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)methanone (19)



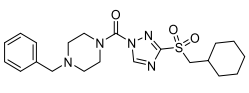
109 (26 mg, 0.063 mmol) was oxidized according General procedure A. Flash column chromatography (25 → 35%) afforded the title compound (18 mg, 0.042 mmol, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.33 – 7.25 (m, 2H), 7.25 – 7.19 (m, 1H), 7.16 – 7.12 (m, 2H), 4.53 – 4.32 (m, 2H), 3.30 (d, *J* = 6.4 Hz, 2H), 3.18 – 2.89 (m, 2H), 2.59 (d, *J* = 6.9 Hz, 2H), 2.16 – 2.02 (m, 1H), 1.96 – 1.86 (m, 2H), 1.90 – 1.74 (m, 1H), 1.75 – 1.59 (m, 2H), 1.38 (qd, *J* = 12.7, 2.9 Hz, 2H), 1.35 – 1.11 (m, 6H), 1.11 (qd, *J* = 12.5, 3.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.50, 148.17, 147.28, 139.56, 129.18, 128.54, 126.38, 60.76, 47.57 (br), 46.53 (br), 42.77, 37.96, 33.06, 32.54, 29.83, 25.78, 25.77.

HRMS: $[M+Na]^+$ calculated for $C_{22}H_{30}N_4O_3S+Na^+$ 453.19308, found 453.19268.

(4-Benzylpiperazin-1-yl)(3-((cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)methanone (20)



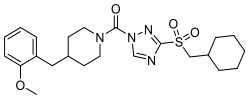
101 (1.5 eq, 65 mg, 0.37 mmol) dissolved in 5 mL dry DCM was added dropwise to an ice-cold solution of triphosgene (3.5 eq, 219 mg, 0.74 mmol) and Na_2CO_3 (5.5 eq, 122 mg, 1.15 mmol) in dry DCM. The mixture was stirred on ice for 1 h, after which it was allowed to warm to RT. 1 h later solids were removed by filtration and volatiles by reduced pressure. Traces of water were removed by co-evaporation with toluene, after which the resulting white powder was dissolved in 5 mL dry DMF. **106** (1 eq, 48 mg, 0.21 mmol) and K_2CO_3 (3.5 eq, 102 mg, 0.74 mmol) were added and the mixture was stirred overnight. Solids were removed by filtration and volatiles by reduced pressure. Flash column chromatography afforded the title compound as off-white crystalline solid (74 mg, 0.171 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.37 – 7.24 (m, 5H), 4.04 – 3.67 (m, 4H), 3.57 (s, 2H), 3.29 (d, *J* = 6.4 Hz, 2H), 2.65 – 2.50 (m, 4H), 2.16 – 2.01 (m, 1H), 1.94 – 1.86 (m, 2H), 1.74 – 1.59 (m, 3H), 1.36 – 1.21 (m, 2H), 1.21 – 1.05 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.50, 148.28, 147.10, 137.15, 129.17, 128.47, 127.52, 62.64, 60.65, 52.82, 52.19, 47.63, 45.74, 32.96, 32.43, 25.69, 25.68.

HRMS: $[M+H]^+$ calculated for $C_{21}H_{29}N_5O_3S+H^+$ 432.20639, found 432.20613.

(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(4-(2-methoxybenzyl)piperidin-1-yl)-methanone (21)



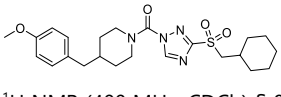
51 (69 mg, 0.16 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 70% EtOAc in pentane) afforded the title compound as gray gum (74 mg, 0.16 mmol, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.20 (td, *J* = 7.8, 1.8 Hz, 1H), 7.06 (dd, *J* = 7.3, 1.7 Hz, 1H), 6.92 – 6.83 (m, 2H), 4.44 – 4.33 (m, 2H), 3.82 (s, 3H), 3.30 (d, *J* = 6.4 Hz, 2H), 3.19 – 2.87 (m, 2H), 2.60 (d, *J* = 7.1 Hz, 2H), 2.15 – 2.02 (m, 1H), 1.97 – 1.83 (m, 3H), 1.77 (s, 2H), 1.75 – 1.59 (m, 3H), 1.46 – 1.31 (m, 2H), 1.32 – 1.14 (m, 3H), 1.18 – 1.03 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.36, 157.59, 148.09, 147.21, 130.95, 127.95, 127.59, 120.31, 110.40, 60.69, 55.29, 47.97, 46.42, 36.73, 36.25, 32.98, 32.48, 31.36, 25.72, 25.70.

HRMS: $[M+H]^+$ calculated for $C_{23}H_{32}N_4O_4S+H^+$ 461.22170, found 461.22158.

(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(4-(4-methoxybenzyl)piperidin-1-yl)-methanone (22)



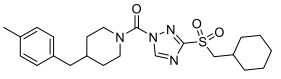
52 (61 mg, 0.14 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 80% EtOAc in pentane) afforded the title compound as gray gum (65 mg, 0.14 mmol, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.09 – 7.01 (m, 2H), 6.88 – 6.79 (m, 2H), 4.46 – 4.38 (m, 2H), 3.79 (s, 3H), 3.30 (d, *J* = 6.3 Hz, 2H), 3.17 – 2.85 (m, 2H), 2.53 (d, *J* = 6.7 Hz, 2H), 2.17 – 2.02 (m, 1H), 1.97 – 1.87 (m, 2H), 1.87 – 1.74 (m, 3H), 1.74 – 1.59 (m, 3H), 1.43 – 1.27 (m, 2H), 1.32 – 1.14 (m, 3H), 1.18 – 1.04 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.47, 158.16, 148.13, 147.25, 131.56, 130.05, 113.89, 60.74, 55.35, 47.96 (br), 46.44 (br), 41.80, 38.07, 33.02, 32.52, 32.02 (br), 31.46 (br), 25.76, 25.74.

HRMS: $[M+Na]^+$ calculated for $C_{23}H_{32}N_4O_4S+Na^+$ 483.2036, found 483.2038.

(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(4-(4-methylbenzyl)piperidin-1-yl)-methanone (23)



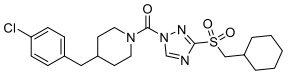
53 (100 mg, 0.24 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 80% EtOAc in pentane) afforded the title compound as gray gum (100 mg, 0.23 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.13 – 7.07 (m, 2H), 7.06 – 6.99 (m, 2H), 4.50 – 4.31 (m, 2H), 3.30 (d, *J* = 6.3 Hz, 2H), 3.18 – 2.84 (m, 2H), 2.55 (d, *J* = 6.7 Hz, 2H), 2.32 (s, 3H), 2.14 – 2.02 (m, 1H), 1.95 – 1.86 (m, 2H), 1.86 – 1.74 (m, 3H), 1.74 – 1.57 (m, 3H), 1.43 – 1.31 (m, 2H), 1.32 – 1.16 (m, 3H), 1.10 (qd, *J* = 12.1, 10.7, 3.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.38, 148.11, 147.19, 136.38, 135.73, 129.10, 128.97, 60.67, 47.88, 46.35, 42.20, 37.88, 32.94, 32.45, 32.13, 31.39, 25.69, 25.67, 21.04.

HRMS: $[M+Na]^+$ calculated for $C_{23}H_{32}N_4O_3S+Na^+$ 467.2087, found 467.2072.

(4-(4-Chlorobenzyl)piperidin-1-yl)(3-((cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)-methanone (24, WEN091)



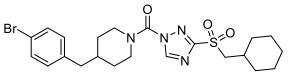
54 (20 mg, 0.046 mmol) was oxidized according General procedure D. Flash column chromatography (0 → 100% Et_2O in pentane) afforded the title compound as white gum (5 mg, 0.011 mmol, 23%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.30 – 7.24 (m, 2H), 7.10 – 7.05 (m, 2H), 4.54 – 4.33 (m, 2H), 3.30 (d, *J* = 6.4 Hz, 2H), 3.20 – 2.84 (m, 2H), 2.57 (d, *J* = 6.8 Hz, 2H), 2.09 (m, 1H), 1.95 – 1.88 (m, 2H), 1.88 – 1.74 (m, 3H), 1.74 – 1.61 (m, 2H), 1.37 (qd, *J* = 12.7, 4.0, 3.2 Hz, 2H), 1.33 – 1.20 (m, 3H), 1.22 – 1.13 (m, 1H), 1.11 (qd, *J* = 12.2, 11.3, 3.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.61, 148.19, 147.30, 137.98, 132.24, 130.50, 128.70, 60.79, 42.11, 37.91, 33.09, 32.57, 25.81, 25.79.

HRMS: $[M+H]^+$ calculated for $C_{22}H_{29}ClN_4O_3S+H^+$ 465.17217, found 465.17183.

(4-(4-Bromobenzyl)piperidin-1-yl)(3-((cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)-methanone (25)



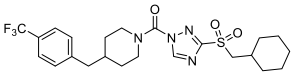
55 (47 mg, 0.098 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 80% EtOAc in pentane) afforded the title compound as gray gum (43 mg, 0.084 mmol, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.44 – 7.38 (m, 2H), 7.06 – 6.98 (m, 2H), 4.51 – 4.35 (m, 2H), 3.30 (d, *J* = 6.4 Hz, 2H), 3.17 – 2.87 (m, 2H), 2.55 (d, *J* = 6.8 Hz, 2H), 2.17 – 2.03 (m, 1H), 1.96 – 1.86 (m, 2H), 1.88 – 1.74 (m, 3H), 1.74 – 1.60 (m, 3H), 1.45 – 1.32 (m, 2H), 1.33 – 1.13 (m, 3H), 1.15 – 1.05 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.49, 148.16, 147.23, 138.47, 131.58, 130.87, 120.15, 60.72, 47.85 (br), 46.44 (br), 42.09, 37.77, 33.01, 32.50, 32.07 (br), 25.74, 25.73.

HRMS: $[M+Na]^+$ calculated for $C_{22}H_{29}BrN_4O_3S+Na^+$ 531.1036 and 533.1015, found 531.1033 and 533.1017.

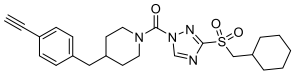
(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone (26)



56 (42 mg, 0.090 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 60% EtOAc in pentane) afforded the title compound as gray gum (38 mg, 0.076 mmol, 85%).

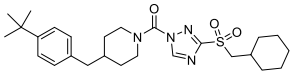
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 4.53 – 4.35 (m, 2H), 3.31 (d, *J* = 6.3 Hz, 2H), 3.19 – 2.86 (m, 2H), 2.66 (d, *J* = 7.0 Hz, 2H), 2.16 – 2.02 (m, 1H), 1.95 – 1.84 (m, 3H), 1.84 – 1.74 (m, 2H), 1.75 – 1.59 (m, 3H), 1.40 (qd, *J* = 12.7, 4.0 Hz, 2H), 1.36 – 1.14 (m, 3H), 1.16 – 1.04 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.54, 148.20, 147.26, 143.68 (q, *J* = 1.2 Hz), 129.46, 128.78 (q, *J* = 32.4 Hz), 125.47 (q, *J* = 3.8 Hz), 124.33 (q, *J* = 272.1 Hz), 60.73, 42.52, 37.74, 33.03, 32.52, 25.74.
HRMS: $[M+H]^+$ calculated for $C_{23}H_{29}F_3N_4O_3S+H^+$ calculated 499.1985, found 499.2000

(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(4-(4-ethynylbenzyl)piperidin-1-yl)-methanone (27)



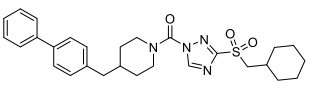
95 (1 eq, 20 mg, 0.064 mmol) dissolved in 5 mL dry THF was added dropwise over the course of 15 min to an ice-cold solution of triphosgene (4.8 eq, 91 mg, 0.31 mmol) and Na_2CO_3 (4.8 eq, 33 mg, 0.31 mmol) in 6 mL dry THF. The mixture was stirred on ice for 1.5 h, after which it was allowed to warm to RT. When TLC analysis showed full conversion (~1.5 h) the mixture was dissolved with EtOAc, washed with water and brine, dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Traces of water were removed by co-evaporation with toluene, after which the residue was dissolved in 5 mL dry DMF. **106** (1.6 eq, 23 mg, 0.10 mmol) and K_2CO_3 (5.0 eq, 44 mg, 0.32 mmol) were added and the mixture was stirred overnight. Water and EtOAc were added and the layers were separated. The aqueous layer was extracted with EtOAc, after which the combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Flash column chromatography (30 → 50% Et_2O in pentane) afforded the title compound (9 mg, 0.020 mmol, 31%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 4.49 – 4.39 (m, 2H), 3.30 (d, *J* = 6.4 Hz, 2H), 3.06 (s, 1H), 3.17 – 2.86 (m, 2H), 2.60 (d, *J* = 5.8 Hz, 2H), 2.15 – 2.04 (m, 1H), 1.95 – 1.88 (m, 2H), 1.88 – 1.77 (m, 3H), 1.70 – 1.59 (m, 2H), 1.43 – 1.38 (m, 4H), 1.33 – 1.26 (m, 2H), 1.11 (qd, *J* = 12.4, 2.9 Hz, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 162.71, 147.31, 140.53, 132.36, 129.20, 120.23, 83.63, 77.13, 60.80, 42.69, 37.84, 33.10, 32.57, 29.85, 24.13, 23.11.

