Discovery of selective diacylglycerol lipase β inhibitors

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Chapter 4

Optimization of glycine sulfonamides as DAGLβ selective inhibitors

4.1 Introduction

2-Arachidonoylglycerol (2-AG) is one of the two main endocannabinoids that play a crucial role in diverse physiological processes, such as synaptic plasticity, memory formation, pain sensation and immune response.[1,2] The synthesis of 2-AG initiates from phosphatidylinositol-4,5-biphosphate (PIP_2), which undergoes sequential transformations by phospholipase C (PLC) and *sn*-1-specific diacylglycerol lipases (DAGL).[1,3] Subsequently, monoacylglycerol lipase (MAGL), along with α/β-hydrolase domain-containing 6 and 12 (ABHD6 and ABHD12), hydrolyzes 2-AG to generate arachidonic acid (AA).[4] Both AA and 2-AG can be oxidized by cyclooxygenase-2 (COX2), leading to the formation of pro-inflammatory prostaglandins and glyceryl prostaglandins, respectively, contributing to inflammation.[5,6] There are two known isoforms of DAGL, namely DAGLα and DAGLβ[3], whose expression levels vary based on tissue and cell types. DAGLα is the dominant isoform in neurons of the central nervous system (CNS), where it produces 2-AG to activate cannabinoid receptor type 1 (CB_1R) to modulate neurotransmitter release.[7–9] In contrast, DAGLβ takes precedence in periphery and immune cells.[8,10,11]

Endocannabinoid signaling, mediated by DAGLα and CB_1R, is closely linked to anxiety, stress and fear responses.[12–14] Knocking out DAGLα resulted in an 80% reduction in brain 2-AG levels, adversely influencing the emotional state of mice and inducing various negative behavioral changes including maternal neglect, fear extinction deficit, reduced hippocampal neurogenesis, and enhanced anxiety-related behaviors.[12] Pharmacological inhibition of DAGLα by DO34 similarly impaired fear extinction learning.[13] Conversely, inhibiting the hydrolysis of 2-AG by MAGL inhibitor JZ184 demonstrated antidepressant and anxiolytic effects.[15,16] These findings underscore the crucial role of 2-AG signaling in the brain and the potential of causing neuropsychiatric side effects by disruption brain 2-AG levels.

DAGLβ was identified as the predominant DAGL in microglia[10] in the brain, and macrophages[8] and dendritic cells[11] of the periphery. DAGLβ deletion notably reduced the basal level of prostaglandin E2 (PGE_2) in the brain without altering 2-AG and AA.[10] Moreover, disrupting DAGLβ protected microglia and macrophages from LPS-induced inflammation by inhibiting inflammatory cytokine production[8,10] and attenuated inflammatory signaling in dendritic cells while preserving its antigen presentation function in adaptive immune responses.[11] Animal studies targeting DAGLβ yielded promising results for anti-inflammation. DAGLβ deletion attenuated LPS-induced hypothermia[10], a profound reduction in core body temperature mediated by neuroinflammatory processes.[17] KT109 treatment, inhibiting DAGLβ, effectively reduced allodynia in chronic constriction injury (CCI) neuropathic pain models and chemotherapy-induced neuropathic pain (CINP) models without inducing side effects such as catalepsy, hypothermia, thermal hypoalgesia and hypomotility.[18] Subtype specific DAGL inhibitors have therefore emerged as a promising strategy to finely tune 2-AG levels while avoiding CNS side effects.

During the structure-activity relationship (SAR) study of glycine sulfonamides for DAGLα/β, as described in Chapter 3, three compounds with different modifications on the

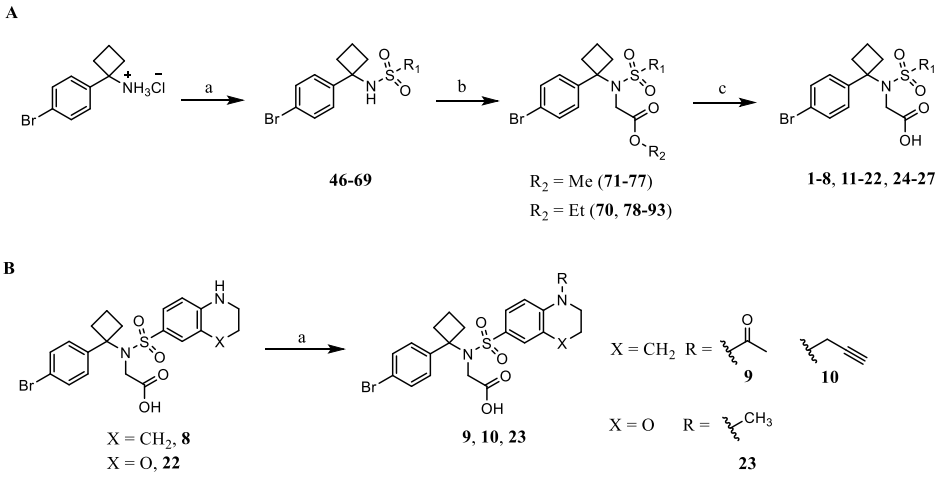
sulfonyl group exhibited subtle yet notable selectivity for DAGLβ. Building upon these initial findings, an extensive SAR study ensued, focusing on further optimizing the sulfonyl group to enhance selectivity. This effort led to the identification of a 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine moiety as the optimal substituent on the sulfonyl group. Subsequent to this discovery, a series of compounds containing a 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine on the sulfonyl group were developed and assessed. Overall, this yielded compounds **27**, **32** and **42-45**, characterized by high potency, good selectivity for DAGLβ, and promising physicochemical properties for further studies.

4.2 Results and discussion

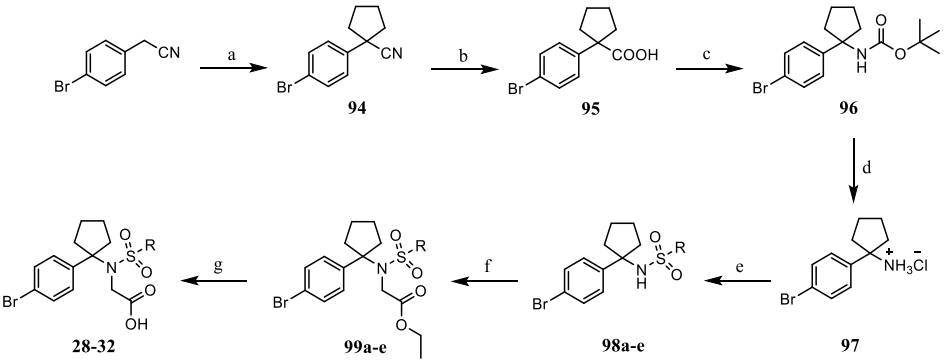
4.2.1 Design and synthesis of glycine sulfonamides 1-45

In Chapter 3, three compounds, featuring different modifications on the sulfonyl, exhibited moderate selectivity for DAGLβ. This observation encouraged an in-depth SAR investigation with a specific emphasis on this region, resulting in the design and synthesis of compounds **1-27**. To further optimize the potency and selectivity, the most selective substituents on the sulfonyl group were combined with modifications in the other regions of the glycine sulfonamide, leading to compounds **28-45**.

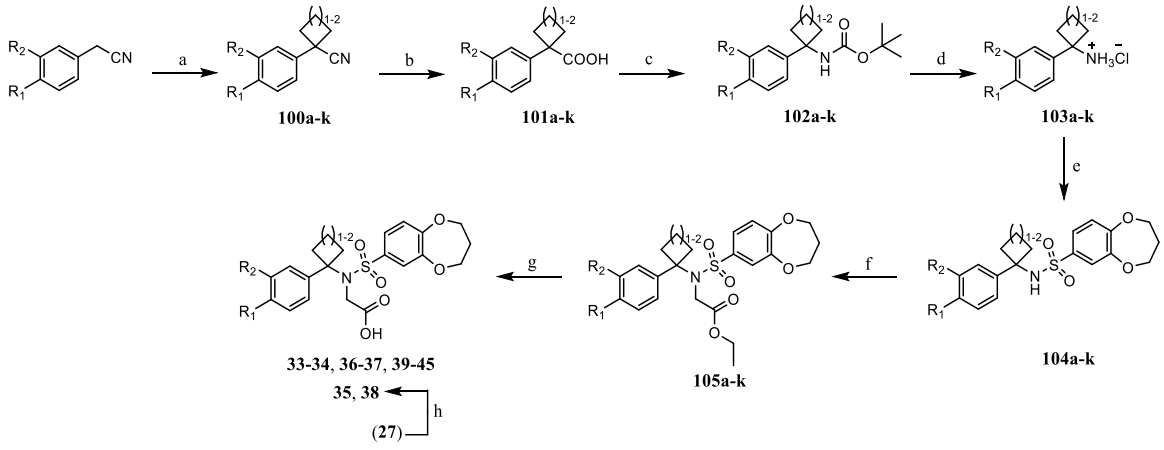
The synthetic route of final compounds **1-27** is depicted in Scheme 4.1, which contains three general steps as described in Chapter 3: coupling between the aminium chloride and sulfonyl chlorides yielded sulfonamides **46-69**; subsequent *N*-alkylation resulted in esters **70-93**, followed by saponification affording glycine sulfonamides **1-8**, **11-22**, and **24-27** (Scheme 4.1A). Compounds **9** and **10** were synthesized from compound **8** via acetylation and alkylation, respectively (Scheme 4.1B). Methylation of **22** yielded **23**. The synthesis of compounds **28-32** (Scheme 4.2) followed a similar procedure as their cyclobutyl counterparts. In brief, cyclopentyl formation through nucleophilic substitution (**94**), followed by nitrile hydrolysis (**95**), diphenylphosphoryl azide-induced Curtius rearrangement and *tert*-butyloxycarbamate formation, yielded compound **96**. Acidolysis (**96** → **97**) followed by sulfonamidation with sulfonyl chlorides formed sulfonamides **98a-e**, which were transformed to glycine sulfonamides **28-32** via alkylation and saponification. Finally, compounds **33-45** were synthesized according to the procedure illustrated in Scheme 4.3, starting from the nitriles. A similar reaction sequence was adopted as shown in Scheme 4.2. Aminium chlorides **103a-k** were condensed with 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**) to form sulfonamides **104a-k**. Subsequent alkylation and saponification yielded the final compounds **33-34**, **36-37** and **39-45**. Glycine sulfonamides **35** and **38** were synthesized from compound **27** via a Suzuki-Miyaura coupling and Pd-catalyzed introduction of the cyano group.



Scheme 4.1 Synthesis of glycine sulfonamides **1-27**. (A) a) corresponding sulfonyl chloride, Et_3N or DIPEA, anhydrous DCM, rt, 20-100%; b) methyl 2-bromoacetate or ethyl 2-bromoacetate, BEMP, anhydrous DMF, 80 °C, 39%-quant.; c) 2 M or 1 M aq. NaOH or 1 M aq. LiOH, MeOH/THF, rt, 8-86%; (B) a) NaH, acetyl chloride or 3-bromoprop-1-yne or CH_3I, anhydrous DMF, rt, 80% for **9**, 19% for **10**, 16% for **23**.



Scheme 4.2 Synthesis of glycine sulfonamides **28-32**. a) 1,4-dibromobutane, TBABr, KOH, toluene, H_2O, reflux, 81%; b) *i.* KOH, ethylene glycol, reflux; *ii.* 6 M aq. HCl in 1,4-dioxane, reflux, 43%; c) DPPA, Et_3N, anhydrous *t*-BuOH, 30 °C-reflux, 54%; d) 3 M aq. HCl in MeOH, rt, 80%; e) corresponding sulfonyl chloride, DIPEA, anhydrous DCM, rt, 30-76%; f) ethyl 2-bromoacetate, BEMP, anhydrous DMF, 80 °C, 25-67%; g) 2 M aq. NaOH or 1 M aq. LiOH, MeOH/THF, rt, 6-59%.