(4-(4-(*tert*-Butyl)benzyl)piperidin-1-yl)(3-((cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)-methanone (28)



58 (48 mg, 0.11 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 80% EtOAc in pentane) afforded the title compound as gray gum (38 mg, 0.078 mmol, 74%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.35 – 7.27 (m, 2H), 7.11 – 7.03 (m, 2H), 4.46 – 4.38 (m, 2H), 3.30 (d, *J* = 6.4 Hz, 2H), 3.16 – 2.87 (m, 2H), 2.56 (d, *J* = 6.9 Hz, 2H), 2.16 – 2.02 (m, 1H), 1.96 – 1.88 (m, 2H), 1.88 – 1.74 (m, 3H), 1.74 – 1.59 (m, 3H), 1.45 – 1.31 (m, 2H), 1.31 (s, 9H), 1.29 – 1.14 (m, 3H), 1.17 – 1.04 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.45, 149.15, 148.14, 147.25, 136.44, 128.81, 125.37, 60.74, 53.56, 47.96 (br), 46.49 (br), 42.17, 37.87, 34.48, 33.02, 32.51, 32.13, 31.48 (br), 25.76, 25.74.
HRMS: $[M+Na]^+$ calculated for $C_{26}H_{38}N_4O_3S+Na^+$ calculated 509.2557, found 509.2553.

(4-([1,1'-Biphenyl]-4-ylmethyl)piperidin-1-yl)(3-((cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)methanone (29)



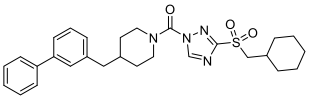
110 (12 mg, 0.024 mmol) was oxidized according to General procedure A. Flash column chromatography (50 → 100% Et_2O in pentane) afforded the title compound as white powder (8 mg, 0.016 mmol, 65%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.61 – 7.55 (m, 2H), 7.56 – 7.50 (m, 2H), 7.47 – 7.40 (m, 2H), 7.34 (tt, *J* = 7.3, 7.3, 1.9, 1.3 Hz, 1H), 7.25 – 7.19 (m, 2H), 4.45 (s, 2H), 3.31 (d, *J* = 6.4 Hz, 1H), 3.21 – 2.90 (m, 2H), 2.64 (d, *J* = 6.5 Hz, 2H), 2.15 – 2.03 (m, 1H), 1.95 – 1.77 (m, 4H), 1.74 – 1.60 (m, 4H), 1.41 (qd, *J* = 12.3, 4.1 Hz, 2H), 1.36 – 1.27 (m, 3H), 1.20 – 1.14 (m, 1H), 1.11 (qd, *J* = 12.5, 4.6 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.58, 148.17, 147.32, 140.99, 139.39, 138.66, 129.63, 128.91, 127.31, 127.28, 127.12, 60.80, 42.42, 37.99, 33.09, 32.57, 25.81, 25.79.

HRMS: $[M+H]^+$ calculated for $C_{28}H_{34}N_4O_3S+H^+$ 507.2424, found 507.2424.

(4-([1,1'-Biphenyl]-3-ylmethyl)piperidin-1-yl)(3-((cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)methanone (30)



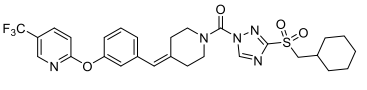
59 (75 mg, 0.16 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 80% EtOAc in pentane) afforded the title compound as colorless oil (64 mg, 0.13 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.62 – 7.54 (m, 2H), 7.48 – 7.40 (m, 3H), 7.39 – 7.31 (m, 3H), 7.12 (dt, *J* = 7.5, 1.3 Hz, 1H), 4.51 – 4.35 (m, 2H), 3.30 (d, *J* = 6.3 Hz, 2H), 3.17 – 2.88 (m, 2H), 2.65 (d, *J* = 6.9 Hz, 2H), 2.16 – 2.01 (m, 1H), 1.95 – 1.86 (m, 3H), 1.87 – 1.77 (m, 2H), 1.74 – 1.58 (m, 3H), 1.40 (qd, *J* = 12.7, 4.2 Hz, 2H), 1.33 – 1.12 (m, 3H), 1.10 (qd, *J* = 12.3, 3.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.41, 148.12, 147.21, 141.44, 141.10, 140.02, 128.89, 128.83, 128.06, 127.93, 127.40, 127.19, 125.18, 60.69, 47.88 (br), 46.33 (br), 42.77, 37.89, 32.96, 32.47, 32.07 (br), 31.51 (br), 25.70, 25.69.

HRMS: $[M+Na]^+$ calculated for $C_{28}H_{24}N_4O_3S+Na^+$ 529.22438, found 529.22330.

(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(4-(3-((5-(trifluoromethyl)pyridin-2-yl)-oxy)benzylidene)piperidin-1-yl)methanone (31)



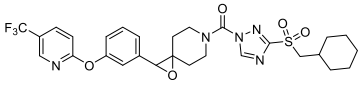
106 (23 mg, 0.10 mmol) was reacted with **105** (1.7 eq, 56 mg, 0.17 mmol) according to General procedure C. The residue was purified by flash column chromatography (10 → 30% EtOAc in pentane) yielding the title compound (11 mg, 0.019 mmol, 19%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.46 – 8.42 (m, 1H), 7.92 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 7.01 – 6.98 (m, 1H), 6.46 (s, 1H), 4.04 – 3.63 (m, 3H), 3.31 (d, *J* = 6.1 Hz, 2H), 2.73 – 2.67 (m, 3H), 2.60 – 2.49 (m, 2H), 2.16 – 2.04 (m, 1H), 1.95 – 1.88 (m, 2H), 1.74 – 1.66 (m, 2H), 1.65 – 1.54 (m, 1H), 1.35 – 1.24 (m, 2H), 1.22 – 1.16 (m, 1H), 1.12 (qd, *J* = 11.9, 3.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.81, 162.74, 153.25, 147.36, 145.63, 138.75, 136.93, 136.90, 136.54, 129.83, 126.14, 125.66, 121.90, 119.98, 111.63, 60.78, 47.36 (br), 33.09, 32.56, 29.84, 25.80, 25.78.

HRMS: $[M+H]^+$ calculated for $C_{28}H_{30}F_3N_5O_4S+H^+$ 590.20434, found 590.20368.

(3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)(2-(3-((5-(trifluoromethyl)pyridin-2-yl)-oxy)phenyl)-1-oxa-6-azaspiro[2.5]octan-6-yl)methanone (32)



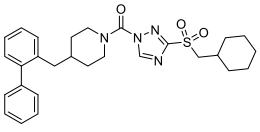
60 (9 mg, 0.016 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 50% EtOAc in pentane) afforded the title compound (6 mg, 9.9 µmol, 61%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.45 – 8.41 (m, 1H), 7.92 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.13 – 7.09 (m, 2H), 7.04 (d, *J* = 8.7 Hz, 1H), 4.07 (s, 1H), 4.31 – 3.54 (m, 4H), 3.36 – 3.20 (m, 2H), 2.14 – 2.03 (m, 1H), 1.93 – 1.87 (m, 2H), 1.80 – 1.60 (m, 4H), 1.61 – 1.51 (m, 3H), 1.31 – 1.23 (m, 3H), 1.21 – 1.04 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.47, 162.83, 153.45, 147.40, 145.61, 136.98, 130.00, 123.44, 121.20, 119.55, 111.73, 63.73, 60.77, 33.09, 32.55, 25.79, 25.77.

HRMS: $[M+H]^+$ calculated for $C_{28}H_{30}F_3N_5O_5S+H^+$ 606.19925, found 606.19882.

(4-([1,1'-Biphenyl]-2-ylmethyl)piperidin-1-yl)(3-((cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)methanone (33)



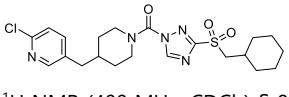
61 (75 mg, 0.16 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 80% EtOAc in pentane) afforded the title compound as colorless oil (77 mg, 0.15 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.44 – 7.38 (m, 2H), 7.38 – 7.30 (m, 1H), 7.31 – 7.24 (m, 5H), 7.24 – 7.18 (m, 1H), 4.31 – 4.19 (m, 2H), 3.28 (d, *J* = 6.4 Hz, 2H), 3.07 – 2.74 (m, 2H), 2.63 (d, *J* = 6.9 Hz, 2H), 2.13 – 2.00 (m, 1H), 1.95 – 1.84 (m, 2H), 1.74 – 1.49 (m, 6H), 1.35 – 1.09 (m, 3H), 1.18 – 1.02 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.28, 148.03, 147.04, 142.36, 141.75, 137.01, 130.27, 129.87, 129.27, 128.22, 127.37, 126.97, 126.20, 60.62, 47.78 (br), 46.18 (br), 39.15, 37.26, 32.92, 32.42, 32.09 (br), 31.18 (br), 25.68, 25.65.

HRMS: $[M+Na]^+$ calculated for $C_{28}H_{24}N_4O_3S+Na^+$ 529.22438, found 529.22325.

(4-((6-Chloropyridin-3-yl)methyl)piperidin-1-yl)(3-((cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)methanone (34)



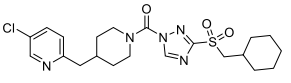
62 (50 mg, 0.12 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 80% EtOAc in pentane) afforded the title compound as white solid (13 mg, 0.028 mmol, 24%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.52 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.61 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.09 (dd, *J* = 8.2, 0.7 Hz, 1H), 4.51 – 4.37 (m, 2H), 3.31 (d, *J* = 6.4 Hz, 2H), 3.23 – 2.92 (m, 2H), 2.75 (d, *J* = 7.2 Hz, 2H), 2.23 – 2.05 (m, 2H), 1.95 – 1.86 (m, 2H), 1.86 – 1.75 (m, 2H), 1.74 – 1.59 (m, 3H), 1.43 (qd, *J* = 12.7, 4.2 Hz, 2H), 1.36 – 1.22 (m, 3H), 1.20 – 1.04 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.53, 157.75, 148.44, 147.64, 147.29, 136.38, 130.06, 124.65, 60.80, 43.94, 36.36, 33.08, 32.55, 25.78, 25.74.

HRMS: $[M+H]^+$ calculated for $C_{21}H_{28}ClN_5O_3S+H^+$ 466.16741, found 466.16649.

(4-((5-Chloropyridin-2-yl)methyl)piperidin-1-yl)(3-((cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazol-1-yl)methanone (35)



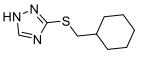
63 (100 mg, 0.23 mmol) was oxidized according General procedure A. Flash column chromatography (20 → 80% EtOAc in pentane) afforded the title compound as white solid (100 mg, 0.22 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.20 (dd, *J* = 2.4, 0.6 Hz, 1H), 7.46 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.29 (dd, *J* = 8.1, 0.7 Hz, 1H), 4.58 – 4.36 (m, 2H), 3.31 (d, *J* = 6.4 Hz, 2H), 3.21 – 2.87 (m, 2H), 2.60 (d, *J* = 7.0 Hz, 2H), 2.17 – 2.03 (m, 1H), 1.96 – 1.87 (m, 2H), 1.87 – 1.75 (m, 3H), 1.76 – 1.60 (m, 3H), 1.39 (qd, *J* = 12.8, 3.4 Hz, 2H), 1.37 – 1.14 (m, 3H), 1.11 (qd, *J* = 11.6, 3.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.60, 150.09, 149.74, 148.23, 147.27, 139.46, 133.76, 124.16, 60.74, 38.97, 37.61, 33.05, 32.53, 25.76.

HRMS: $[M+H]^+$ calculated for $C_{21}H_{28}ClN_5O_3S+H^+$ 466.16741, found 466.16652.

3-((Cyclohexylmethyl)thio)-1*H*-1,2,4-triazole (36)

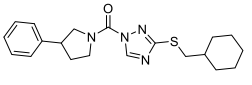


1*H*-1,2,4-triazole-3-thiol (1 eq, 2.00 g, 19.8 mmol) was dissolved in 70 mL dry DMF and (bromomethyl)cyclohexane (1 eq, 2.76 mL, 19.8 mmol) was added carefully. K_2CO_3 (0.73 eq, 2.00 g, 14.4 mmol) was added and the mixture was stirred for 6 h, during which it turned light purple and finally white and cloudy. The mixture was diluted with EtOAc and washed with water. The aqueous layer was extracted with EtOAc, after which the combined organic layers were washed with brine, dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Flash column chromatography (20 → 40% EtOAc in pentane) afforded the title compound as white crystalline solid (3.43 g, 17.4 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.13 (s, 1H), 8.20 (s, 1H), 3.08 (d, *J* = 7.0 Hz, 2H), 1.91 – 1.80 (m, 2H), 1.76 – 1.61 (m, 3H), 1.69 – 1.52 (m, 1H), 1.31 – 1.05 (m, 3H), 0.98 (qd, *J* = 11.7, 3.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.29, 147.61, 39.96, 37.84, 32.49, 26.22, 25.95.

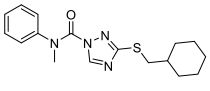
(3-((Cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)(3-phenylpyrrolidin-1-yl)methanone (39)



36 (51 mg, 0.26 mmol) was reacted with 3-phenylpyrrolidine (1.4 eq, 55 µL, 0.37 mmol) according to General procedure C. The residue was purified by flash column chromatography (0 → 25% EtOAc in pentane) yielding the title compound as a white crystalline solid (79 mg, 0.21 mmol, 82%). HPLC showed presence of a single product (rt = 6.81 min). NMR showed two products which are probably conformationally restricted isomers (ratio ~1:1), as reported before for similar compounds (data not published).

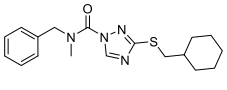
Conformer 1:
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.38 – 7.31 (m, 2H), 7.30 – 7.23 (m, 3H), 4.44 (dd, *J* = 11.9, 7.6 Hz, 1H), 4.24 (ddd, *J* = 11.5, 8.1, 2.9 Hz, 1H), 4.09 – 3.99 (m, 1H), 3.98 – 3.86 (m, 1H), 3.50 – 3.39 (m, 1H), 3.05 (d, *J* = 6.8 Hz, 2H), 2.45 – 2.30 (m, 1H), 2.17 – 2.00 (m, 1H), 1.92 – 1.86 (m, 2H), 1.78 – 1.70 (m, 2H), 1.70 – 1.56 (m, 2H), 1.35 – 0.96 (m, 3H), 0.96 – 0.85 (m, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.51, 147.17, 147.09, 140.22, 128.82, 127.27, 127.08, 55.99, 49.73, 45.05, 38.82, 37.91, 33.90, 32.64, 26.26, 26.07.
Conformer 2:
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.38 – 7.31 (m, 2H), 7.30 – 7.23 (m, 3H), 4.13 (dd, *J* = 12.0, 7.6 Hz, 1H), 3.98 – 3.86 (m, 1H), 3.78 – 3.71 (m, 1H), 3.68 (dd, *J* = 11.9, 9.5 Hz, 1H), 3.50 – 3.39 (m, 1H), 3.02 – 2.89 (m, 2H), 2.45 – 2.30 (m, 1H), 2.17 – 2.00 (m, 1H), 1.84 – 1.78 (m, 2H), 1.70 – 1.56 (m, 4H), 1.35 – 0.96 (m, 5H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.51, 147.17, 147.09, 139.92, 128.82, 127.18, 127.03, 54.43, 48.66, 42.05, 38.82, 37.83, 32.55, 31.07, 26.28, 25.98.

3-((Cyclohexylmethyl)thio)-*N*-methyl-*N*-phenyl-1*H*-1,2,4-triazole-1-carboxamide (40)



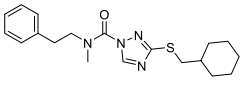
36 (50 mg, 0.25 mmol) was reacted with *N*-methylaniline (1.5 eq, 41 µL, 0.38 mmol) according to General procedure C. The residue was purified by flash column chromatography (0 → 20% EtOAc in pentane) yielding the title compound as a white crystalline solid (65 mg, 0.20 mmol, 78%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.40 – 7.28 (m, 2H), 7.32 – 7.24 (m, 1H), 7.16 – 7.09 (m, 2H), 3.51 (s, 3H), 2.56 (d, *J* = 7.0 Hz, 2H), 1.78 – 1.59 (m, 5H), 1.45 – 1.30 (m, 1H), 1.30 – 1.05 (m, 3H), 0.85 (qd, *J* = 13.6, 12.8, 4.0 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.21, 152.91, 148.62, 146.71, 143.58, 129.53, 127.56, 126.18, 40.62, 38.41, 37.32, 32.48, 26.30, 25.95.

***N*-Benzyl-3-((cyclohexylmethyl)thio)-*N*-methyl-1*H*-1,2,4-triazole-1-carboxamide (41)**



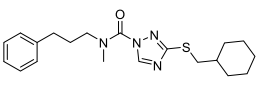
36 (50 mg, 0.25 mmol) was reacted with *N*-methylbenzylamine (1.5 eq, 51 µL, 0.38 mmol) according to General procedure C. The residue was purified by flash column chromatography (10 → 20% EtOAc in pentane) yielding the title compound as gray oil (74 mg, 0.22 mmol, 85%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.40 – 7.26 (m, 5H), 5.23 – 4.48 (m, 2H), 3.49 – 2.60 (m, 5H), 2.11 – 1.39 (m, 5H), 1.33 – 1.04 (m, 4H), 1.03 – 0.64 (m, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.60, 149.72, 135.91, 128.84, 127.98, 54.46, 38.67, 37.79, 32.54, 26.28, 26.04.

3-((Cyclohexylmethyl)thio)-*N*-methyl-*N*-phenethyl-1*H*-1,2,4-triazole-1-carboxamide (42)



36 (51 mg, 0.26 mmol) was reacted with *N*-methylphenethylamine (1.4 eq, 50 mg, 0.37 mmol) according to General procedure C. The residue was purified by flash column chromatography (15 → 20% EtOAc in pentane) yielding the title compound as a yellowish oil (41 mg, 0.11 mmol, 44%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 – 8.30 (m, 1H), 7.32 – 7.25 (m, 2H), 7.25 – 7.20 (m, 1H), 7.25 – 7.07 (m, 2H), 4.11 – 3.57 (m, 2H), 3.37 – 3.06 (m, 3H), 3.04 (d, *J* = 6.9 Hz, 2H), 2.99 (t, *J* = 7.6 Hz, 2H), 1.91 – 1.84 (m, 2H), 1.76 – 1.69 (m, 2H), 1.69 – 1.57 (m, 2H), 1.33 – 1.06 (m, 3H), 1.00 (qd, *J* = 12.1, 3.4 Hz, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.30, 149.38, 138.07, 128.86, 128.80, 126.85, 52.81 (br), 38.89, 37.97, 36.76 (br), 33.81 (br), 32.67, 26.35, 26.11.

3-((Cyclohexylmethyl)thio)-*N*-methyl-*N*-(3-phenylpropyl)-1*H*-1,2,4-triazole-1-carboxamide (43)

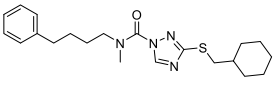


36 (20 mg, 0.10 mmol) was reacted with **66** (1.5 eq, 32 mg, 0.15 mmol) according to General procedure C. The residue was purified by flash column chromatography (15 → 20% EtOAc in pentane) yielding the title compound as a colorless oil (16 mg, 0.043 mmol, 43%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.32 – 7.25 (m, 2H), 7.23 – 7.16 (m, 3H), 3.87 – 3.41 (m, 2H), 3.38 – 3.06 (m, 3H), 3.04 (d, *J* = 6.8 Hz, 2H), 2.70 – 2.63 (m, 2H), 2.09 – 2.00 (m, 2H), 1.92 – 1.84 (m, 2H), 1.77 – 1.69 (m, 2H), 1.69 – 1.62 (m, 1H), 1.65 – 1.57 (m, 1H), 1.25 – 1.09 (m, 3H), 1.00 (qd, *J* = 12.4, 3.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.39, 136.02, 128.65, 128.35, 126.30, 50.93, 38.90, 37.98, 36.65, 32.99, 32.73, 30.45, 29.83, 26.37, 26.14.

3-((Cyclohexylmethyl)thio)-*N*-methyl-*N*-(4-phenylbutyl)-1*H*-1,2,4-triazole-1-carboxamide (44)

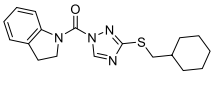


36 (30 mg, 0.15 mmol) was reacted with *N*-methyl-4-phenylbutylamine (1.5 eq, 36 mg, 0.22 mmol) according to General procedure C. The residue was purified by flash column chromatography (10 → 20% EtOAc in pentane) yielding the title compound as a gray oil (30 mg, 0.078 mmol, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.33 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 3.81 – 3.44 (m, 2H), 3.28 – 3.06 (m, 3H), 3.04 (d, *J* = 6.8 Hz, 2H), 2.66 (t, *J* = 7.3 Hz, 2H), 1.93 – 1.84 (m, 2H), 1.77 – 1.65 (m, 5H), 1.69 – 1.56 (m, 1H), 1.31 – 1.08 (m, 5H), 1.00 (qd, *J* = 11.7, 3.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.31, 141.88, 128.50, 128.46, 126.04, 51.07, 38.85, 37.92, 35.61, 32.70, 29.81, 28.42, 26.34, 26.10.

(3-((Cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)(indolin-1-yl)methanone (45)

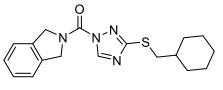


36 (55 mg, 0.28 mmol) was reacted with indoline (1.4 eq, 43 µL, 0.38 mmol) according to General procedure C. The residue was purified by flash column chromatography (0 → 10% EtOAc in pentane) yielding the title compound (yield not determined).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.20 (m, 2H), 7.16 – 7.07 (m, 1H), 4.57 (t, *J* = 8.3 Hz, 2H), 3.21 (t, *J* = 8.3 Hz, 2H), 3.06 (d, *J* = 6.8 Hz, 2H), 1.96 – 1.85 (m, 2H), 1.80 – 1.59 (m, 4H), 1.31 – 1.10 (m, 3H), 1.02 (qd, *J* = 12.0, 3.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.70, 147.09, 146.19, 142.16, 132.05, 127.70, 125.19, 124.97, 117.56, 51.29, 38.88, 37.94, 32.69, 28.73, 26.31, 26.10.