Scheme 4.3 Synthesis of glycine sulfonamides **33-45**. a) 1,3-dibromopropane or 1,4-dibromobutane, TBABr, KOH, toluene, H_2O, reflux, 24-87%; b) KOH, ethylene glycol, reflux, or 9 M aq. H_2SO_4, reflux, 45%-quant.; c)

DPPA, Et_3N, anhydrous *t*-BuOH, 30 °C-reflux, 27-93%; d) 3 M aq. HCl in MeOH, rt, 38-100%; e) 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**), DIPEA, anhydrous DCM, rt, 39-88%; f) ethyl 2-bromoacetate, BEMP, anhydrous DMF, 80 °C, 58-86%; g) 1 M aq. LiOH, MeOH/THF, rt, 29%-99%; h) Methyl boronic acid, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, K_2CO_3, 1,4-dioxane/H_2O, 85 °C, 49% for **35**; $Pd(OAc)_2$, $K_4Fe(CN)_6 \cdot 3H_2O$, Na_2CO_3, *i*-PrOH, H_2O, DMF, 100 °C, 12% for **38**.

4.2.2 Biochemical evaluation and structure-activity-relationship of compounds 1-45

4.2.2.1 Optimization of the sulfonyl substituent

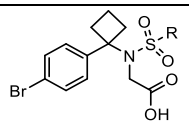
The biochemical activities of compounds **1-27**, with varying sulfonyl substituents, were evaluated using the DAGL EnzChek lipase substrate assay and the corresponding results are presented in Table 4.1. In Chapter 3, three compounds (**49**, **51** and **52** in Chapter 3**)** exhibited around a 3-fold selectivity for DAGLβ over DAGLα. Building upon this, the optimization started by reintroducing the cyclobutyl moiety to the glycine sulfonamide core structure in compounds **1-3**, resulting in an increase in potency and a slight improvement in selectivity compared to their counterparts without the cyclobutyl moiety. In light of this observation, compounds **4-7**, featuring similar sulfonyl substituents, were designed, synthesized, and evaluated. Compounds **4-6** demonstrated, however, a reduction in potency for both DAGL enzymes, likely attributed to the orientation of these sulfonyl substituents. In line, compound **7** was significantly more potent than its counterpart **5**. However, none of these compounds displayed an improved selectivity for DAGLβ compared to compound **3**.

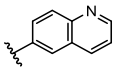
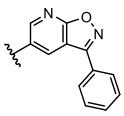
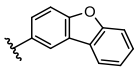
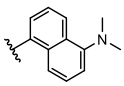
To further extend the SAR study and identify more selective compounds, diverse substituents were systematically investigated. The incorporation of a tetrahydroquinoline onto the sulfonyl led to compound **8**, which showed moderate and comparable activity for DAGLα and DAGLβ. Introducing an acetyl (**9**) or a propargyl (**10**) on the amine resulted in decreased potency. Removing a phenyl ring in compound **3** gave rise to compound **11** with a benzofuran moiety. This caused approximately a 10-fold reduction in potency compared to compound **3**. The selectivity was retained, while the lipophilic efficiency (LipE) was enhanced due to lower lipophilicity. This outcome suggests that the phenyl ring plays an important role for potency. Substituting the furan in compound **11** to a dioxolane resulted in compound **12,** which demonstrated a 3-fold selectivity for DAGLβ. Expanding the five-membered dioxolane to a six-membered dioxane in compound **13** brought a remarkable increase in both potency and selectivity. Compound **13** exhibited a negative logarithm of the half-maximal inhibitory concentration (pIC_{50}) of 7.59 ± 0.06 and a 20-fold selectivity for DAGLβ.

Subsequent modifications were based on compound **13**. Opening the dioxane resulted in compound **14** with 3- and 4-methoxy groups. This modification led to a more than 100-fold decrease in potency and a complete loss of selectivity for DAGLβ. Changing 3-methoxy to a benzyloxy (compound **15**) improved potency, particularly for DAGLα. Meanwhile, changing 4-methoxy or both methoxy groups to a benzyloxy (compounds **16** and **17**) retained most of the activity for both DAGL enzymes. Introducing a double bond (compound **18**) as well as substituting the *para* oxygen with a methylene (compound **19**) decreased potency for DAGLβ,

but increased potency for DAGLα, resulting in lower selectivity. Introducing a dimethyl group near the *para* oxygen in **13** (compound **20**) led to decreased selectivity. Conversely, introducing the dimethyl group near the *meta* oxygen (compound **21)** retained most of potency and selectivity. Substituting the *para* oxygen in **13** to an amine led to compound **22**, which exhibited a reduction in potency and selectivity. Introducing a methyl group to the amine (compound **23**) regained some potency. Introduction of a chlorine on the *meta* position of the phenyl ring (compound **24**) further restored potency as well as selectivity. Changing the methylmorpholine in **23** to a methylmorpholinone (compound **25)** reduced the activity likely due to increased hydrophilicity. Expanding the six-membered dioxane to an eight-membered dioxocane (compound **26**) increased potency for DAGLα while retaining potency for DAGLβ, resulting in a decrease in selectivity. However, expanding dioxane to a seven-membered dioxepane obtained compound **27**, which displayed a notable decrease in the potency for DAGLα but not for DAGLβ. Compound **27** exhibited a pIC_{50} of 7.48 ± 0.09 and a selectivity of 36-fold for DAGLβ, representing the compound with the highest selectivity thus far. Additionally, this compound demonstrated high lipophilic efficiency (a LipE of 6.1), indicating favourable druglikeness.

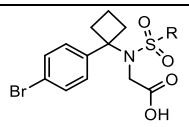
Table 4.1 Biochemical results and physicochemical properties of glycine sulfonamides **1-27**.[a]

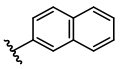
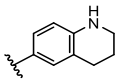
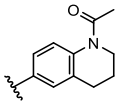
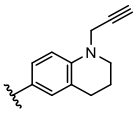
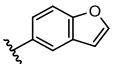
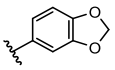
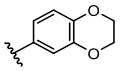
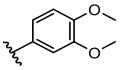
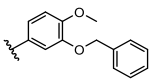
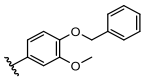
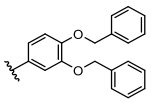
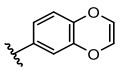


ID	R	pIC_{50} DAGLβ	pIC_{50} DAGLα	Apparent selectivity	cLogD	tPSA (Å^2)	LipE DAGLβ
1		6.08 ± 0.09	5.33 ± 0.13	5.6	1.4	99	4.7
2		6.47 ± 0.13	5.72 ± 0.04	5.6	1.9	125	4.6
3		7.85 ± 0.14	7.03 ± 0.03	6.6	2.9	99	5.0
4		5.27 ± 0.07	5.20 ± 0.10	1.3	1.3	99	4.0
5		6.01 ± 0.08	5.49 ± 0.07	3.3	2.3	86	3.7
6		6.39 ± 0.08	5.82 ± 0.08	3.7	2.2	89	4.2

[a]The negative logarithm of the half-maximal inhibitory concentration (pIC_{50}) was determined using the EnzChek lipase substrate assay. The apparent selectivity regards the selectivity for DAGLβ over DAGLα. The calculated logarithm of the *n*-octanol-water partition coefficient at pH 7.4 (cLogD) and the topological polar surface area (tPSA) were calculated using DataWarrior 5.0.0. Lipophilic efficiency (LipE) was computed using the formula LipE = pIC_{50} – cLogD.

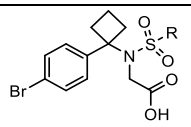
Table 4.1 (continued) Biochemical results and physicochemical properties of glycine sulfonamides **1-27**.[a]

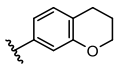
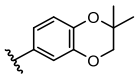
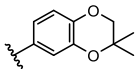
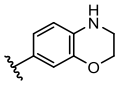
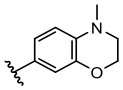
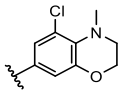
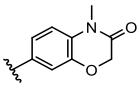
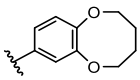
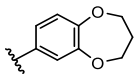


ID	R	pIC_{50} DAGLβ	pIC_{50} DAGLα	Apparent selectivity	cLogD	tPSA (Å^2)	LipE DAGLβ
7		7.89 ± 0.12	7.22 ± 0.04	4.7	2.3	86	5.6
8		6.46 ± 0.09	6.32 ± 0.05	1.4	1.1	98	5.4
9		5.52 ± 0.12	5.48 ± 0.08	1.1	1.6	106	3.9
10		6.16 ± 0.10	6.31 ± 0.08	0.7	1.5	89	4.7
11		6.84 ± 0.12	6.15 ± 0.10	4.9	1.6	99	5.2
12		6.16 ± 0.24	5.72 ± 0.16	2.8	1.2	104	5.0
13		7.59 ± 0.06	6.29 ± 0.05	20	1.1	104	6.5
14		5.29 ± 0.21	5.49 ± 0.10	0.6	1.0	104	4.3
15		5.61 ± 0.14	6.62 ± 0.06	0.1	2.4	104	3.2
16		5.37 ± 0.18	5.44 ± 0.07	0.9	2.4	104	3.0
17		5.43 ± 0.14	5.64 ± 0.11	0.6	3.8	104	1.6
18		7.32 ± 0.11	6.66 ± 0.06	4.6	0.8	104	6.5

[a]The negative logarithm of the half-maximal inhibitory concentration (pIC_{50}) was determined using the EnzChek lipase substrate assay. The apparent selectivity regards the selectivity for DAGLβ over DAGLα. The calculated logarithm of the *n*-octanol-water partition coefficient at pH 7.4 (cLogD) and the topological polar surface area (tPSA) were calculated using DataWarrior 5.0.0. Lipophilic efficiency (LipE) was computed using the formula LipE = pIC_{50} – cLogD.

Table 4.1 (continued) Biochemical results and physicochemical properties of glycine sulfonamides **1-27**.[a]



ID	R	pIC_{50} DAGLβ	pIC_{50} DAGLα	Apparent selectivity	cLogD	tPSA (Å^2)	LipE DAGLβ
19		6.85 ± 0.10	6.43 ± 0.06	2.6	1.7	95	5.2
20		6.75 ± 0.21	6.70 ± 0.07	1.1	1.7	104	5.0
21		7.28 ± 0.23	6.06 ± 0.11	17	1.7	104	5.6
22		5.92 ± 0.10	5.82 ± 0.21	1.3	0.5	107	5.4
23		6.40 ± 0.10	6.16 ± 0.18	1.7	0.9	98	5.5
24		7.04 ± 0.13	5.94 ± 0.13	13	1.5	98	5.5
25		5.47 ± 0.30	5.37 ± 0.21	1.3	0.3	115	5.2
26		7.56 ± 0.16	6.73 ± 0.08	6.8	1.7	104	5.9
27		7.48 ± 0.09	5.93 ± 0.16	35	1.4	104	6.1

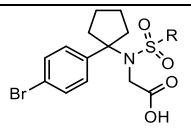
[a]The negative logarithm of the half-maximal inhibitory concentration (pIC_{50}) was determined using the EnzChek lipase substrate assay. The apparent selectivity regards the selectivity for DAGLβ over DAGLα. The calculated logarithm of the *n*-octanol-water partition coefficient at pH 7.4 (cLogD) and the topological polar surface area (tPSA) were calculated using DataWarrior 5.0.0. Lipophilic efficiency (LipE) was computed using the formula LipE = pIC_{50} – cLogD.