(3-((Cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)(isoindolin-2-yl)methanone (46)

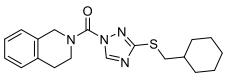


36 (50 mg, 0.25 mmol) was reacted with isoindoline (1.5 eq, 43 µL, 0.38 mmol) according to General procedure C. The residue was purified by flash column chromatography (0 → 20% EtOAc in pentane) yielding the title compound as a white crystalline solid (76 mg, 0.22 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.35 – 7.21 (m, 4H), 5.34 (s, 2H), 5.02 (s, 2H), 3.08 (d, *J* = 6.8 Hz, 2H), 1.99 – 1.90 (m, 2H), 1.82 – 1.73 (m, 2H), 1.77 – 1.64 (m, 2H), 1.36 – 1.12 (m, 3H), 1.04 (qd, *J* = 12.0, 3.3 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.84, 147.23, 146.73, 136.55, 134.29, 127.94, 122.63, 122.53, 55.55, 54.87, 38.92, 38.00, 32.72, 26.32, 26.14.

(3-((Cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)(3,4-dihydroisoquinolin-2(1*H*)-yl)-methanone (47)

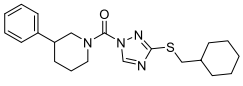


36 (50 mg, 0.25 mmol) was reacted with 1,2,3,4-tetrahydroisoquinoline (1.5 eq, 50 µL, 0.38 mmol) according to General procedure C. The residue was purified by flash column chromatography (10 → 20% EtOAc in pentane) yielding the title compound as a gray oil (83 mg, 0.23 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.26 – 7.02 (m, 4H), 5.28 – 4.64 (m, 2H), 4.29 – 3.73 (m, 2H), 3.09 – 2.99 (m, 4H), 1.96 – 1.87 (m, 2H), 1.80 – 1.60 (m, 3H), 1.33 – 1.09 (m, 4H), 1.02 (qd, *J* = 12.0, 3.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.59, 148.60, 147.37, 147.36, 147.34, 134.07, 132.27, 128.83, 127.10, 126.66, 126.34, 38.81, 37.88, 32.66, 29.74, 26.30, 26.07.

(3-((Cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)(3-phenylpiperidin-1-yl)methanone (48)

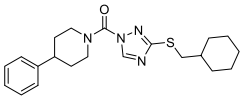


36 (51 mg, 0.26 mmol) was reacted with 3-phenylpiperidine (1.2 eq, 50 µL, 0.30 mmol) according to General procedure C. The residue was purified by flash column chromatography (0 → 100% EtOAc in pentane) yielding the title compound (59 mg, 0.15 mmol, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.43 – 7.35 (m, 2H), 7.38 – 7.31 (m, 2H), 7.35 – 7.24 (m, 1H), 5.94 (s, 1H), 4.44 – 4.32 (m, 1H), 3.72 – 3.45 (m, 2H), 3.08 – 2.95 (m, 1H), 2.90 (d, *J* = 6.8 Hz, 2H), 2.53 – 2.44 (m, 1H), 2.11 – 1.97 (m, 1H), 1.95 – 1.86 (m, 1H), 1.84 – 1.75 (m, 1H), 1.78 – 1.60 (m, 5H), 1.59 – 1.49 (m, 1H), 1.36 – 1.06 (m, 4H), 1.00 (qd, *J* = 11.7, 3.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.48, 163.34, 149.53, 147.61, 147.37, 138.14, 128.91, 127.12, 126.74, 56.23, 43.67, 42.94, 38.77, 38.64, 37.77, 37.75, 32.68, 32.57, 32.55, 27.95, 26.35, 26.32, 26.11, 26.08, 25.73, 19.44.

(3-((Cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)(4-phenylpiperidin-1-yl)methanone (49)

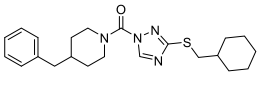


36 (50 mg, 0.25 mmol) was reacted with 4-phenylpiperidine (1.5 eq, 61 mg, 0.38 mmol) according to General procedure C. The residue was purified by flash column chromatography (0 → 20% EtOAc in pentane) yielding the title compound as a white crystalline solid (50 mg, 0.13 mmol, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.37 – 7.29 (m, 2H), 7.28 – 7.19 (m, 3H), 5.02 – 4.45 (m, 2H), 3.19 – 3.06 (m, 2H), 3.03 (d, *J* = 6.8 Hz, 2H), 2.83 (tt, *J* = 12.1, 3.9 Hz, 1H), 2.01 – 1.77 (m, 5H), 1.80 – 1.58 (m, 4H), 1.31 – 1.08 (m, 4H), 0.99 (qd, *J* = 11.8, 3.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.46, 148.42, 147.45, 144.82, 128.75, 126.82, 126.78, 47.12 (br), 42.61, 38.84, 37.91, 33.27, 32.69, 26.33, 26.10.

(4-Benzylpiperidin-1-yl)(3-((cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)methanone (50)

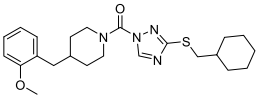


36 (50 mg, 0.25 mmol) was reacted with 4-benzylpiperidine (1.5 eq, 67 µL, 0.38 mmol) according to General procedure C. The residue was purified by flash column chromatography (0 → 20% EtOAc in pentane) yielding the title compound as a white crystalline solid (76 mg, 0.19 mmol, 75%).

Analytical data on next page.

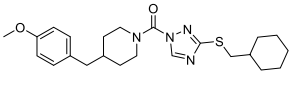
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.32 – 7.25 (m, 2H), 7.24 – 7.18 (m, 1H), 7.16 – 7.12 (m, 2H), 4.80 – 4.25 (m, 2H), 3.02 (d, *J* = 6.8 Hz, 2H), 2.99 – 2.88 (m, 2H), 2.58 (d, *J* = 7.1 Hz, 2H), 1.93 – 1.86 (m, 2H), 1.86 – 1.79 (m, 1H), 1.79 – 1.57 (m, 5H), 1.37 (qd, *J* = 12.9, 4.2 Hz, 2H), 1.30 – 1.09 (m, 4H), 0.99 (qd, *J* = 12.1, 3.4 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.28, 148.31, 147.32, 139.76, 129.12, 128.42, 126.22, 46.71 (br), 42.91, 38.80, 38.09, 37.84, 32.65, 32.01, 29.75, 26.32, 26.08.

(3-(((Cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)(4-(2-methoxybenzyl)piperidin-1-yl)-methanone (51)



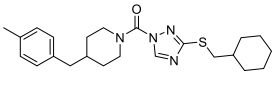
36 (1.7 eq, 461 mg, 2.34 mmol) was reacted with **90** (1 eq, 275 mg, 1.34 mmol) according to General procedure C. The residue was purified by flash column chromatography (0 → 20% EtOAc in pentane) yielding the title compound as a colorless oil (417 mg, 0.97 mmol, 72%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.20 (td, *J* = 7.8, 1.8 Hz, 1H), 7.06 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.92 – 6.83 (m, 2H), 4.71 – 4.30 (m, 2H), 3.82 (s, 3H), 3.02 (d, *J* = 6.8 Hz, 2H), 3.00 – 2.86 (m, 2H), 2.59 (d, *J* = 7.1 Hz, 2H), 1.94 – 1.80 (m, 3H), 1.77 – 1.70 (m, 4H), 1.70 – 1.58 (m, 2H), 1.37 (qd, *J* = 12.4, 4.2 Hz, 2H), 1.30 – 1.09 (m, 3H), 1.00 (qd, *J* = 12.0, 3.4 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.24, 157.64, 148.35, 147.33, 130.98, 128.23, 127.53, 120.30, 110.41, 55.32, 38.83, 37.88, 37.00, 36.44, 32.68, 32.16, 26.36, 26.11.

(3-(((Cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)(4-(4-methoxybenzyl)piperidin-1-yl)-methanone (52)



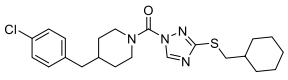
36 (1.5 eq, 264 mg, 1.34 mmol) was reacted with **91** (1 eq, 183 mg, 0.89 mmol) according to General procedure C. The residue was purified by flash column chromatography (20% EtOAc in pentane) yielding the title compound as a gray oil (157 mg, 0.37 mmol, 41%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.09 – 7.01 (m, 2H), 6.87 – 6.79 (m, 2H), 4.71 – 4.36 (m, 2H), 3.79 (s, 3H), 3.02 (d, *J* = 6.8 Hz, 2H), 2.99 – 2.86 (m, 2H), 2.52 (d, *J* = 6.9 Hz, 2H), 1.94 – 1.85 (m, 2H), 1.85 – 1.69 (m, 6H), 1.69 – 1.59 (m, 1H), 1.41 – 1.27 (m, 2H), 1.30 – 1.09 (m, 3H), 1.00 (qd, *J* = 12.0, 3.2 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.27, 158.06, 148.31, 147.32, 131.78, 130.01, 113.80, 55.30, 47.31, 41.98, 38.81, 38.24, 37.84, 32.65, 31.97, 26.33, 26.08.

(3-(((Cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)(4-(4-methylbenzyl)piperidin-1-yl)-methanone (53)



36 (1.5 eq, 680 mg, 3.45 mmol) was reacted with **92** (1 eq, 435 mg, 2.30 mmol) according to General procedure C. The residue was purified by flash column chromatography (0 → 20% EtOAc in pentane) yielding the title compound as a yellow oil (305 mg, 0.74 mmol, 32%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.15 – 7.07 (m, 2H), 7.06 – 6.99 (m, 2H), 4.73 – 4.29 (m, 2H), 3.01 (d, *J* = 6.8 Hz, 2H), 2.99 – 2.88 (m, 2H), 2.54 (d, *J* = 6.9 Hz, 2H), 2.32 (s, 3H), 1.95 – 1.85 (m, 2H), 1.85 – 1.79 (m, 1H), 1.79 – 1.69 (m, 4H), 1.69 – 1.58 (m, 2H), 1.36 (qd, *J* = 12.5, 4.7 Hz, 2H), 1.29 – 1.09 (m, 3H), 0.99 (qd, *J* = 11.9, 3.4 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.24, 148.27, 147.30, 136.62, 135.63, 129.06, 128.98, 47.27 (br), 42.43, 38.78, 38.12, 37.82, 32.62, 31.99, 26.30, 26.06, 21.05.

(4-(4-Chlorobenzyl)piperidin-1-yl)(3-((cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)-methanone (54)

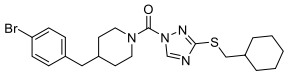


36 (17 mg, 0.086 mmol) was reacted with **102** (1.1 eq, 20 mg, 0.095 mmol) according to General procedure C. The residue was purified by flash column chromatography (0 → 30% EtOAc in pentane) yielding the title compound as a white gum (29 mg, 0.067 mmol, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.30 – 7.22 (m, 2H), 7.11 – 7.03 (m, 2H), 4.85 – 4.27 (m, 2H), 3.02 (d, *J* = 6.9 Hz, 2H), 2.99 – 2.89 (m, 2H), 2.56 (d, *J* = 7.0 Hz, 2H), 1.94 – 1.86 (m, 2H), 1.86 – 1.76 (m, 1H), 1.81 – 1.70 (m, 6H), 1.69 – 1.57 (m, 1H), 1.35 (qd, *J* = 12.5, 4.1 Hz, 2H), 1.24 – 1.08 (m, 2H), 1.00 (qd, *J* = 12.0, 3.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.40, 148.36, 147.39, 138.22, 132.08, 130.48, 128.61, 42.28, 38.87, 38.08, 37.90, 32.71, 31.98, 29.82, 26.37, 26.13.

(4-(4-Bromobenzyl)piperidin-1-yl)(3-((cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)-methanone (55)

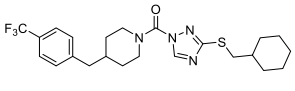


36 (1.7 eq, 233 mg, 1.18 mmol) was reacted with **93** (1 eq, 200 mg, 0.69 mmol) according to General procedure C. The residue was purified by flash column chromatography (20% EtOAc in pentane) yielding the title compound as a colorless oil (140 mg, 0.29 mmol, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.44 – 7.37 (m, 2H), 7.06 – 6.97 (m, 2H), 4.86 – 4.26 (m, 2H), 3.02 (d, *J* = 6.8 Hz, 2H), 2.99 – 2.88 (m, 2H), 2.54 (d, *J* = 7.0 Hz, 2H), 1.93 – 1.85 (m, 2H), 1.86 – 1.75 (m, 1H), 1.79 – 1.69 (m, 4H), 1.69 – 1.57 (m, 2H), 1.35 (qd, *J* = 13.1, 4.3 Hz, 2H), 1.21 (tdd, *J* = 19.3, 13.7, 10.3 Hz, 3H), 1.00 (qd, *J* = 12.1, 3.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.38, 148.33, 147.36, 138.72, 131.54, 130.86, 120.07, 42.31, 38.85, 37.99, 37.88, 32.68, 31.96, 26.35, 26.11.

(3-((Cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone (56)

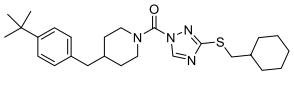


36 (1.5 eq, 153 mg, 0.78 mmol) was reacted with **94** (1 eq, 126 mg, 0.52 mmol) according to General procedure C. The residue was purified by flash column chromatography (20% EtOAc in pentane) yielding the title compound as a yellowish oil (150 mg, 0.32 mmol, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.30 – 7.24 (m, 2H), 4.85 – 4.26 (m, 2H), 3.02 (d, *J* = 6.8 Hz, 2H), 3.00 – 2.89 (m, 2H), 2.65 (d, *J* = 7.2 Hz, 2H), 1.94 – 1.79 (m, 3H), 1.79 – 1.57 (m, 6H), 1.38 (qd, *J* = 12.7, 4.0 Hz, 2H), 1.26 – 1.07 (m, 3H), 1.00 (qd, *J* = 12.0, 3.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.43, 148.34, 147.38, 143.92 (q, *J* = 1.2 Hz), 129.44, 128.95 (q, *J* = 32.3 Hz), 125.42 (q, *J* = 3.8 Hz), 124.36 (q, *J* = 271.7 Hz), 42.73, 38.85, 37.95, 37.89, 32.68, 31.98, 26.34, 26.11.

(4-(4-(*tert*-Butyl)benzyl)piperidin-1-yl)(3-((cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)-methanone (57)

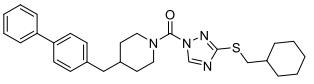


36 (1.5 eq, 320 mg, 1.62 mmol) was reacted with **96** (1 eq, 250 mg, 1.08 mmol) according to General procedure C. The residue was purified by flash column chromatography (0 → 20% EtOAc in pentane) yielding the title compound as a yellowish oil (132 mg, 0.29 mmol, 27%).

Analytical data on next page.

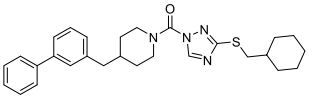
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.35 – 7.26 (m, 2H), 7.11 – 7.03 (m, 2H), 4.69 – 4.33 (m, 2H), 3.73 – 3.45 (m, 2H), 3.02 (d, *J* = 6.9 Hz, 2H), 2.99 – 2.89 (m, 2H), 2.55 (d, *J* = 7.0 Hz, 2H), 1.95 – 1.86 (m, 2H), 1.86 – 1.77 (m, 2H), 1.77 – 1.69 (m, 2H), 1.69 – 1.57 (m, 2H), 1.37 (qd, *J* = 12.4, 3.7 Hz, 2H), 1.31 (s, 9H), 1.25 – 1.09 (m, 2H), 1.00 (qd, *J* = 11.9, 3.1 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.28, 149.01, 148.33, 147.32, 136.67, 128.79, 125.29, 47.34 (br), 43.66, 42.37, 38.82, 38.05, 37.86, 32.67, 32.06 (br), 31.47, 26.34, 26.10.

(4-([1,1'-Biphenyl]-4-ylmethyl)piperidin-1-yl)(3-((cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)methanone (58)



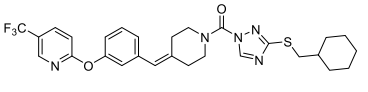
36 (1 eq, 50 mg, 0.24 mmol) was reacted with **104** (1.2 eq, 79 mg, 0.31 mmol) according to General procedure C. The residue was purified by flash column chromatography (0 → 40% Et_2O in pentane) afforded the title compound (20 mg, 0.042 mmol, 17%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.62 – 7.56 (m, 2H), 7.56 – 7.50 (m, 2H), 7.48 – 7.39 (m, 2H), 7.39 – 7.29 (m, 1H), 7.26 – 7.17 (m, 2H), 4.78 – 4.31 (m, 2H), 3.02 (d, *J* = 6.8 Hz, 2H), 3.07 – 2.89 (m, 2H), 2.63 (d, *J* = 7.0 Hz, 2H), 1.93 – 1.86 (m, 3H), 1.86 – 1.77 (m, 2H), 1.77 – 1.70 (m, 2H), 1.69 – 1.58 (m, 1H), 1.40 (qd, *J* = 12.8, 4.2 Hz, 2H), 1.17 (m, 4H), 1.00 (qd, *J* = 12.2, 3.0 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.37, 148.39, 147.39, 140.99, 139.25, 138.92, 129.61, 128.88, 127.27, 127.20, 127.09, 42.60, 38.88, 38.16, 37.90, 32.71, 32.10, 26.38, 26.14.

(4-([1,1'-Biphenyl]-3-ylmethyl)piperidin-1-yl)(3-((cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)methanone (59)



36 (1.5 eq, 206 mg, 1.04 mmol) was reacted with **97** (1 eq, 175 mg, 0.70 mmol) according to General procedure C. The residue was purified by flash column chromatography (10 → 30% EtOAc in pentane) yielding the title compound as a gray oil (280 mg, 0.59 mmol, 85%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.61 – 7.54 (m, 2H), 7.48 – 7.39 (m, 3H), 7.38 – 7.30 (m, 2H), 7.18 – 7.13 (m, 1H), 7.13 – 7.08 (m, 1H), 4.76 – 4.29 (m, 2H), 3.01 (d, *J* = 6.8 Hz, 2H), 2.98 – 2.87 (m, 2H), 2.63 (d, *J* = 7.0 Hz, 2H), 1.92 – 1.82 (m, 3H), 1.82 – 1.74 (m, 2H), 1.74 – 1.67 (m, 2H), 1.68 – 1.57 (m, 2H), 1.38 (qd, *J* = 12.6, 4.1 Hz, 2H), 1.28 – 1.08 (m, 3H), 0.98 (qd, *J* = 12.0, 3.4 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.26, 148.26, 147.30, 141.36, 141.12, 140.24, 128.81, 128.79, 128.04, 127.91, 127.35, 127.16, 125.06, 42.97, 38.76, 38.09, 37.81, 32.60, 32.01, 26.28, 26.04.

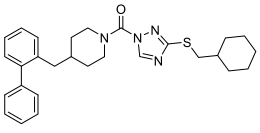
(3-((Cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)(4-(3-((5-(trifluoromethyl)pyridin-2-yl)oxy)-benzylidene)piperidin-1-yl)methanone (60)



36 (21 mg, 0.11 mmol) was reacted with **105** (1.3 eq, 46 mg, 0.14 mmol) according to General procedure C. The residue was purified by flash column chromatography (10 → 40%) yielding the title compound as gray oil (38 mg, 0.068 mmol, 64%).

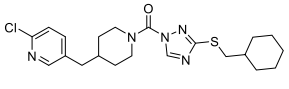
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.44 (m, 1H), 7.92 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.14 – 7.07 (m, 1H), 7.07 – 6.97 (m, 3H), 6.44 (s, 1H), 4.11 – 3.54 (m, 4H), 3.03 (d, *J* = 6.8 Hz, 2H), 2.71 – 2.63 (m, 2H), 2.52 (t, *J* = 5.9 Hz, 2H), 1.94 – 1.82 (m, 2H), 1.73 (dt, *J* = 11.7, 3.0 Hz, 2H), 1.71 – 1.58 (m, 2H), 1.34 – 1.17 (m, 2H), 1.21 – 1.10 (m, 1H), 1.00 (qd, *J* = 11.9, 3.3 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.80, 163.61, 153.16, 148.36, 147.47, 145.59 (q, *J* = 4.5 Hz), 138.96, 137.51, 136.86 (q, *J* = 3.2 Hz), 129.74, 126.17, 125.08, 121.93 (q, *J* = 87.1 Hz), 121.91, 119.79, 111.56, 38.85, 37.90, 32.70, 26.34, 26.11.

(4-([1,1'-Biphenyl]-2-ylmethyl)piperidin-1-yl)(3-((cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)methanone (61)



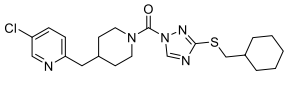
36 (1.5 eq, 206 mg, 1.04 mmol) was reacted with **98** (1 eq, 175 mg, 0.70 mmol) according to General procedure C. The residue was purified by flash column chromatography (10 → 30% EtOAc in pentane) yielding the title compound as a gray oil (220 mg, 0.46 mmol, 67%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.44 – 7.37 (m, 2H), 7.37 – 7.32 (m, 1H), 7.32 – 7.23 (m, 5H), 7.23 – 7.19 (m, 1H), 4.58 – 4.19 (m, 2H), 3.00 (d, *J* = 6.7 Hz, 2H), 2.91 – 2.73 (m, 2H), 2.62 (d, *J* = 7.0 Hz, 2H), 1.93 – 1.82 (m, 2H), 1.76 – 1.68 (m, 2H), 1.69 – 1.59 (m, 3H), 1.59 – 1.51 (m, 2H), 1.25 – 1.07 (m, 5H), 0.99 (qd, *J* = 12.4, 3.4 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.22, 148.22, 147.31, 142.44, 141.86, 137.27, 130.33, 129.95, 129.32, 128.23, 127.37, 127.00, 126.17, 39.43, 38.79, 37.86, 37.48, 32.66, 31.90 (br), 26.33, 26.09.

(4-((6-Chloropyridin-3-yl)methyl)piperidin-1-yl)(3-((cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)methanone (62)



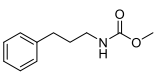
36 (1.5 eq, 155 mg, 0.78 mmol) was reacted with **99** (1 eq, 110 mg, 0.52 mmol) according to General procedure C. The residue was purified by flash column chromatography (20 → 40% EtOAc in pentane) yielding the title compound as a colorless oil (150 mg, 0.35 mmol, 66%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 – 8.71 (m, 1H), 8.54 (q, *J* = 2.5 Hz, 1H), 7.62 (dt, *J* = 8.0, 2.2 Hz, 1H), 7.12 (dt, *J* = 8.3, 1.8 Hz, 1H), 4.74 – 4.33 (m, 2H), 3.04 – 2.99 (m, 2H), 3.12 – 2.92 (m, 2H), 2.77 (d, *J* = 7.2 Hz, 2H), 2.20 – 2.09 (m, 1H), 1.92 – 1.82 (m, 2H), 1.80 – 1.54 (m, 6H), 1.49 – 1.34 (m, 2H), 1.31 – 1.09 (m, 3H), 1.06 – 0.91 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.13, 156.86, 148.12, 147.56, 147.25, 136.26, 129.84, 124.52, 43.80, 38.67, 37.63, 36.38, 32.46, 31.73 (br), 26.13, 26.11.

(4-((5-Chloropyridin-2-yl)methyl)piperidin-1-yl)(3-((cyclohexylmethyl)thio)-1*H*-1,2,4-triazol-1-yl)methanone (63)



36 (1.5 eq, 155 mg, 0.78 mmol) was reacted with **100** (1 eq, 110 mg, 0.52 mmol) according to General procedure C. The residue was purified by flash column chromatography (20 → 40% EtOAc in pentane) yielding the title compound as a colorless oil (175 mg, 0.40 mmol, 77%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 1.8 Hz, 1H), 8.26 – 8.21 (m, 1H), 7.50 (dt, *J* = 8.2, 2.1 Hz, 1H), 7.30 (dd, *J* = 8.3, 2.5 Hz, 1H), 4.73 – 4.44 (m, 2H), 3.02 (d, *J* = 6.9 Hz, 2H), 3.05 – 2.89 (m, 2H), 2.60 (d, *J* = 7.1 Hz, 2H), 1.93 – 1.81 (m, 3H), 1.80 – 1.54 (m, 6H), 1.46 – 1.32 (m, 2H), 1.31 – 1.09 (m, 3H), 1.05 – 0.90 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.27, 149.72, 149.29, 148.15, 147.31, 139.59, 134.05, 124.09, 38.91, 38.71, 37.66, 37.51, 32.50, 31.63 (br), 26.14, 26.12.