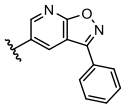
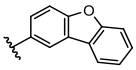
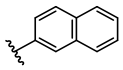
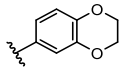
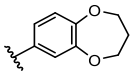
4.2.2.2 Combination of the optimal sulfonyl substituents and modifications on the amine moiety

Based on a previously published SAR study with glycine sulfonamides for DAGLα[19], a (4-bromophenyl)cyclopentane on the amine was combined with the optimal sulfonyl substituents, leading to compounds **28-32** (Table 4.2). Remarkably, the potencies of compounds **28-32** were found to be comparable to their cyclobutyl counterparts. Specifically, compound **31** was 2-fold less potent than its counterpart **13**, while compound **32** was 4-fold more potent than its counterpart **27**. Furthermore, in comparison with the cyclobutyl analogs, the cyclopentyl

slightly decreased the selectivity of compounds, except for compound **32**. In conclusion, compound **32**, featuring a 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine on the sulfonyl and a (4-bromophenyl)cyclopentane on the amine, was the most potent and selective inhibitor so far, exhibiting a pIC_{50} of 8.08 ± 0.13 and a selectivity of 37-fold for DAGLβ.

Table 4.2 Biochemical results and physicochemical properties of glycine sulfonamides **28-32**.[a]



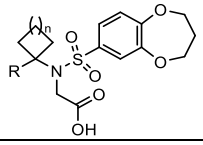
ID	R	pIC_{50} DAGLβ	pIC_{50} DAGLα	Apparent selectivity	cLogD	tPSA (Å^2)	LipE DAGLβ
28		6.38 ± 0.11	5.88 ± 0.10	3.2	2.2	125	4.2
29		7.71 ± 0.14	7.07 ± 0.08	4.4	3.2	99	4.5
30		8.00 ± 0.06	7.40 ± 0.06	4.0	2.7	86	5.3
31		7.19 ± 0.15	5.98 ± 0.18	16	1.4	104	5.8
32		8.08 ± 0.13	6.51 ± 0.06	37	1.8	104	6.3

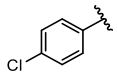
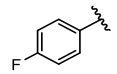
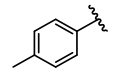
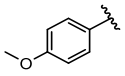
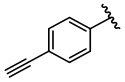
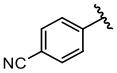
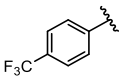
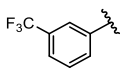
[a]The negative logarithm of the half-maximal inhibitory concentration (pIC_{50}) was determined using the EnzChek lipase substrate assay. The apparent selectivity regards the selectivity for DAGLβ over DAGLα. The calculated logarithm of the *n*-octanol-water partition coefficient at pH 7.4 (cLogD) and the topological polar surface area (tPSA) were calculated using DataWarrior 5.0.0. Lipophilic efficiency (LipE) was computed using the formula LipE = pIC_{50} – cLogD.

Finally, the substitution pattern of the benzyl group was investigated (compounds **33-45**, Table 4.3). Changing the bromine in compound **27** to chlorine or fluorine yielded compounds **33** and **34**, respectively, which displayed a significant reduction in potency and selectivity. This reduction may be caused by a decreased size of these substituents. Substituting the bromine to a methyl (**35**) or a methoxy (**36**) also significantly decreased the potency and selectivity, which may be due to the electron-donating property of these two groups. Therefore, larger electron-withdrawing groups were investigated. Altering the bromine to an alkyne (**37**) reduced both potency and selectivity, while replacing it with a more electron-withdrawing cyano group (**38**) decreased potency, but it retained most of the selectivity. The reduction in potency may be explained by an increased hydrophilicity of the cyano group. Based on these observations, electron-withdrawing and lipophilic substituents, trifluoromethyl and trifluoromethoxy, were introduced, resulting in compounds **39-41**. Compound **39**, with a *para* trifluoromethyl group, displayed slightly higher potency, but lower selectivity than compound **27**. Moving the trifluoromethyl group from the *para* position to the *meta* position resulted in compound **40**,

which had a slightly decreased potency and selectivity. Compound **41**, with a *para* trifluoromethoxy moiety, displayed a significant increase in potency but a slight decrease in selectivity compared with compound **27**. As both *para* and *meta* substitutions were allowed, electron withdrawing and lipophilic groups were subsequently introduced at these two positions. Compound **42** with 3- and 4-dichloride exhibited a significant increase in potency compared with compound **27**. Notably, its selectivity was also slightly increased. Changing the *para* chloride to a larger trifluoromethyl group (**43**) further improved potency and retained selectivity. Based on compound **32**, the cyclopentyl group was introduced, resulting in compounds **44** and **45**. Compound **44** exhibited higher potency and selectivity than compound **42**, while compound **45** showed similar potency and selectivity to its counterpart **43**. To conclude, compound **42-45** were the most optimal compounds with high potency and selectivity for DAGLβ.

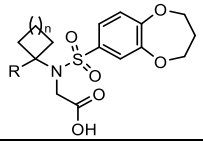
Table 4.3 Biochemical results and physicochemical properties of glycine sulfonamides **33-45**.[a]

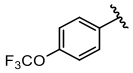
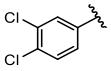
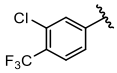
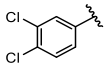
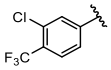


ID	n	R	pIC_{50} DAGLβ	pIC_{50} DAGLα	Apparent selectivity	cLogD	tPSA (Å^2)	LipE DAGLβ
33	1		7.30 ± 0.17	6.02 ± 0.13	19	1.3	104	6.0
34	1		6.84 ± 0.16	5.58 ± 0.09	18	0.8	104	6.0
35	1		7.02 ± 0.13	6.07 ± 0.09	8.9	1.1	104	5.9
36	1		6.41 ± 0.20	5.14 ± 0.14	19	0.6	114	5.8
37	1		6.94 ± 0.10	5.73 ± 0.07	16	0.8	104	6.1
38	1		6.74 ± 0.07	5.22 ± 0.06	33	0.5	128	6.2
39	1		7.55 ± 0.16	6.08 ± 0.06	30	1.6	104	6.0
40	1		7.44 ± 0.06	5.99 ± 0.05	28	1.6	104	5.8

[a]The negative logarithm of the half-maximal inhibitory concentration (pIC_{50}) was determined using the EnzChek lipase substrate assay. The apparent selectivity regards the selectivity for DAGLβ over DAGLα. The calculated logarithm of the *n*-octanol-water partition coefficient at pH 7.4 (cLogD) and the topological polar surface area (tPSA) were calculated using DataWarrior 5.0.0. Lipophilic efficiency (LipE) was computed using the formula LipE = pIC_{50} – cLogD.

Table 4.3 (continued) Biochemical results and physicochemical properties of glycine sulfonamides **33-45**.[a]



ID	n	R	pIC_{50} DAGLβ	pIC_{50} DAGLα	Apparent selectivity	cLogD	tPSA (Å^2)	LipE DAGLβ
41	1		7.78 ± 0.10	6.29 ± 0.07	31	1.8	114	6.0
42	1		7.88 ± 0.09	6.27 ± 0.07	41	1.9	104	6.0
43	1		7.94 ± 0.08	6.34 ± 0.09	40	2.2	104	5.7
44	2		8.07 ± 0.09	6.36 ± 0.05	51	2.3	104	5.8
45	2		7.96 ± 0.06	6.37 ± 0.05	39	2.5	104	5.5

[a]The negative logarithm of the half-maximal inhibitory concentration (pIC_{50}) was determined using the EnzChek lipase substrate assay. The apparent selectivity regards the selectivity for DAGLβ over DAGLα. The calculated logarithm of the *n*-octanol-water partition coefficient at pH 7.4 (cLogD) and the topological polar surface area (tPSA), were calculated using DataWarrior 5.0.0. Lipophilic efficiency (LipE) was computed using the formula LipE = pIC_{50} – cLogD.

4.3 Conclusion

In this Chapter, a comprehensive structure-activity relationship (SAR) study was conducted, focusing on the modification of the sulfonyl group of the glycine sulfonamide chemotype. The exploration led to the discovery of 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine moiety as the optimal substituent on the sulfonyl group. To further optimize the potency and selectivity, investigations were extended to other components of this chemotype while maintaining the 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine moiety on the sulfonyl group. Within this study, compound **44** emerged as the most potent and selective compound, displaying a pIC_{50} of 8.07 ± 0.09 and a selectivity of 51-fold for DAGLβ over DAGLα. Importantly, compound **44** also exhibited desirable druglike properties, including a cLogD of 2.3 and a LipE of 5.8. Alongside compound **44**, compounds **27**, **32**, **42**, **43**, and **45** also showed promising potency, selectivity and physiochemical characteristics. These findings position these compounds as the first-in-class DAGLβ selective inhibitors deserving further profiling and exploration.

4.4 Acknowledgements

Danique van Workum and Brian Herry are acknowledged for their contribution to the synthesis and biochemical evaluation. Hans van den Elst is kindly acknowledged for preparative HPLC purification and HRMS measurements.

4.5 Experimental methods

Biology

EnzChek lipase substrate assay for DAGLα and DAGLβ in 384-well plate

The DAGL EnzChek lipase substrate assay was performed as described in Chapter 3.

Chemistry

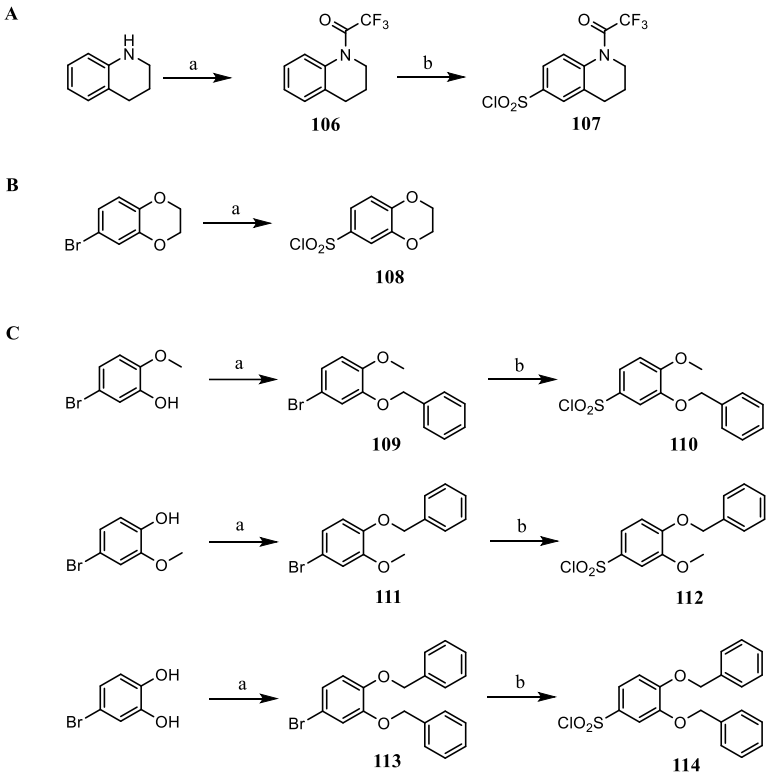
General remarks

All purchased chemicals were used without purification unless stated otherwise. All reactions were performed in oven-dried or flame-dried glassware. Anhydrous solvents were dried by activated 3 Å or 4 Å molecular sieves. Thin layer chromatography (TLC) analysis was performed on Merck silica gel 60 F_{254} aluminium sheets and the compounds were visualized by using UV absorption at 254 nm and/or $KMnO_4$ staining (5 g/L $KMnO_4$ and 25 g/L K_2CO_3 in water). TLC plates were analysed with the Advion CMS Plate Express® connected to the Advion Expression® L-MS using 90% MeOH in H_2O with 0.1% formic acid as the solvent. Liquid chromatography-mass spectrometry (LC-MS) analysis was performed on a Thermo Finnigan LCQ Advantage MAX ion-trap mass spectrometer (ESI^+) coupled to a Surveyor HPLC system equipped with a C18 column (50 × 4.6 mm, 3 µm particle size, Macherey-Nagel) or a Thermo Finnigan LCQ Fleet ion-trap mass spectrometer (ESI^+) coupled to a Vanquish UHPLC system using H_2O, CH_3CN and 0.1% aq. TFA as eluents. Purification was performed on manual silica gel column chromatography (40-63 µm, 60 Å silica gel, Macherey-Nagel) or automated silica gel column chromatography (40-63 µm, 60 Å pre-packed silica gel, Screening Devices) on a Biotage Isolera™ Four 3.0 system. Alternatively, purification was performed using preparative HPLC on a Waters Acquity Ultra performance LC equipped with a C18 column (21 × 150 mm, 5 µm particle size, Phenomenex). ^1H and ^{13}C spectra were recorded on a Bruker AV 400 MHz (400 MHz for ^1H and 101 MHz for ^{13}C) or AV 500 MHz (500 MHz for ^1H and 126 MHz for ^{13}C) or AV 850 MHz spectrometer (850 MHz for ^1H and 214 MHz for ^{13}C) in deuterated solvents. Chemical shifts are reported in ppm with tetramethylsilane (TMS) or solvent resonance as the internal standard ($CDCl_3$: δ 7.26 for ^1H, δ 77.16 for ^{13}C; CD_3OD: δ 3.31 for ^1H, 49.00 for ^{13}C; DMSO-*d6*: δ 2.50 for ^1H, δ 39.52 for ^{13}C). Data is reported as follows: chemical shifts δ (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, q = quartet, quintet = p, bs = broad singlet, m = multiplet), coupling constants *J* (Hz) and integration. High resolution mass spectrometry (HRMS) analysis was performed on