Methyl (3-phenylpropyl)carbamate (65)

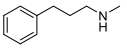


To an ice-cold solution of 3-phenylpropylamine (**64**, 84 µL, 0.59 mmol) and DIPEA (2 eq, 206 µL, 1.19 mmol) in DCM (5 mL), methyl chloroformate (1.5 eq, 84 µL, 0.89 mmol) was added. The mixture was allowed to warm to RT and stirred for 2 h. After full reaction conversion the mixture was washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Flash column chromatography (0-30% EtOAc in pentane) afforded the title compound (96 mg, 0.50 mmol, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 3H), 7.21 – 7.11 (m, 2H), 4.73 (s, 1H), 3.65 (s, 3H), 3.20 (q, *J* = 6.7 Hz, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 1.82 (p, *J* = 7.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.25, 141.51, 128.54, 128.45, 126.07, 52.10, 40.73, 33.11, 31.71.

***N*-methyl-3-phenylpropylamine (66)**

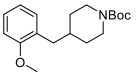


To an ice-cold solution of **65** (96 mg, 0.50 mmol) in dry THF (10 mL), $LiALH_4$ (3 eq, 1.5 mL 1 M in THF, 1.50 mmol) was added dropwise, after which the reaction mixture was heated to reflux for 72 h. The mixture was cooled on ice, diluted with Et_2O and quenched with water and 15% aq. NaOH. It was then warmed to RT, dried over $MgSO_4$, filtrated and concentrated *in vacuo*. For flash column chromatography a solution of 10% sat. aq. NH_4OH in MeOH was prepared. Elution with 10% of this solution in DCM afforded the title compound as yellow oil (46 mg, 0.31 mmol, 62%).

^{1}H NMR (400 MHz, MeOD) δ 7.32 – 7.22 (m, 2H), 7.22 – 7.11 (m, 3H), 2.70 – 2.54 (m, 4H), 2.39 (s, 3H), 1.88 – 1.78 (m, 2H).

^{13}C NMR (101 MHz, MeOD) δ 143.16, 129.41, 129.36, 126.94, 51.89, 35.72, 34.40, 31.74.

***tert*-Butyl 4-(2-methoxybenzyl)piperidine-1-carboxylate (79)**

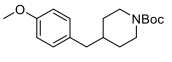


N-Boc 4-methylenepiperidine (**67**, 1 eq, 300 µL, 1.48 mmol) was coupled to 2-bromoanisole (**68**, 2 eq, 381 µL, 3.06 mmol) according to General procedure B. Flash column chromatography (2% EtOAc in pentane) afforded the title compound as colorless oil (410 mg, 1.34 mmol, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (td, *J* = 7.9, 1.8 Hz, 1H), 7.06 (dd, *J* = 7.3, 1.8 Hz, 1H), 6.91 – 6.81 (m, 2H), 4.10 – 4.00 (m, 2H), 3.81 (s, 3H), 2.63 (td, *J* = 12.9, 2.6 Hz, 2H), 2.54 (d, *J* = 7.1 Hz, 2H), 1.78 – 1.62 (m, 1H), 1.63 – 1.55 (m, 2H), 1.45 (s, 9H), 1.16 (qd, *J* = 12.3, 4.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.73, 155.05, 131.05, 128.83, 127.32, 120.25, 110.40, 79.26, 55.36, 44.15, 37.27, 36.69, 32.24, 28.62.

***tert*-Butyl 4-(4-methoxybenzyl)piperidine-1-carboxylate (80)**

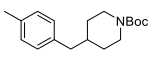


N-Boc 4-methylenepiperidine (**67**, 1.5 eq, 700 µL, 3.44 mmol) was coupled to 4-bromoanisole (**69**, 1 eq, 286 µL, 2.30 mmol) according to General procedure B. Flash column chromatography (2% EtOAc in pentane) afforded the title compound as colorless oil (701 mg, 2.30 mmol, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.97 (m, 2H), 6.83 – 6.75 (m, 2H), 4.20 – 3.93 (m, 2H), 3.73 (s, 3H), 2.65 – 2.54 (m, 2H), 2.43 (d, *J* = 6.8 Hz, 2H), 1.63 – 1.53 (m, 3H), 1.44 (s, 9H), 1.09 (qd, *J* = 12.1, 4.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.66, 154.48, 131.87, 129.71, 113.38, 78.77, 54.81, 41.95, 38.06, 31.69, 28.22.

***tert*-Butyl 4-(4-methylbenzyl)piperidine-1-carboxylate (81)**

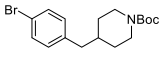


N-Boc 4-methylenepiperidine (**67**, 1.3 eq, 700 µL, 3.44 mmol) was coupled to 4-iodotoluene (**70**, 1 eq, 293 µL, 2.25 mmol) according to General procedure B. Flash column chromatography (2% EtOAc in pentane) afforded the title compound as orange oil (500 mg, 1.73 mmol, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 – 7.05 (m, 2H), 7.05 – 6.98 (m, 2H), 4.19 – 3.94 (m, 2H), 2.68 – 2.56 (m, 2H), 2.49 (d, *J* = 6.8 Hz, 2H), 2.31 (s, 3H), 1.93 – 1.77 (m, 1H), 1.72 – 1.56 (m, 2H), 1.45 (s, 9H), 1.13 (qd, *J* = 12.8, 5.9 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.93, 137.17, 135.40, 129.04, 128.97, 79.25, 42.75, 38.30, 32.11, 28.52, 21.06.

***tert*-Butyl 4-(4-bromobenzyl)piperidine-1-carboxylate (82)**

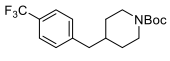


N-Boc 4-methylenepiperidine (**67**, 1 eq, 300 µL, 1.48 mmol) was coupled to 1-bromo-4-iodobenzene (**71**, 3.3 eq, 2.10 g, 7.42 mmol) according to General procedure B. Flash column chromatography (2% EtOAc in pentane) afforded the title compound as brown wax (230 mg, 0.65 mmol, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 2H), 7.03 – 6.98 (m, 2H), 4.07 (dt, *J* = 13.7, 3.0 Hz, 2H), 2.62 (td, *J* = 13.2, 2.6 Hz, 2H), 2.48 (d, *J* = 6.9 Hz, 2H), 1.73 – 1.54 (m, 3H), 1.45 (s, 9H), 1.13 (qd, *J* = 12.3, 4.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.95, 139.26, 131.42, 130.94, 119.84, 79.41, 44.00 (br), 42.61, 38.17, 31.98, 28.57.

***tert*-Butyl 4-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (83)**

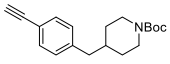


N-Boc 4-methylenepiperidine (**67**, 1 eq, 303 µL, 1.49 mmol) was coupled to 1-iodo-4-(trifluoromethyl)benzene (**72**, 1.5 eq, 332 µL, 2.26 mmol) according to General procedure B. Flash column chromatography (2 → 5% EtOAc in pentane) afforded the title compound as brown wax (510 mg, 1.49 mmol, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 4.24 – 3.91 (m, 2H), 2.72 – 2.54 (m, 2H), 2.59 (d, *J* = 7.2 Hz, 2H), 1.72 – 1.63 (m, 1H), 1.64 – 1.55 (m, 2H), 1.45 (s, 9H), 1.15 (qd, *J* = 12.3, 4.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.92, 144.46 (q, *J* = 1.5 Hz), 129.47, 128.44 (q, *J* = 32.3 Hz), 125.26 (q, *J* = 3.8 Hz), 124.42 (q, *J* = 271.7 Hz), 79.41, 43.00, 38.10, 31.97, 28.53.

***tert*-Butyl 4-(4-ethynylbenzyl)piperidine-1-carboxylate (84)**

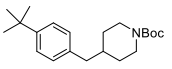


N-Boc 4-methylenepiperidine (**67**, 1 eq, 300 µL, 1.48 mmol) was coupled to 1-bromo-4-ethynylbenzene (**73**, 1.1 eq, 410 mg, 2.27 mmol) according to General procedure B. Flash column chromatography (1 → 3% EtOAc in pentane) afforded the title compound as colorless oil (95 mg, 0.32 mmol, 22%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.11 – 7.05 (m, 2H), 4.17 – 3.96 (m, 2H), 3.04 (s, 1H), 2.62 (td, *J* = 12.4, 12.4, 2.8 Hz, 2H), 2.52 (d, *J* = 7.0 Hz, 2H), 1.72 – 1.57 (m, 1H), 1.62 – 1.54 (m, 2H), 1.45 (s, 9H), 1.13 (qd, *J* = 12.5, 4.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.87, 141.28, 132.08, 129.16, 119.76, 83.71, 79.31, 76.88, 43.97 (br), 43.08, 38.08, 31.97, 28.52.

***tert*-Butyl 4-(4-(*tert*-butyl)benzyl)piperidine-1-carboxylate (85)**

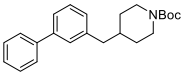


N-Boc 4-methylenepiperidine (**67**, 1 eq, 300 µL, 1.48 mmol) was coupled to 4-*tert*-butyliodobenzene (**74**, 1.2 eq, 320 µL, 1.81 mmol) according to General procedure B. Flash column chromatography (1 → 2% EtOAc in pentane) afforded the title compound as colorless oil (285 mg, 0.86 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.10 – 7.03 (m, 2H), 4.11 – 4.02 (m, 2H), 2.63 (td, *J* = 13.2, 2.5 Hz, 2H), 2.50 (d, *J* = 6.8 Hz, 2H), 1.72 – 1.58 (m, 3H), 1.45 (s, 9H), 1.31 (s, 9H), 1.14 (qd, *J* = 12.4, 4.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.04, 148.84, 137.28, 128.90, 125.23, 79.33, 44.13, 42.73, 38.24, 34.50, 32.14, 31.55, 28.61.

***tert*-Butyl 4-([1,1'-biphenyl]-3-ylmethyl)piperidine-1-carboxylate (86)**

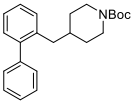


N-Boc 4-methylenepiperidine (**67**, 1 eq, 300 µL, 1.48 mmol) was coupled to 3-bromo-1,1′-biphenyl (**75**, 1.5 eq, 376 µL, 2.25 mmol) according to General procedure B. Flash column chromatography (2 → 3% EtOAc in pentane) afforded the title compound as yellow oil (450 mg, 1.28 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.51 (m, 2H), 7.42 – 7.34 (m, 3H), 7.34 – 7.32 (m, 1H), 7.32 – 7.23 (m, 2H), 7.10 – 7.02 (m, 1H), 4.19 – 3.92 (m, 2H), 2.65 – 2.49 (m, 2H), 2.53 (d, *J* = 7.2 Hz, 2H), 1.70 – 1.55 (m, 3H), 1.44 (s, 9H), 1.17 – 1.04 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.50, 140.97, 140.95, 140.44, 128.51, 128.46, 127.85, 127.69, 127.01, 126.90, 124.59, 78.83, 43.01, 37.96, 31.79, 28.24.