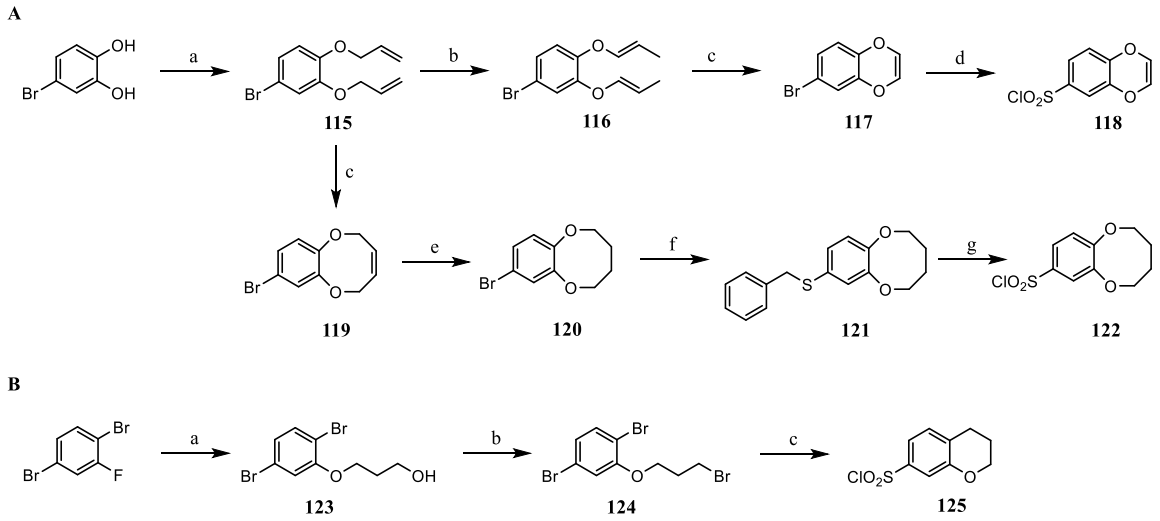
a Thermo Finnigin LTQ Orbitrap mass spectrometer equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 mL/min, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000) and dioctyl phthalate (m/z = 391.28428) as a lock mass.

Synthesis of sulfonyl chlorides

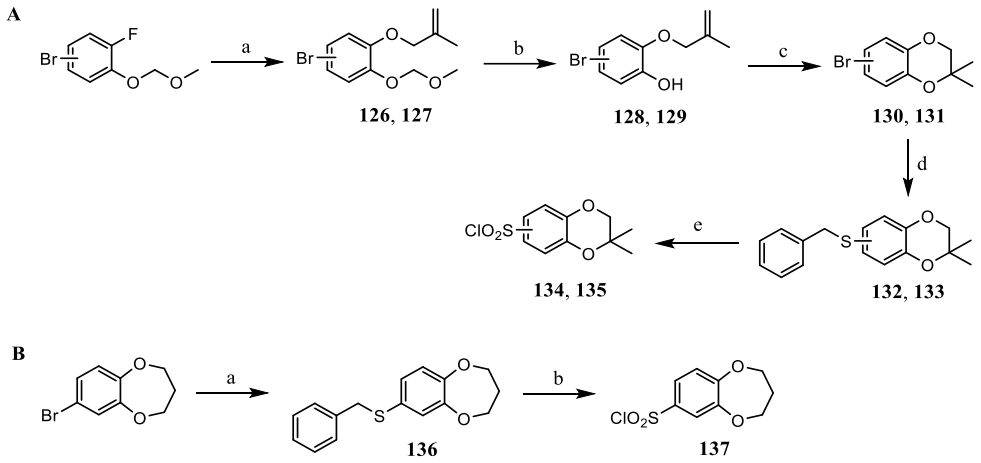
The sulfonyl chlorides used in the synthesis of the final compounds outlined in Table 4.1 were prepared following the procedures depicted in Schemes 4.4-4.7. Sulfonyl chloride **107** was synthesized by trifluoroacetylation of tetrahydroisoquinoline, followed by chlorosulfonation using chlorosulfonic acid (Scheme 4.4A). Sulfonyl chloride **108** was obtained from the bromide-containing starting material via a two-step chlorosulfonation (Scheme 4.4B).[20] This process involved a bromide-lithium exchange and nucleophilic addition to sulfur dioxide, followed by oxidative chlorination using *N*-chlorosuccinimide. Similarly, sulfonyl chlorides **110**, **112** and **114** were made in a comparable fashion (Scheme 4.4C). Sulfonyl chlorides **118** and **122** (Scheme 4.5A) were obtained from 4-bromobenzene-1,2-diol through a series of synthetic steps. The process involved initial allylation (**115**), followed by Ruthenium-catalyzed isomerization[21], resulting in enol-ether **116**. Subsequent ring-closing metathesis and a two-step chlorosulfonation yielded sulfonyl chloride **118**. For the synthesis of **122**, ring-closing metathesis of **119**, catalytic hydrogenation (**120**), and Pd-catalyzed aromatic substitution (**121**) were performed, followed by chlorosulfonation.[22] Nucleophilic aromatic substitution at 1,4-dibromo-2-fluorobenzene with propane-1,3-diol[23] followed by phosphorus tribromide treatment afforded tribromide **124** (Scheme 4.5B). The subsequent two-step chlorosulfonation yielded sulfonyl chloride **125**. Sulfonyl chlorides **134** and **135** (Scheme 4.6A) were synthesized starting from 4-bromo-2-fluoro-1-(methoxymethoxy)benzene and 4-bromo-1-fluoro-2-(methoxymethoxy)benzene, respectively. The synthesis involved nucleophilic aromatic substitution, MEM group cleavage and ring-closure, resulting in compounds **130** and **131**. A second nucleophilic aromatic substitution followed by chlorosulfonation led to the formation of sulfonyl chlorides **134** and **135**. Compound **137** was synthesized (Scheme 4.6B) through nucleophilic aromatic substitution and chlorosulfonation. Sulfonyl chlorides **142**, **145** and **148** (Scheme 4.7) were synthesized from intermediate **138**, derived from 2-amino-5-bromophenol and 2-chloroacetyl chloride. Then, amide reduction (**139**) followed by sequential trifluoro acetylation, nucleophilic aromatic substitution and chlorosulfonation formed sulfonyl chloride **142**. Methylation of **138** and **139** obtained compounds **143** and **146**, respectively. These were then transformed to sulfonyl chlorides **145** and **148** via nucleophilic aromatic substitution and chlorosulfonation, and nucleophilic aromatic substitution and chlorosulfonation/chlorination processes, respectively.



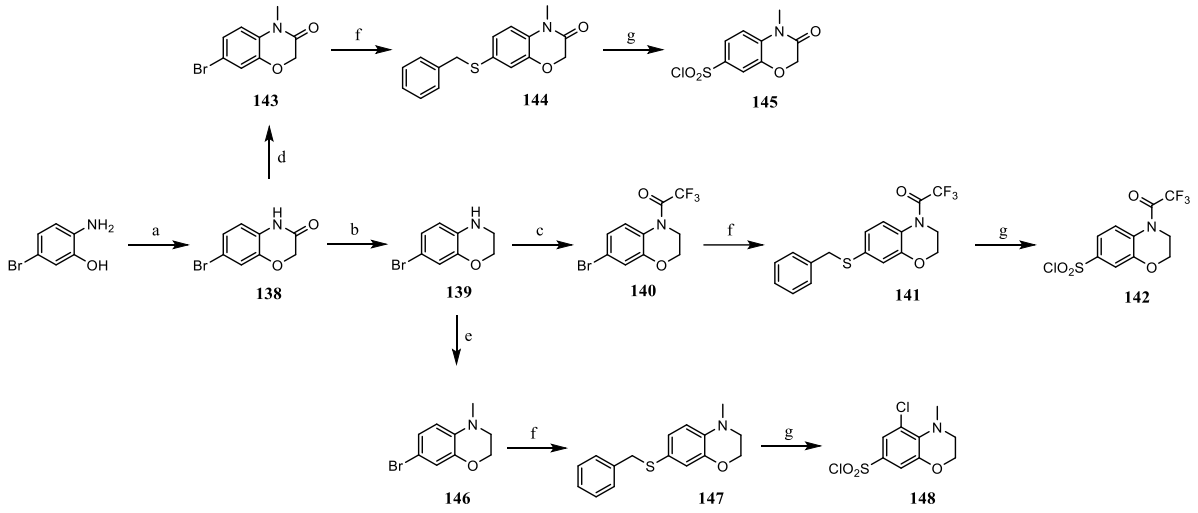
Scheme 4.4 Synthesis of sulfonyl chlorides **107**, **108**, **110**, **112** and **114**. (A) a) TFAA, Et_3N, Et_2O, rt, 87%; b) HSO_3Cl, anhydrous DCM, 0 °C-rt, 52%; (B) a) *i.* *n*-BuLi, anhydrous THF, -78 °C; *ii.* SO_2 in hexane, anhydrous THF, -78 to -40 °C; *iii.* *N*-chlorosuccinimide, DCM, 0 °C, 27%; (C) a) benzyl bromide, K_2CO_3, anhydrous DMF, rt or 90-106 °C, 67% for **109**, 92% for **111**, 75% for **113**; b) *i.* *n*-BuLi, anhydrous THF, -78 °C; *ii.* SO_2, anhydrous THF, -78 to -40 °C; *iii.* *N*-chlorosuccinimide, DCM, 0 °C, 39% for **110**, 71% for **112**, 38% for **114**.



Scheme 4.5 Synthesis of sulfonyl chlorides **118**, **122**, **125**. (A) a) 3-bromoprop-1-ene, K_2CO_3, anhydrous DMF, 60 °C, 25%; b) $RuClH(CO)(PPh_3)_3$, anhydrous benzene, 80 °C, 46%; c) Grubbs catalyst (II), anhydrous DCM, reflux, 88% for **117**, 22% for **119**; d) *i.* *n*-BuLi, anhydrous THF, -78 °C; *ii.* SO_2, anhydrous THF, -78 to -40 °C; *iii.* *N*-chlorosuccinimide, DCM, 0 °C, 49%; e) $RhCl(PPh_3)_3$, H_2, EtOH, 50 °C, 63%; f) benzyl mercaptan, DIPEA, xantphos, $Pd_2(dba)_3$, 1,4-dioxane, 100 °C, 75%; g) *N*-chlorosuccinimide, AcOH, H_2O, rt, 84%; (B) a) propane-1,3-diol, *t*-BuOK, 1-methylpyrrolidin-2-one, 100 °C, 80%; b) PBr_3, toluene, 0 °C-rt, 71%; c) *i.* *n*-BuLi, anhydrous THF, -78 °C; *ii.* SO_2, anhydrous THF, -78 to -40 °C; *iii.* *N*-chlorosuccinimide, DCM, 0 °C, 50%.

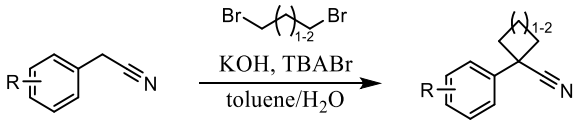


Scheme 4.6 Synthesis of sulfonyl chloride **134**, **135**, and **137**. (A) a) NaH, 2-methylprop-2-en-1-ol, anhydrous DMF, 0 °C-rt, 61% for **126**, 51% for **127**; b) TFA, DCM, 0 °C, 80%; c) HCOOH, reflux, 35% for **130**, 41% for **131**; d) benzyl mercaptan, DIPEA, xantphos, $Pd_2(dba)_3$, 1,4-dioxane, 100 °C, 74% for **132**, 87% for **133**; e) *N*-chlorosuccinimide, AcOH, H_2O, rt, 96% for **134**, quant. for **135**; (B) a) benzyl mercaptan, DIPEA, xantphos, $Pd_2(dba)_3$, 1,4-dioxane, 100 °C, 74%; b) *N*-chlorosuccinimide, AcOH, H_2O, rt, 96%.



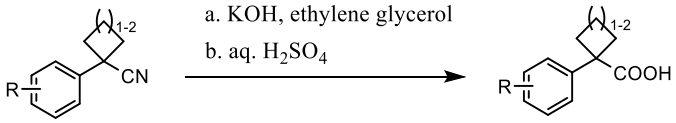
Scheme 4.7 Synthesis of sulfonyl chlorides **143**, **145** and **148**. a) 2-chloroacetyl chloride, K_2CO_3, anhydrous DMF, 80 °C, 81%; b) borane-THF complex, anhydrous THF, reflux, 88%; c) TFAA, Et_3N, Et_2O, 0 °C-rt, 92%; d) *t*-BuOK, CH_3I, anhydrous DMF, rt, 57%; e) NaH, CH_3I, anhydrous DMF, 0 °C-rt, 76%; f) benzyl mercaptan, DIPEA, xantphos, $Pd_2(dba)_3$, 1,4-dioxane, 100 °C, 88% for **141**, 61% for **144**, 56% for **147**; g) *N*-chlorosuccinimide, AcOH, H_2O, rt, 74% for **142**, quant. for **145**, 69% for **148**.

General procedure A



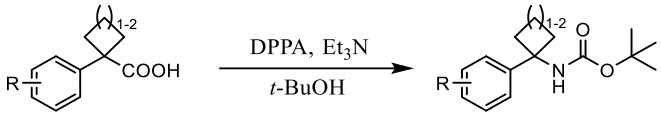
A mixture of corresponding phenyl acetonitrile (1 eq), 1,3-dibromopropane or 1,4-dibromobutane (1 eq) and TBABr (0.1 eq) in toluene (0.35 M) and solid KOH (8 eq) in H_2O (75% w/w) was heated to 100 °C with occasionally slow stirring to facilitate liquification of the inorganic phase. The reaction was then refluxed with continuous vigorous stirring for 1-2 h. The mixture was diluted in water and extracted 3× with EtOAc. Combined organic layers were washed with sat. NH_4Cl, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to afford the product**.**

General procedure B



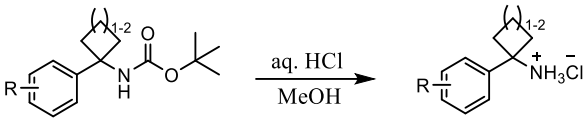
The mixture of corresponding nitrile (1 eq) and KOH (6 eq) in ethylene glycol (0.4-0.8 M) was refluxed until completion. The mixture was diluted in water and washed 1× with Et_2O. The pH of water layer was adjusted by 2 M aq. HCl solution to 2 and extracted 3× with EtOAc. The combined organic layers were dried by anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to afford the product. Alternatively, the mixture of corresponding nitrile (1 eq) in 9 M aq. H_2SO_4 (0.4 M) was refluxed until the reaction finished. The mixture was diluted in EtOAc and extracted 3× with 3 M aq. NaOH. The aqueous layer was adjusted to pH 2 by using 2 M aq. HCl and the fluffy precipitate was extracted 3× with EtOAc. The combined organic layers were washed with brine, dried by anhydrous Na_2SO_4, filtered and concentrated to obtain the product.

General procedure C



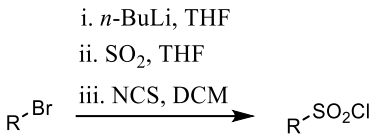
To a solution of corresponding carboxylic acid (1 eq) in anhydrous *t*-BuOH (0.08-0.2 M) with 4 Å molecular sieves was added diphenylphosphoryl azide (1 eq) and Et_3N (1.1 eq). The reaction was stirred at 30 °C for 1 h and then reflux until completion. The mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography to afford the product.

General procedure D



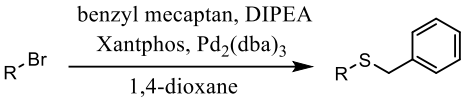
Boc-protected amine (1 eq) was dissolved in 3 M aq. HCl in MeOH and the reaction was stirred at rt until completion. The solvent was removed and the residue was washed 2× with Et_2O and filtered to afford the product.

General procedure E



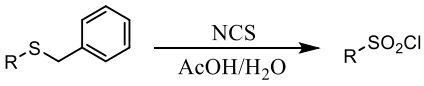
To a solution of corresponding aromatic bromide in anhydrous THF (0.15 M) at -78 °C was added *n*-BuLi (1-2 eq) dropwise and the mixture was stirred at -78 °C for 1-2 h. SO_2 (1.2 M in THF, 1.5 eq) was added and the mixture was stirred between -78 °C to -40 °C for 1 h, and at rt for 1 h. The mixture was concentrated and diluted in anhydrous DCM (0.15 M). *N*-chlorosuccinimide (1.2-1.5 eq) was added portion-wise at 0 °C and the mixture was stirred at 0 °C for 1 h. The mixture was diluted in DCM and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to afford the product.

General procedure F



To a stirred solution of the corresponding aromatic bromide in degassed 1,4-dioxane (0.24 M) was added DIPEA (2 eq) and the mixture was purged with N_2 for 30 min. Subsequently, xantphos (0.1 eq), $Pd_2(dba)_3$ (0.05 eq) and benzyl mercaptan (1 eq) were added and the reaction mixture was heated at 100 °C for 4 h. The reaction mixture was filtered through Celite. The filtrate was poured into water and extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to afford the product.

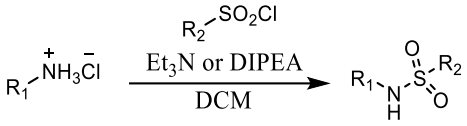
General procedure G



To a stirred solution of the corresponding benzyl sulfane (1 eq) in AcOH/H_2O (7.5:1, 0.23 M) was added *N*-chlorosuccinimide (4 eq) portion-wise and the mixture was stirred at rt for 2-6 h. The reaction mixture was diluted in water and extracted 3× with EtOAc. The combined organic

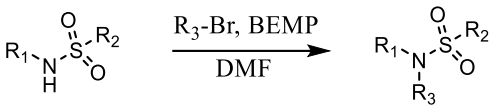
layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to afford the product.

General procedure H



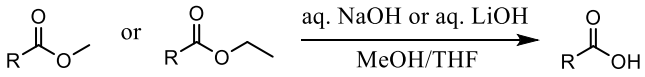
To a mixture of corresponding aminium chloride (1 eq) and Et_3N or DIPEA (3-12 eq) in anhydrous DCM at 0 °C was added corresponding sulfonyl chloride (1-2 eq). The reaction was stirred at rt until completion. The mixture was diluted in water or 0.2 M aq. HCl and extracted 3× with DCM. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to afford the product.

General procedure I



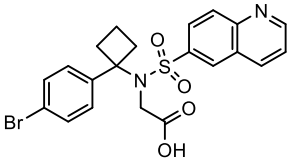
To a solution of corresponding sulfonamide (1 eq) in anhydrous DMF was added methyl 2-bromoacetate or ethyl 2-bromoacetate (1.5-3 eq) and 2-(tert-butylimino)-*N*,*N*-diethyl-1,3-dimethyl-1,3,2λ^5-diazaphosphinan-2-amine (1 M BEMP in hexane, 1.5-3 eq) and the reaction was heated to 80 °C. After completion, the mixture was diluted in EtOAc and washed with water or 0.2 M aq. HCl and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to afford the product.

General procedure J



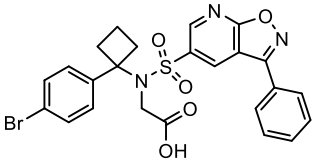
To a solution of corresponding methyl or ethyl esters (1 eq) in MeOH/THF (1:1, 0.1 M) was added 1 M or 2 M aq. NaOH or 1 M aq. LiOH (2-6 eq) and the reaction was stirred at rt. After completion, the mixture was diluted in 0.1 M aq. HCl and extracted 3× with EtOAc. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography or preparative HPLC to afford the product.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-(quinolin-6-ylsulfonyl)glycine (1)



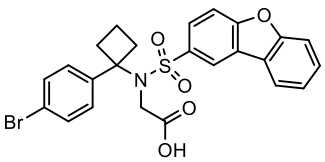
The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-(quinolin-6-ylsulfonyl)glycinate (**70**, 30 mg, 0.060 mmol, 1 eq) and 1 M aq. LiOH (361 µL, 0.361 mmol, 6 eq). Total time: 2 h at rt. Silica gel column chromatography (5-10% MeOH in DCM) afforded the product (12 mg, 0.025 mmol, 41%). ^{1}H NMR (400 MHz, DMSO) δ 9.01 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.46 – 8.40 (m, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 1.9 Hz, 1H), 7.66 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.60 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 4.25 (s, 2H), 2.80 – 2.67 (m, 2H), 2.49 – 2.40 (m, 2H), 1.71 – 1.61 (m, 1H), 1.44 – 1.35 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 171.66, 152.27, 146.18, 141.62, 141.30, 135.96, 130.56, 129.33, 129.28, 129.27, 128.21, 123.57, 122.76, 120.65, 64.73, 48.65, 34.42, 14.14. HRMS $[C_{21}H_{19}BrN_2O_4+H]^+$: 475.03217/477.03005 calculated, 475.03195/477.02957 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((3-phenylisoxazolo[5,4-*b*]pyridin-5-yl)sulfonyl)glycine (2)



The title compound was synthesized according to general procedure **J** using methyl _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((3-phenylisoxazolo[5,4-*b*]pyridin-5-yl)sulfonyl)glycinate (**71**, 29 mg, 0.052 mmol, 1 eq) and 1 M aq. NaOH (187 µL, 0.187 mmol, 3.6 eq). Total time: overnight at rt. Silica gel column chromatography (10-30% EtOAc in *n*-pentane with a drop of conc. HCl) afforded the product as a white solid (13.6 mg, 25.0 µmol, 48%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 8.82 (d, *J* = 2.2 Hz, 1H), 8.36 (d, *J* = 2.2 Hz, 1H), 7.95 – 7.90 (m, 2H), 7.64 – 7.59 (m, 3H), 7.33 – 7.28 (m, 2H), 7.12 – 7.08 (m, 2H), 4.36 (s, 2H), 2.84 – 2.74 (m, 2H), 2.56 – 2.47 (m, 2H), 1.80 – 1.72 (m, 1H), 1.59 – 1.49 (m, 1H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 172.65, 170.86, 158.46, 149.90, 141.07, 136.55, 133.38, 132.01, 131.62, 130.09, 130.00, 128.31, 127.84, 122.33, 112.00, 66.16, 48.61, 35.37, 14.87. HRMS $[C_{24}H_{20}BrN_3O_5S+H]^+$: 542.03798/544.03589 calculated, 542.03778/544.03560 found.