***tert*-Butyl 4-([1,1'-biphenyl]-2-ylmethyl)piperidine-1-carboxylate (87)**

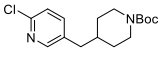


N-Boc 4-methylenepiperidine (**67**, 1 eq, 348 µL, 1.71 mmol) was coupled to 2-iodo-1,1′-biphenyl (**76**, 1.3 eq, 396 µL, 2.25 mmol) according to General procedure B. Flash column chromatography (0 → 4% EtOAc in pentane) afforded the title compound as colorless oil (600 mg, 1.71 mmol, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 2H), 7.32 – 7.28 (m, 1H), 7.28 – 7.21 (m, 4H), 7.21 – 7.12 (m, 2H), 3.97 – 3.92 (m, 2H), 2.54 (d, *J* = 6.9 Hz, 2H), 2.51 – 2.44 (m, 2H), 1.89 – 1.79 (m, 1H), 1.56 – 1.44 (m, 2H), 1.41 (s, 9H), 0.92 (qd, *J* = 12.4, 4.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.62, 142.26, 141.84, 137.55, 130.02, 129.81, 129.18, 127.95, 127.08, 126.69, 125.77, 78.95, 41.79, 39.55, 37.54, 31.77, 28.35.

***tert*-Butyl 4-((6-chloropyridin-3-yl)methyl)piperidine-1-carboxylate (88)**

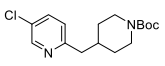


N-Boc 4-methylenepiperidine (**67**, 1 eq, 315 µL, 1.55 mmol) was coupled to 2-chloro-5-iodopyridine (**77**, 1.2 eq, 433 mg, 1.81 mmol) according to General procedure B. Flash column chromatography (5 → 10% EtOAc in pentane) afforded the title compound as white solid (482 mg, 1.55 mmol, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (t, *J* = 2.2 Hz, 1H), 7.45 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.26 (dd, *J* = 8.1, 1.7 Hz, 1H), 4.19 – 3.97 (m, 2H), 2.70 – 2.58 (m, 2H), 2.53 (d, *J* = 6.9 Hz, 2H), 1.93 – 1.75 (m, 1H), 1.64 – 1.56 (m, 2H), 1.48 – 1.40 (m, 9H), 1.19 – 1.08 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.72, 149.98, 149.17, 139.38, 134.35, 123.85, 79.37, 39.21, 37.78, 31.68, 28.40.

tert-Butyl 4-((5-chloropyridin-2-yl)methyl)piperidine-1-carboxylate (89)

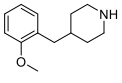


N-Boc 4-methylenepiperidine (**68**, 1 eq, 300 µL, 1.48 mmol) was coupled to 2-bromo-5-chloropyridine (**78**, 1.5 eq, 439 µL, 2.28 mmol) according to General procedure B. Flash column chromatography (0 → 20% EtOAc in pentane) afforded the title compound as colorless oil (400 mg, 1.29 mmol, 87%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.50 (s, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 4.15 – 4.00 (m, 2H), 2.68 (d, *J* = 6.4 Hz, 2H), 2.00 – 1.86 (m, 1H), 1.59 (d, *J* = 13.1 Hz, 2H), 1.45 (s, 9H), 1.26 – 1.13 (m, 2H).

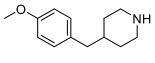
^{13}C NMR (101 MHz, CDCl3) δ 158.33, 154.72, 148.05, 135.87, 129.47, 124.34, 79.15, 43.29, 42.39, 36.68, 31.81, 28.38.

4-(2-Methoxybenzyl)piperidine (90)



79 (410 mg, 1.34 mmol) was dissolved in 1,4-dioxane containing 4 M HCl (10 mL) and the mixture was stirred for 16 h. All volatiles were removed *in vacuo*. The residue was dissolved in 5 M aq. KOH and extracted with DCM and $CHCl_3$. The combined organic layers were concentrated *in vacuo*, affording the title compound as yellowish wax (275 mg, 1.34 mmol, quant.), which was used immediately in the next reaction.

4-(4-Methoxybenzyl)piperidine (91)

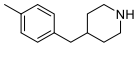


80 (273 mg, 0.89 mmol) was dissolved in 1,4-dioxane containing 4 M HCl (5 mL) and the mixture was stirred for 18 h. All volatiles were removed *in vacuo*. The residue was dissolved in 5 M aq. KOH and extracted with DCM. The combined organic layers were concentrated *in vacuo*, affording the title compound as yellow wax (183 mg, 0.89 mmol, quant.).

^{1}H NMR (400 MHz, MeOD) δ 7.09 – 7.00 (m, 2H), 6.86 – 6.77 (m, 2H), 3.76 (s, 3H), 3.11 – 3.02 (m, 2H), 2.58 (td, *J* = 12.5, 2.5 Hz, 2H), 2.48 (d, *J* = 6.8 Hz, 2H), 1.73 – 1.65 (m, 2H), 1.65 – 1.55 (m, 1H), 1.26 – 1.12 (m, 2H).

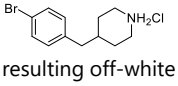
^{13}C NMR (101 MHz, MeOD) δ 158.75, 132.80, 130.65, 114.30, 55.55, 46.31, 43.07, 38.52, 32.48.

4-(4-Methylbenzyl)piperidine (92)



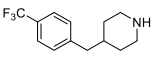
81 (500 mg, 1.73 mmol) was dissolved in 1,4-dioxane containing 4 M HCl (5 mL) and the mixture was stirred for 16 h. All volatiles were removed *in vacuo*. The residue was dissolved in 5 M aq. KOH and extracted with DCM. The combine organic layers were concentrated *in vacuo*, affording the title compound as orange oil (327 mg, 1.73 mmol, quant.), which was used immediately in the next reaction.

4-(4-Bromobenzyl)piperidin-1-ium chloride (93)



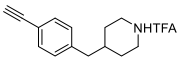
82 (230 mg, 0.65 mmol) was dissolved in 1,4-dioxane containing 4 M HCl (5 mL) and the mixture was stirred for 3 h. All volatiles were removed *in vacuo*. The resulting off-white solid was used immediately in the next reaction.

4-(4-(Trifluoromethyl)benzyl)piperidine (94)



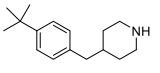
83 (250 mg, 0.73 mmol) was dissolved in 1,4-dioxane (8 mL). To this HCl (20 eq, 3.64 mL 4 M in 1,4-dioxane) was added and the mixture was stirred for 28 h. All volatiles were removed *in vacuo*. The resulting off-white solid was dissolved in EtOAc and extracted with 1 M aq. HCl. The pH of the aquous layer was set to 14 with 5 M aq. NaOH, after which the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtrated and concentrated *in vacuo*, affording the title compound as off-white oil (126 mg, 0.52 mmol, 71%), which was used immediately in the next reaction.

4-(4-Ethynylbenzyl)piperidin-1-ium 2,2,2-trifluoroacetate (95)



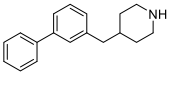
84 (20 mg, 0.067 mmol) was dissolved in dry DCM (2 mL) and cooled on ice. TFA (10 eq, 51 µL, 0.67 mmol) was added dropwise, after which the mixture was allowed to warm to RT and stirred overnight. When TLC showed full conversion all volatiles were removed *in vacuo*. The residue was used immediately in the next reaction

4-(4-(*tert*-Butyl)benzyl)piperidine (96)



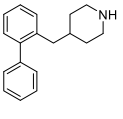
85 (270 mg, 0.81 mmol) was dissolved in 1,4-dioxane (8 mL). To this HCl (10 eq, 2.0 mL 4 M in 1,4-dioxane, 8.1 mmol) was added and the mixture was stirred for 5 h. All volatiles were removed *in vacuo*. $CHCl_3$ (5 mL) and 5 M aq. KOH (5 mL) were added to the resulting white solid and the layers were separated. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were concentrated *in vacuo*, affording the title compound as yellow oil (188 mg, 0.76 mmol, 93%), which was used immediately in the next reaction.

4-([1,1'-Biphenyl]-3-ylmethyl)piperidine (97)



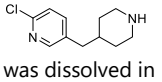
86 (450 mg, 1.28 mmol) was dissolved in 1,4-dioxane containing 4 M HCl (5 mL) and the mixture was stirred for 21 h. All volatiles were removed *in vacuo*. The residue was dissolved in 1 M aq. HCl and washed with $CHCl_3$. The pH of the aqueous layer was set to 14 with 5 M aq. KOH, after which the aquous layer was extracted with $CHCl_3$. The combined organic layers were concentrated *in vacuo*, affording the title compound as yellow oil (247 mg, 0.98 mmol, 77%), which was used immediately in the next reaction.

4-([1,1'-Biphenyl]-2-ylmethyl)piperidine (98)



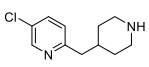
87 (600 mg, 1.71 mmol) was dissolved in 1,4-dioxane containing 4 M HCl (5 mL) and the mixture was stirred for 16 h. All volatiles were removed *in vacuo*. The residue was dissolved in 1 M aq. HCl and washed with $CHCl_3$. The pH of the aqueous layer was set to 14 with 5 M aq. KOH, after which the aquous layer was extracted with $CHCl_3$. The combined organic layers were concentrated *in vacuo*, affording the title compound as yellow oil (350 mg, 1.39 mmol, 82%), which was used immediately in the next reaction.

2-Chloro-5-(piperidin-4-ylmethyl)pyridine (99)



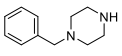
88 (482 mg, 1.55 mmol) was dissolved in 1,4-dioxane containing 4 M HCl (5 mL) and the mixture was stirred for 21 h. All volatiles were removed *in vacuo*. The residue was dissolved in 1 M aq. HCl and washed with $CHCl_3$. The pH of the aqueous layer was set to 14 with 5 M aq. KOH, after which the aquous layer was extracted with $CHCl_3$. The combined organic layers were concentrated *in vacuo*, affording the title compound as yellow oil (247 mg, 1.17 mmol, 76%), which was used immediately in the next reaction.

5-Chloro-2-(piperidin-4-ylmethyl)pyridine (100)



89 (279 mg, 0.90 mmol) was dissolved in 1,4-dioxane containing 4 M HCl (5 mL) and the mixture was stirred for 16 h. All volatiles were removed *in vacuo*. The residue was dissolved in 1 M aq. HCl and washed with $CHCl_3$. The pH of the aqueous layer was set to 14 with 5 M aq. KOH, after which the aquous layer was extracted with $CHCl_3$. The combined organic layers were concentrated *in vacuo*, affording the title compound as colorless oil (190 mg, 0.90 mmol, quant.), which was used immediately in the next reaction.

1-Benzylpiperazine (101)

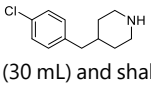


Piperazine (6 eq, 500 mg, 5.80 mmol) was dissolved in dry THF (10 mL) and heated to reflux. To this benzyl chloride (1 eq, 0.11 mL, 0.97 mmol) was added dropwise, leading to formation of white precipitate. After refluxing for 2.5 h full conversion was confirmed using TLC and the mixture was cooled and filtrated. Solids were washed with THF (5 mL) and EtOAc (5 mL) after which the combined filtrates were concentrated *in vacuo*. The resulting white crystalline solid was suspended in 8 mL 1 M aq. KOH + 5% brine and extracted with DCM and EtOAc until the aqueous layer was clear. The combined organic layers were dried over $MgSO_4$, filtrated and concentrated *in vacuo*. For flash column chromatography a 10% sat. aq. NH_4OH solution in MeOH was used. Elution with 0 → 20% of this solution in EtOAc afforded the title compound as colorless oil (145 mg, 0.82 mmol, 85%).

^{1}H NMR (400 MHz, MeOD) δ 7.35 – 7.26 (m, 4H), 7.29 – 7.22 (m, 1H), 3.47 (s, 2H), 2.80 (app. t, *J* = 5.0 Hz, 4H), 2.53 – 2.29 (m, 4H).

^{13}C NMR (101 MHz, MeOD) δ 138.35, 130.63, 129.30, 128.38, 64.48, 54.59, 46.08.