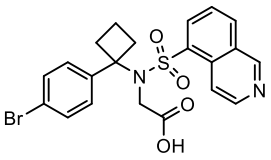
_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-(dibenzo[*b*,*d*]furan-2-ylsulfonyl)glycine (3)



The title compound was synthesized according to general procedure **J** using methyl _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-(dibenzo[*b*,*d*]furan-2-ylsulfonyl)glycinate (**72**, 39 mg, 0.074 mmol, 1 eq) and 1 M aq. NaOH (0.35 mL, 0.35 mmol, 4.7 eq). Total time: 3 h at rt. Silica gel column chromatography (10-30% EtOAc in *n*-pentane with a drop of conc. HCl) afforded the product as a white solid (24 mg, 0.047 mmol, 63%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 7.90 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.79 (dd, *J* = 2.0, 0.6 Hz, 1H), 7.62 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.57 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.40 (td, *J* = 7.4, 1.1 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.22 – 7.18 (m, 2H), 4.15 (s, 2H), 2.94 – 2.80 (m, 2H), 2.57 – 2.45 (m, 2H), 1.83 – 1.71 (m, 1H), 1.63 – 1.49 (m, 1H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 172.98, 158.39, 157.71, 142.07, 136.24, 131.66, 129.75, 128.99, 126.69, 125.05, 124.27,

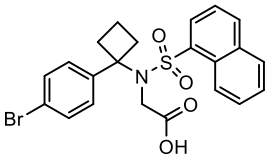
123.65, 122.09, 121.94, 121.19, 112.41, 112.11, 66.00, 48.62, 35.56, 15.03. HRMS $[C_{24}H_{20}BrNO_5S+Na]^+$: 536.01378/538.01168 calculated, 536.01367/538.01160 found.

N-(1-(4-Bromophenyl)cyclobutyl)-*N*-(isoquinolin-5-ylsulfonyl)glycine (4)



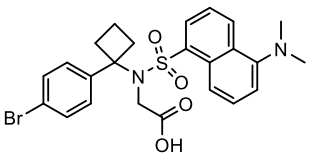
The title compound was synthesized according to general procedure **J** using methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-(isoquinolin-5-ylsulfonyl)glycinate (**73**, 13.5 mg, 28.0 µmol, 1 eq) and 2 M aq. NaOH (56.0 µL, 0.112 mmol, 4 eq). Preparative HPLC afforded the product as a white powder (1.0 mg, 2.1 µmol, 8%). ^{1}H NMR (400 MHz, DMSO) δ 9.37 (d, *J* = 0.9 Hz, 1H), 8.58 (d, *J* = 6.2 Hz, 1H), 8.32 (d, *J* = 8.1 Hz, 1H), 8.13 (dt, *J* = 6.1, 1.1 Hz, 1H), 8.09 – 8.03 (m, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.32 – 7.25 (m, 2H), 7.17 – 7.10 (m, 2H), 4.29 (s, 2H), 2.83 – 2.76 (m, 2H), 2.67 (p, *J* = 1.8 Hz, 1H), 2.47 – 2.37 (m, 2H), 2.33 (p, *J* = 1.8 Hz, 1H). HRMS $[C_{21}H_{19}BrN_2O_4S+H]^+$: 475.03217/477.03005 calculated, 475.03215/477.02999 found.

N-(1-(4-Bromophenyl)cyclobutyl)-*N*-(naphthalen-1-ylsulfonyl)glycine (5)



The title compound was synthesized according to general procedure **J** using methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-(naphthalen-1-ylsulfonyl)glycinate (**74**, 37 mg, 0.077 mmol, 1 eq) and 2 M aq. NaOH (154 µL, 0.308 mmol, 4 eq). Silica gel column chromatography (30-70% EtOAc in *n*-heptane with a drop of conc. HCl) afforded the product as a white powder (13 mg, 0.027 mmol, 35%). ^{1}H NMR (400 MHz, DMSO) δ 12.78 (bs, 1H), 8.40 – 8.31 (m, 1H), 8.13 (dt, *J* = 8.4, 1.0 Hz, 1H), 8.05 – 7.98 (m, 1H), 7.87 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.68 – 7.57 (m, 2H), 7.45 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.22 – 7.14 (m, 2H), 4.24 (s, 2H), 2.86 – 2.73 (m, 2H), 2.48 – 2.38 (m, 2H), 1.75 – 1.63 (m, 1H), 1.44 – 1.28 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 171.11, 141.50, 136.57, 133.70, 133.67, 130.35, 129.22, 128.93, 128.78, 127.82, 127.61, 126.68, 124.38, 124.28, 120.45, 64.86, 47.87, 34.03, 14.17. HRMS $[C_{22}H_{20}BrNO_4S+Na]^+$: 496.01886/498.01675 calculated, 496.01875/498.01659 found.

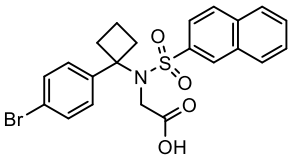
N-(1-(4-Bromophenyl)cyclobutyl)-*N*-((5-(dimethylamino)naphthalen-1-yl)sulfonyl)glycine (6)



The title compound was synthesized according to general procedure **J** using methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((5-(dimethylamino)naphthalen-1-yl)-sulfonyl)glycinate (**75**, 49 mg, 0.093 mmol, 1 eq) and 2 M aq. NaOH (186 µL, 0.372 mmol, 4 eq). Preparative HPLC afforded the product as a white powder (5.0 mg, 9.6 µmol, 10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dt, *J* = 8.6, 1.1 Hz, 1H), 8.24 (d, *J* = 8.7 Hz, 1H), 8.02 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.51 (dd, *J* = 8.7, 7.6 Hz, 1H), 7.42 (dd, *J* = 8.6, 7.4 Hz, 1H), 7.28 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.24 – 7.15 (m, 4H), 4.23 (s, 2H), 3.01 (s, 6H), 2.95 – 2.82 (m, 2H), 2.52 – 2.43 (m, 2H), 1.84 – 1.73 (m, 1H), 1.56 – 1.47 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.07, 149.19, 140.99, 137.11, 131.15, 129.93, 129.70, 129.41, 129.11, 129.06, 127.94, 124.00, 121.74,

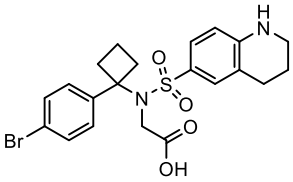
121.13, 115.93, 65.84, 47.97, 45.87, 34.56, 14.78. HRMS $[C_{24}H_{25}BrN_2O_4S+H]^+$: 517.07912/519.07701 calculated, 517.07893/519.07678 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-(naphthalen-2-ylsulfonyl)glycine (7)



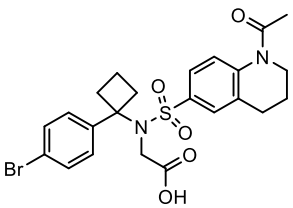
The title compound was synthesized according to general procedure **J** using methyl _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-(naphthalen-2-ylsulfonyl)glycinate (**76**, 43 mg, 0.089 mmol, 1 eq) and 2 M aq. NaOH (187 µL, 0.356 mmol, 4 eq). Silica gel column chromatography (30-70% EtOAc in _n_-heptane with a drop of conc. HCl) afforded the product as a white powder (25 mg, 0.052 mmol, 59%). ^{1}H NMR (400 MHz, DMSO) δ 8.00 – 7.85 (m, 4H), 7.71 – 7.57 (m, 2H), 7.48 (dd, _J_ = 8.7, 2.0 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.28 – 7.20 (m, 2H), 4.17 (s, 2H), 2.79 – 2.67 (m, 2H), 2.49 – 2.41 (m, 2H), 1.73-1.61 (m, 1H), 1.48 – 1.32 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 171.46, 141.55, 137.98, 133.86, 131.42, 130.66, 129.34, 129.22, 128.69, 128.67, 127.65, 127.39, 122.19, 120.62, 64.70, 48.00, 34.39, 14.14. HRMS$[C_{22}H_{20}BrNO_4S+Na]^+$: 496.01886/498.01675 calculated, 496.01877/498.01660 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((1,2,3,4-tetrahydroquinolin-6-yl)sulfonyl)glycine (8)



The title compound was synthesized according to general procedure **J** using methyl _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((1-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroquinolin-6-yl)sulfonyl)glycinate (**77**, 23 mg, 0.039 mmol, 1 eq) and 2 M aq. NaOH (78.0 µL, 0.156 mmol, 4 eq). Total time: overnight at rt. Preparative HPLC afforded the product as an off-white solid (7.0 mg, 0.015 mmol, 37%). ^{1}H NMR (500 MHz, DMSO) δ 7.47 – 7.36 (m, 4H), 7.00 (dd, _J_ = 8.6, 2.3 Hz, 1H), 6.44 (s, 2H), 6.28 (d, _J_ = 8.6 Hz, 1H), 3.73 (s, 2H), 3.20 – 3.14 (m, 2H), 2.89 – 2.81 (m, 2H), 2.47 – 2.42 (m, 2H), 2.37 – 2.29 (m, 2H), 1.78 – 1.71 (m, 2H), 1.70 – 1.60 (m, 1H), 1.48-1.37 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 157.89, 157.65, 148.22, 130.44, 129.42, 127.83, 126.20, 119.89, 118.28, 111.37, 64.19, 49.55, 40.37, 34.33, 26.51, 20.66, 14.45. HRMS $[C_{21}H_{23}BrN_2O_4S+H]^+$: 479.06347/481.06135 calculated, 479.06355/481.06145 found.