4-(4-Chlorobenzyl)piperidine (102)

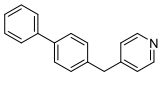


4-(4-Chlorobenzyl)pyridine (1 eq, 1.71 mL, 9.82 mmol), PtO_2 (0.04 eq, 89 mg, 0.39 mmol) and hydrochloric acid (1 eq, 818 µL 12 M, 9.82 mmol) were added to EtOH (30 mL) and shaken for 24 h under 3 bar H_2 in a Parr reaction vessel. Catalyst was removed by filtration and volatiles under reduced pressure. Flash column chromatography (5 → 15% 7 M methanolic ammonia in EtOAc) afforded the title compound as yellow oil (1.79 g, 8.53 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.19 (m, 2H), 7.10 – 7.02 (m, 2H), 3.03 (dt, *J* = 12.6, 3.0 Hz, 2H), 2.54 (td, *J* = 12.3, 2.1 Hz, 2H), 2.49 (d, *J* = 6.5 Hz, 2H), 1.66 (bs, 1H), 1.64 – 1.55 (m, 2H), 1.58 – 1.51 (m, 1H), 1.13 (qd, *J* = 13.8, 13.3, 3.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.09, 131.58, 130.55, 128.31, 46.80, 43.22, 38.48, 33.44.

4-([1,1'-Biphenyl]-4-ylmethyl)pyridine (103)

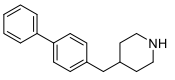


In a MW vial, a solution of 4-(4-chlorobenzyl)pyridine (1 eq, 172 µL, 0.97 mmol) in dry 1,4-dioxane (1.5 mL) was purged with N_2, to which then $CsCO_3$ (1.7 eq, 550 mg, 1.69 mmol), phenylboronic acid (1.6 eq, 193 mg, 1.58 mmol), $Pd_2(dba)_3$ (0.04 eq, 34 mg, 0.037 mmol) and tricyclohexylphosphane (0.09 eq, 24 mg, 0.086 mmol) were sequentially added. The vial was sealed and heated to 100°C overnight. When product formation was confirmed with LC/MS analysis, the mixture was cooled to RT and diluted with EtOAc. Catalyst was removed by filtration and volatiles under reduced pressure. Flash column chromatography (30 → 60% Et_2O in pentane) afforded the title compound (140 mg, 0.57 mmol, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 – 8.48 (m, 2H), 7.60 – 7.48 (m, 4H), 7.47 – 7.38 (m, 2H), 7.37 – 7.29 (m, 1H), 7.27 – 7.19 (m, 2H), 7.16 – 7.10 (m, 2H), 3.99 (s, 2H).

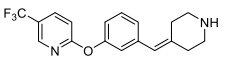
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.86, 150.04, 149.93, 140.76, 139.73, 138.00, 129.54, 128.87, 127.53, 127.37, 127.10, 124.31, 40.94.

4-([1,1'-Biphenyl]-4-ylmethyl)piperidine (104)



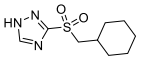
A solution of **103** (1 eq, 89 mg, 0.36 mmol) in EtOH (3 mL) was purged with N_2, to which then PtO_2 (0.05 eq, 4 mg, 0.018 mmol) and hydrochloric acid (1 eq, 30 µL 12 M, 0.36 mmol) were added. The mixture was then purged with H_2 (1 atm) and stirred for 24 h. Catalyst was removed by filtration and volatiles under reduced pressure, affording the title compound which was used immediately in the next reaction.

2-(3-(Piperidin-4-ylidenemethyl)phenoxy)-5-(trifluoromethyl)pyridine (105)



To a solution of *tert*-butyl 4-(3-((5-(trifluoromethyl)pyridin-2-yl)oxy)benzylidene)piperidine-1-carboxylate[58] (98 mg, 0.23 mmol) in 1.5 mL EtOAc, hydrochloric acid (30 eq, 572 µL 12 M, 6.86 mmol) was added dropwise and the mixture was stirred for two days. When TLC analysis showed full conversion the mixture was washed with sat. aq. $NaHCO_3$ followed by extraction with DCM. The combined organic layers were dried over $MgSO_4$, filtrated and concentrated *in vacuo* to afford the title compound which was used immediately in the next reaction.

3-((Cyclohexylmethyl)sulfonyl)-1*H*-1,2,4-triazole (106)

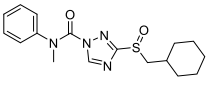


36 (1.20 g, 6.08 mmol) was dissolved in 20 mL dry DCM and cooled on ice. Peracetic acid (5 eq, 30 mmol, 5.8 mL 35% in AcOH) was added dropwise, after which the mixture was allowed to warm to RT and stirred for 72 h. The mixture was diluted with DCM and washed with water. The aqueous layer was extracted with $CHCl_3$ with a little MeOH, after which the combined organic layers were dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Flash column chromatography (0 → 6% MeOH in DCM) afforded the title compound as white crystalline solid (1.08 g, 4.72 mmol, 78%).

^{1}H NMR (400 MHz, MeOD) δ 8.70 (s, 1H), 3.31 (d, *J* = 6.1 Hz, 2H), 2.02 – 1.87 (m, 1H), 1.90 – 1.79 (m, 2H), 1.75 – 1.58 (m, 3H), 1.36 – 1.12 (m, 3H), 1.11 (qd, *J* = 11.8, 3.4 Hz, 2H).

^{13}C NMR (101 MHz, MeOD) δ 162.97, 146.97, 61.81, 33.98, 33.82, 26.83.

3-((Cyclohexylmethyl)sulfinyl)-*N*-methyl-*N*-phenyl-1*H*-1,2,4-triazole-1-carboxamide (107)

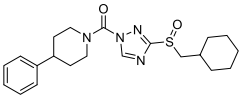


40 (53 mg, 0.16 mmol) was oxidized according to General procedure D. Flash column chromatography (0 → 50% EtOAc in pentane) afforded the title compound as gray gum (42 mg, 0.12 mmol, 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.44 – 7.26 (m, 3H), 7.19 – 7.10 (m, 2H), 3.56 (s, 3H), 2.99 – 2.84 (m, 1H), 2.65 – 2.50 (m, 1H), 1.98 – 1.87 (m, 2H), 1.87 – 1.77 (m, 1H), 1.77 – 1.69 (m, 2H), 1.38 – 1.13 (m, 4H), 1.12 – 0.87 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.23, 148.06, 147.35, 142.62, 129.72, 128.11, 126.10, 61.01, 40.60, 32.24, 32.01, 25.92, 25.81.

(3-((Cyclohexylmethyl)sulfinyl)-1*H*-1,2,4-triazol-1-yl)(4-phenylpiperidin-1-yl)methanone (108)

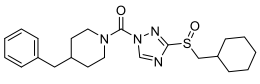


49 (38 mg, 0.099 mmol) was oxidized according General procedure D. Flash column chromatography (0 → 50% EtOAc in pentane) afforded the title compound as white powder (33 mg, 0.082 mmol, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.41 – 7.29 (m, 2H), 7.28 – 7.18 (m, 3H), 4.87 – 4.43 (m, 2H), 3.30 (dd, *J* = 13.0, 5.1 Hz, 1H), 3.37 – 3.05 (m, 2H), 2.99 (dd, *J* = 13.0, 8.7 Hz, 1H), 2.84 (tt, *J* = 12.1, 3.9 Hz, 1H), 2.11 – 1.64 (m, 9H), 1.46 – 1.03 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.72, 148.29, 147.75, 144.48, 128.79, 126.86, 126.80, 61.33, 47.22 (br), 42.41, 33.37, 32.60, 32.27, 29.78, 26.02, 25.97, 25.69.

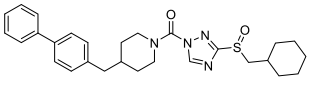
(4-Benzylpiperidin-1-yl)(3-((cyclohexylmethyl)sulfinyl)-1*H*-1,2,4-triazol-1-yl)methanone (109)



50 (51 mg, 0.128 mmol) was oxidized according General procedure D. Flash column chromatography (0 → 50% EtOAc in pentane) afforded the title compound as gray gum (42 mg, 0.101 mmol, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.34 – 7.26 (m, 2H), 7.25 – 7.18 (m, 1H), 7.17 – 7.11 (m, 2H), 4.64 – 4.30 (m, 2H), 3.28 (dd, *J* = 13.1, 5.2 Hz, 1H), 2.97 (dd, *J* = 13.0, 8.8 Hz, 1H), 3.16 – 2.89 (m, 1H), 2.59 (d, *J* = 7.1 Hz, 2H), 2.08 – 2.01 (m, 2H), 2.01 – 1.92 (m, 1H), 1.91 – 1.64 (m, 7H), 1.45 – 1.06 (m, 7H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.56, 148.15, 147.62, 139.57, 129.12, 128.45, 126.27, 61.30, 46.38 (br), 42.75, 37.93, 33.32, 32.55, 32.22, 25.99, 25.93, 25.65.

(4-([1,1'-Biphenyl]-4-ylmethyl)piperidin-1-yl)(3-((cyclohexylmethyl)sulfinyl)-1*H*-1,2,4-triazol-1-yl)methanone (110)



58 (20 mg, 0.042 mmol) was oxidized according to General procedure D. Flash column chromatography (40 → 60% EtOAc in pentane) afforded the title compound as white powder (17 mg, 0.035 mmol, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.61 – 7.56 (m, 2H), 7.56 – 7.50 (m, 2H), 7.47 – 7.40 (m, 2H), 7.34 (tt, *J* = 6.8, 1.2 Hz, 1H), 7.25 – 7.19 (m, 2H), 4.65 – 4.35 (m, 2H), 3.28 (app. dd, *J* = 13.0, 5.2 Hz, 1H), 3.17 – 2.90 (m, 2H), 2.97 (app. dd, *J* = 13.0, 8.8 Hz, 1H), 2.64 (d, *J* = 6.9 Hz, 2H), 2.09 – 2.01 (m, 1H), 2.01 – 1.93 (m, 1H), 1.92 – 1.79 (m, 3H), 1.78 – 1.64 (m, 2H), 1.48 – 1.36 (m, 2H), 1.36 – 1.20 (m, 4H), 1.21 – 1.06 (m, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.64, 147.72, 140.99, 139.33, 138.74, 129.63, 128.89, 127.29, 127.25, 127.11, 61.40, 42.46, 38.03, 33.41, 32.62, 32.29, 26.06, 26.01, 25.73.

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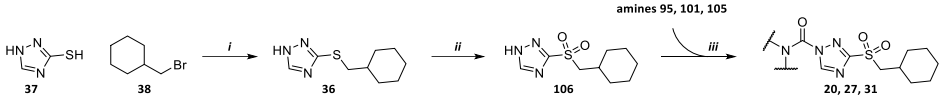
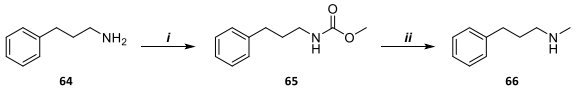
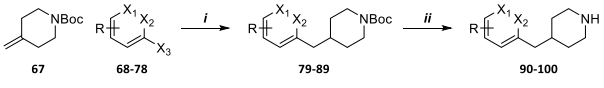
Supplementary Information



Supplementary Scheme S2.1. Alternative synthetic route for PLA2G4E inhibitors. Reagents and conditions: *i*) K_2CO_3, DMF, 6 h RT; *ii*) AcOOH, DCM, 6 h 0°C → RT; *iii*) 1. **95**, **101** or **105**, triphosgene, Et_3N or DIPEA, THF, 3 h 0°C → RT, then 2. **106**, K_2CO_3, DMF, o/n RT.



Supplementary Scheme S2.2. Methylation of 3-phenylpropylamine. Reagents and conditions: *i*) Methyl chloroformate, DIPEA, DCM, 2 h 0°C → RT; *ii*) $LiAlH_4$, THF, 0°C → reflux, 72 h.



Supplementary Scheme S2.3. Synthesis of 4-benzylpiperidine derivatives. Reagents and conditions: *i*) 1. **67**, 9-BBN, THF, 6 h 0°C → RT, then 2. **68**-**78**, $Pd(dppf)Cl_2$, K_2CO_3, THF/DMF/H_2O, o/n reflux. *ii*) HCl, 1,4-dioxane, o/n RT. X_1, X_2 = CH or N, X_3 = I or Br.