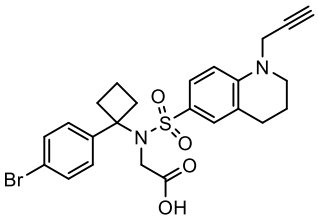
_N_-((1-Acetyl-1,2,3,4-tetrahydroquinolin-6-yl)sulfonyl)-_N_-(1-(4-bromophenyl)cyclobutyl)glycine (9)



To a solution of _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((1,2,3,4-tetrahydroquinolin-6-yl)sulfonyl)glycine (**8**, 30 mg, 0.063 mmol, 1 eq) in anhydrous THF (0.6 mL, 0.1 M) was added NaH (60% w/w in mineral oil, 10 mg, 0.025 mmol, 4 eq). The mixture was stirred at rt for 1 h. Acetyl chloride (26.8 µL, 0.375 mmol, 6 eq) was added and the mixture was stirred at rt for overnight. The mixture was diluted in 0.1 M aq. HCl and extracted 3× with EtOAc. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC to afford the product as a white solid (26 mg, 0.050 mmol, 80%). ^{1}H NMR (500 MHz, DMSO) δ 12.81 (bs, 1H), 7.52 (d, _J_ = 9.0 Hz, 1H), 7.34 (s, 4H), 7.26 (dd, _J_ = 8.7, 2.4 Hz, 1H), 6.77 (d,

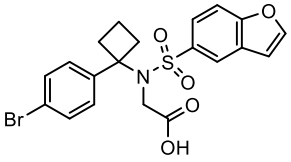
J = 2.3 Hz, 1H), 4.13 (s, 2H), 3.67 (t, *J* = 6.2 Hz, 2H), 2.78 – 2.68 (m, 2H), 2.55 (t, *J* = 6.6 Hz, 2H), 2.48 – 2.40 (m, 2H), 2.20 (s, 3H), 1.85 (p, *J* = 6.5 Hz, 2H), 1.75 – 1.65 (m, 1H), 1.47 – 1.34 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 169.68, 141.73, 141.56, 135.69, 131.15, 130.55, 129.36, 126.79, 124.05, 120.41, 64.40, 48.19, 44.12, 34.58, 26.41, 23.44, 23.03, 14.10. HRMS $[C_{23}H_{25}BrN_2O_5S+H]^+$: 521.07403/523.07193 calculated, 521.07417/523.07207 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((1-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroquinolin-6-yl)sulfonyl)glycine (10)



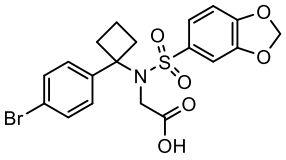
To a solution of *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((1,2,3,4-tetrahydroquinolin-6-yl)sulfonyl)glycine (**8**, 30 mg, 0.063 mmol, 1 eq) in anhydrous THF (0.6 mL, 0.1 M) was added NaH (60% w/w in mineral oil, 10 mg, 0.025 mmol, 4 eq). The mixture was stirred at rt for 1 h. 3-bromoprop-1-yne (23.7 µL, 0.313 mmol, 5 eq) was added and the mixture was stirred at rt for overnight. The mixture was diluted in 0.1 M aq. HCl and extracted 3× with EtOAc. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC to afford the product as a yellow solid (6.0 mg, 0.012 mmol, 19%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.20 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.60 (s, 1H), 6.52 (d, *J* = 8.8 Hz, 1H), 4.01 (d, *J* = 2.4 Hz, 2H), 3.96 (s, 2H), 3.37 (t, *J* = 5.8 Hz, 2H), 2.83 – 2.75 (m, 2H), 2.59 – 2.52 (m, 4H), 2.22 (t, *J* = 2.4 Hz, 1H), 1.95 (p, *J* = 6.1 Hz, 2H), 1.86 – 1.80 (m, 1H), 1.61 – 1.53 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.08, 141.60, 131.45, 129.12, 128.03, 127.53, 123.30, 121.64, 110.33, 78.58, 71.82, 65.51, 49.36, 40.72, 35.32, 27.65, 21.74, 14.88. HRMS $[C_{24}H_{25}BrN_2O_4S+Na]^+$: 539.06106/541.05896 calculated, 539.06081/541.05867 found.

_N_-(Benzofuran-5-ylsulfonyl)-_N_-(1-(4-bromophenyl)cyclobutyl)glycine (11)



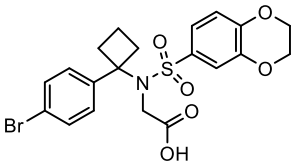
The title compound was synthesized according to general procedure **J** using ethyl *N*-(benzofuran-5-ylsulfonyl)-*N*-(1-(4-bromophenyl)cyclobutyl)glycinate (**78**, 7.7 mg, 0.016 mmol, 1 eq) and 1 M aq. LiOH (48 µL, 0.048 mmol, 3 eq). Total time: 4.5 h at rt. Silica gel column chromatography (3-10% MeOH in DCM) afforded the product (4.6 mg, 0.010 mmol, 64%). ^{1}H NMR (400 MHz, DMSO) δ 8.12 (d, *J* = 2.2 Hz, 1H), 7.71 (t, *J* = 1.3 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.46 – 7.41 (m, 2H), 7.32 – 7.27 (m, 2H), 6.96 (d, *J* = 2.2 Hz, 1H), 3.86 (s, 2H), 2.90 – 2.78 (m, 2H), 2.39 – 2.29 (m, 2H), 1.69 – 1.57 (m, 1H), 1.47 – 1.34 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 155.39, 147.90, 142.80, 137.18, 130.52, 129.44, 126.92, 123.19, 120.90, 120.12, 111.17, 107.31, 64.60, 49.82, 34.16, 14.37. HRMS $[C_{20}H_{18}BrNO_5S+Na]^+$: 485.99813/487.99601 calculated, 485.99846/487.99614 found.

_N_-(Benzo[_d_][1,3]dioxol-5-ylsulfonyl)-_N_-(1-(4-bromophenyl)cyclobutyl)glycine (12)



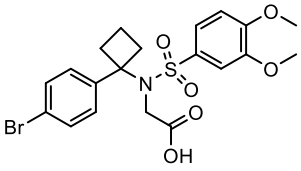
The title compound was synthesized according to the general procedure **J** using ethyl _N_-(benzo[_d_][1,3]dioxol-5-ylsulfonyl)-_N_-(1-(4-bromophenyl)cyclobutyl)glycinate (**79**, 49 mg, 0.099 mmol, 1 eq) and 1 M aq. LiOH (591 µL, 0.591 mmol, 6 eq). Total time: 2 h at rt. Silica gel column chromatography (10% MeOH in DCM) afforded the product (31 mg, 0.066 mmol, 67%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 7.35 – 7.26 (m, 4H), 7.05 (dd, _J_ = 8.2, 1.9 Hz, 1H), 6.70 (d, _J_ = 1.8 Hz, 1H), 6.69 (d, _J_ = 8.3 Hz, 1H), 6.03 (s, 2H), 4.06 (s, 2H), 2.87 – 2.76 (m, 2H), 2.50 – 2.42 (m, 2H), 1.81 – 1.72 (m, 1H), 1.61 – 1.48 (m, 1H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 173.01, 151.67, 148.32, 142.21, 135.12, 131.66, 129.65, 123.13, 121.90, 108.20, 107.90, 103.00, 65.81, 48.64, 35.27, 14.95. HRMS $[C_{19}H_{18}BrNO_6S+Na]^+$: 489.99304/491.99093 calculated, 489.99298/491.99076 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((2,3-dihydrobenzo[_b_][1,4]dioxin-6-yl)sulfonyl)glycine (13)



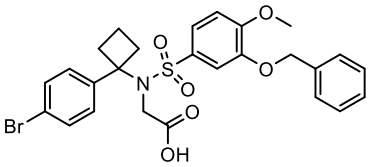
The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((2,3-dihydrobenzo[_b_][1,4]dioxin-6-yl)sulfonyl)glycinate (**80**, 22 mg, 0.043 9 mmol, 1 eq) and 2 M aq. NaOH (86 µL, 0.086 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (10-30% EtOAc in dis. _n_-pentane with a drop of con. HCl) afforded the product as a white solid (15 mg, 0.031 mmol, 72%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.28 – 7.23 (m, 2H), 6.97 (dd, _J_ = 8.6, 2.3 Hz, 1H), 6.74 (d, _J_ = 8.6 Hz, 1H), 6.71 (d, _J_ = 2.3 Hz, 1H), 4.31 – 4.20 (m, 4H), 4.05 (s, 2H), 2.86 – 2.75 (m, 2H), 2.50 – 2.41 (m, 2H), 1.80 – 1.71 (m, 1H), 1.59 – 1.48 (m, 1H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 172.75, 147.64, 143.49, 141.93, 133.91, 131.54, 129.48, 121.83, 120.87, 117.61, 117.19, 65.63, 65.07, 64.72, 48.47, 35.24, 14.86. HRMS $[C_{20}H_{20}BrNO_6S+Na]^+$: 504.00869/506.00659 calculated, 504.00884/506.00676 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((3,4-dimethoxyphenyl)sulfonyl)glycine (14)



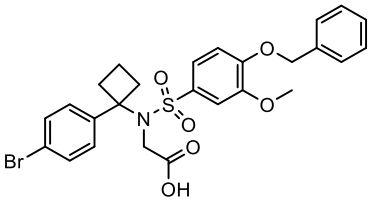
The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((3,4-dimethoxyphenyl)sulfonyl)glycinate (**81**, 30 mg, 0.059 mmol, 1 eq) and 1 M aq. LiOH (234 µL, 0.234 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (20-50% EtOAc in dis. _n_-pentane with a drop of conc. HCl) afforded the product as a white solid (21 mg, 0.043 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$+MeOD) δ 7.35 (s, 4H), 7.15 (dd, _J_ = 8.4, 2.2 Hz, 1H), 7.11 (d, _J_ = 2.2 Hz, 1H), 6.77 (d, _J_ = 8.5 Hz, 1H), 4.08 (s, 2H), 3.93 (s, 3H), 3.84 (s, 3H), 2.88 – 2.74 (m, 2H), 2.52 – 2.41 (m, 2H), 1.84 – 1.71 (m, 1H), 1.63 – 1.51 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$+MeOD) δ 172.13, 152.12, 148.51, 141.56, 133.10, 131.01, 129.09, 121.29, 121.10, 109.95, 109.68, 65.25, 56.00, 55.89, 47.58, 34.44, 14.46. HRMS $[C_{20}H_{22}BrNO_6S+NH_4]^+$: 501.06895/503.06685 calculated, 501.06877/503.06651 found.

_N_-((3-(Benzyloxy)-4-methoxyphenyl)sulfonyl)-_N_-(1-(4-bromophenyl)cyclobutyl)glycine (15)



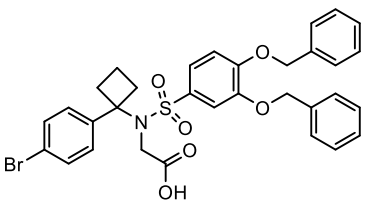
The title compound was synthesized according to the general procedure **J** using ethyl _N_-((3-(benzyloxy)-4-methoxyphenyl)sulfonyl)-_N_-(1-(4-bromophenyl)cyclobutyl)glycinate (**82**, 20 mg, 0.034 mmol, 1 eq) and 1 M aq. LiOH (136 µL, 0.136 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (20-40% EtOAc in dis. *n*-pentane with a drop of conc. HCl) afforded the product as a white powder (9.0 mg, 0.016 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H), 7.43 – 7.37 (m, 2H), 7.35 – 7.28 (m, 3H), 7.19 – 7.14 (m, 2H), 7.12 (d, *J* = 2.2 Hz, 1H), 7.02 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.72 (d, *J* = 8.6 Hz, 1H), 5.13 (s, 2H), 3.94 (s, 3H), 3.91 (s, 2H), 2.73 – 2.62 (m, 2H), 2.44 – 2.36 (m, 2H), 1.75 – 1.66 (m, 1H), 1.55 – 1.46 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.52, 153.13, 147.58, 141.26, 136.42, 132.51, 131.35, 129.05, 128.89, 128.35, 127.59, 121.75, 121.65, 112.09, 110.57, 70.95, 65.38, 56.36, 47.96, 34.67, 14.64. HRMS $[C_{26}H_{26}BrNO_6S+NH_4]^+$: 577.10025/579.09818 calculated, 577.10021/579.09804 found.

_N_-((4-(Benzyloxy)-3-methoxyphenyl)sulfonyl)-_N_-(1-(4-bromophenyl)cyclobutyl)glycine (16)



The title compound was synthesized according to the general procedure **J** using ethyl _N_-((4-(benzyloxy)-3-methoxyphenyl)sulfonyl)-_N_-(1-(4-bromophenyl)cyclobutyl)glycinate (**83**, 19 mg, 0.032 mmol, 1 eq) and 1 M aq. LiOH (130 µL, 0.130 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (20-40% EtOAc in dis. *n*-pentane with a drop of conc. HCl) afforded the product as a white powder (15 mg, 0.027 mmol, 83%). ^{1}H NMR (500 MHz, MeOD+$CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.39 – 7.35 (m, 2H), 7.33 – 7.27 (m, 5H), 7.04 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.02 (d, *J* = 2.2 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 5.16 (s, 2H), 4.11 (s, 2H), 3.79 (s, 3H), 2.87 – 2.78 (m, 2H), 2.49 – 2.40 (m, 2H), 1.79 – 1.71 (m, 1H), 1.58 – 1.50 (m, 1H). ^{13}C NMR (126 MHz, MeOD+$CDCl_3$) δ 173.19, 152.35, 150.00, 142.62, 137.17, 134.38, 131.82, 130.03, 129.34, 128.89, 128.25, 122.02, 121.66, 113.21, 111.12, 71.69, 66.14, 56.47, 48.56, 35.41, 15.11. HRMS $[C_{26}H_{26}BrNO_6S+NH_4]^+$: 577.10025/579.09818 calculated, 577.09999/579.09781 found.

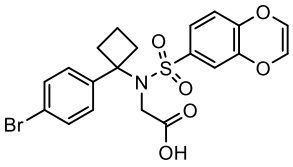
_N_-((3,4-bis(Benzyloxy)phenyl)sulfonyl)-_N_-(1-(4- bromophenyl)cyclobutyl)glycine (17)



The title compound was synthesized according to the general procedure **J** using ethyl _N_-((3,4-bis(benzyloxy)phenyl)sulfonyl)-_N_-(1-(4-bromophenyl)cyclobutyl)glycinate (**84**, 20 mg, 0.029 mmol, 1 eq) and 1 M aq. LiOH (177 µL, 0.177 mmol, 6 eq). Total time: 4 h at rt. Silica gel column chromatography (20-40% EtOAc in dis. *n*-pentane with a drop of

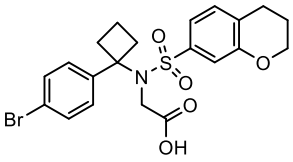
conc. HCl) afforded the product (4.9 mg, 7.7 µmol, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 4H), 7.42 – 7.28 (m, 8H), 7.21 – 7.14 (m, 2H), 7.14 (d, *J* = 2.2 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 5.21 (s, 2H), 5.12 (s, 2H), 3.93 (s, 2H), 2.73 – 2.63 (m, 2H), 2.44 – 2.36 (m, 2H), 1.76 – 1.66 (m, 1H), 1.56 – 1.43 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.53, 152.38, 148.15, 141.30, 136.61, 136.31, 133.04, 131.35, 129.07, 128.82, 128.79, 128.31, 128.24, 127.52, 127.35, 121.66, 121.63, 113.03, 113.00, 71.10, 65.40, 47.94, 34.67, 34.26, 14.64. HRMS $[C_{32}H_{30}BrNO_6+Na]^+$: 658.08694/660.08494 calculated, 658.08667/660.08451 found.

_N_-(Benzo[_b_][1,4]dioxin-6-ylsulfonyl)-_N_-(1-(4-bromophenyl)cyclobutyl)glycine (18)



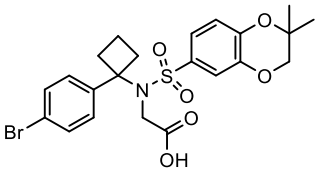
The title compound was synthesized according to the general procedure **J** using ethyl *N*-(benzo[*b*][1,4]dioxin-6-ylsulfonyl)-*N*-(1-(4-bromophenyl)cyclobutyl)glycinate (**85**, 15 mg, 0.030 mmol, 1 eq) and 1 M aq. LiOH (118 µL, 0.118 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (20-30% EtOAc in dis. *n*-pentane with a drop of conc. HCl) afforded the product as a white solid (6.5 mg, 0.014 mmol, 46%). ^{1}H NMR (500 MHz, MeOD+$CDCl_3$) δ 7.41 – 7.34 (m, 2H), 7.32 – 7.25 (m, 2H), 6.95 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H), 5.91 – 5.85 (m, 2H), 4.02 (s, 2H), 2.84 – 2.71 (m, 2H), 2.50 – 2.43 (m, 2H), 1.81 – 1.72 (m, 1H), 1.60 – 1.50 (m, 1H). ^{13}C NMR (126 MHz, MeOD+$CDCl_3$) δ 172.50, 146.68, 142.85, 141.84, 137.01, 131.62, 129.48, 127.56, 127.00, 124.12, 122.07, 116.36, 115.68, 65.72, 48.30, 35.13, 14.84. HRMS $[C_{20}H_{18}BrNO_6S+NH_4]^+$: 497.03765/499.03560 calculated, 497.03741/499.03515 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-(chroman-7-ylsulfonyl)glycine (19)



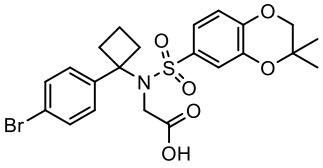
The title compound was synthesized according to the general procedure **J** using ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-(chroman-7-ylsulfonyl)glycinate (**86**, 24 mg, 0.047 mmol, 1 eq) and 1 M aq. LiOH (189 µL, 0.189 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (20-30% EtOAc in dis. *n*-pentane with a drop of conc. HCl) afforded the product as a white solid (16 mg, 0.033 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$+MeOD) δ 7.35 – 7.24 (m, 4H), 7.01 – 6.96 (m, 1H), 6.92 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 4.25 – 4.17 (m, 2H), 4.11 (s, 2H), 2.91 – 2.77 (m, 4H), 2.54 – 2.44 (m, 2H), 2.07 – 1.98 (m, 2H), 1.84 – 1.73 (m, 1H), 1.64 – 1.50 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$+MeOD) δ 171.86, 154.22, 140.85, 139.29, 130.60, 129.55, 128.57, 126.85, 120.98, 117.63, 114.97, 66.28, 64.73, 47.68, 34.31, 24.39, 21.27, 13.93. HRMS $[C_{21}H_{22}BrNO_5S+NH_4]^+$: 497.07403/499.07192 calculated, 497.07396/499.07175 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((2,2-dimethyl-2,3-dihydrobenzo[_b_][1,4]dioxin-6-yl)sulfonyl)glycine (20)



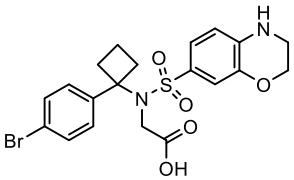
The title compound was synthesized according to the general procedure **J** using ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)glycinate (**87**, 31.5 mg, 59.0 µmol, 1 eq) and 1 M aq. LiOH (234 µL, 0.234 mmol, 4 eq). Total time: 4 h at rt. Silica gel column chromatography (20-30% EtOAc in dis. *n*-pentane with a drop of conc. HCl) afforded the product as a white solid (25 mg, 49 µmol, 84%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 7.35 – 7.24 (m, 4H), 6.98 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.73 (d, *J* = 2.3 Hz, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 4.04 (s, 2H), 3.89 (s, 2H), 2.89 – 2.76 (m, 2H), 2.52 – 2.42 (m, 2H), 1.82 – 1.69 (m, 1H), 1.59 – 1.46 (m, 1H), 1.32 (s, 6H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 172.92, 146.99, 142.39, 142.16, 133.37, 131.67, 129.64, 121.99, 121.63, 117.89, 116.77, 74.12, 72.31, 65.80, 48.55, 35.40, 23.43, 14.97. HRMS $[C_{22}H_{24}BrNO_6S+NH_4]^+$: 527.08460/529.08251 calculated, 527.08469/529.08251 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((3,3-dimethyl-2,3-dihydrobenzo[_b_][1,4]dioxin-6-yl)sulfonyl)glycine (21)



The title compound was synthesized according to the general procedure **J** using ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((3,3-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)glycinate (**88**, 42 mg, 0.078 mmol, 1 eq) and 1 M aq. LiOH (313 µL, 0.313 mmol, 4 eq). Total time: 4 h at rt. Silica gel column chromatography (20-30% EtOAc in dis. *n*-pentane with a drop of conc. HCl) afforded the product as a white solid (27 mg, 0.053 mmol, 68%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 7.34 – 7.25 (m, 4H), 6.97 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 1H), 4.05 (s, 2H), 3.92 (s, 2H), 2.88 – 2.77 (m, 2H), 2.52 – 2.42 (m, 2H), 1.82 – 1.71 (m, 1H), 1.60 – 1.47 (m, 1H), 1.31 (s, 6H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 172.98, 146.57, 142.79, 142.21, 134.27, 131.70, 129.67, 121.89, 120.72, 117.47, 117.18, 73.41, 72.53, 65.79, 48.59, 35.44, 23.35, 15.00. HRMS $[C_{22}H_{24}BrNO_6S+NH_4]^+$: 527.08460/529.08251 calculated, 527.08486/529.08261 found.

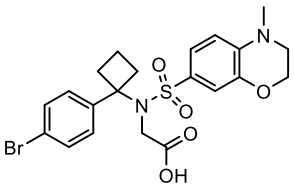
_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]oxazin-7-yl)sulfonyl)glycine (22)



The title compound was synthesized according to the general procedure **J** using ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)sulfonyl)glycinate (**89**, 30 mg, 0.059 mmol, 1 eq) and 1 M aq. LiOH (356 µL, 0.356 mmol, 6 eq). Total time: 2 h at rt. Silica gel column chromatography (5-10% MeOH in DCM) afforded the product as a white solid (11 mg, 0.023 mmol, 39%). ^{1}H NMR (400 MHz, DMSO+MeOD) δ 7.34 – 7.27 (m, 4H), 6.76 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.44 (d, *J* = 2.1 Hz, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 4.07 – 4.03 (m, 2H), 3.91 (s, 2H), 3.33 – 3.26 (m, 2H), 2.76 – 2.65 (m, 2H), 2.40 – 2.32 (m, 2H), 1.71 – 1.60 (m, 1H), 1.47 – 1.36 (m, 1H). ^{13}C NMR (101 MHz, DMSO+MeOD)

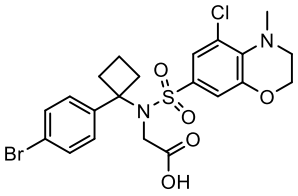
δ 172.73, 143.19, 142.41, 139.80, 131.53, 129.96, 127.98, 121.91, 121.39, 115.78, 113.42, 65.53, 65.11, 48.02, 40.39, 35.20, 14.89. HRMS $[C_{20}H_{21}BrN_2O_5S+Na]^+$: 503.02468/505.02257 calculated, 503.02460/505.02245 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((4-methyl-3,4-dihydro-2_H_-benzo[_b_][1,4]oxazin-7-yl)sulfonyl)glycine (23)



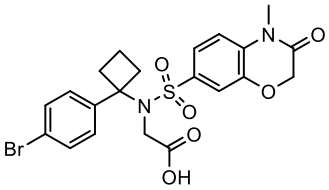
To a solution of *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)sulfonyl)glycine (**22**, 12 mg, 26 µmol, 1 eq) in anhydrous DMF (111 µL, 0.23 M) was added NaH (60% w/w in mineral oil, 2.0 mg, 0.051 mmol, 2 eq) portion-wise at 0 °C under N_2. The mixture was stirred at 0 °C for 20 min. CH_3I (3.5 µL, 0.056 mmol, 2.2 eq) was following added and the mixture was stirred at 0 °C for 30 min and at rt for 48 h. The reaction was quenched by water and extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by HPLC to afford the product (2.0 mg, 4.0 µmol, 16%). ^{1}H NMR (500 MHz, DMSO) δ 7.38 (s, 4H), 6.90 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.53 (d, *J* = 8.6 Hz, 1H), 6.48 (d, *J* = 2.2 Hz, 1H), 4.19 (t, *J* = 4.4 Hz, 2H), 3.94 (s, 2H), 3.45-3.24 (m, 2H), 2.90 (s, 3H), 2.76 – 2.66 (m, 2H), 2.41 – 2.35 (m, 2H), 1.73 – 1.64 (m, 1H), 1.48 – 1.37 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 169.66, 142.17, 139.68, 130.55, 129.21, 121.09, 120.28, 113.50, 110.16, 64.37, 63.99, 48.03, 47.75, 37.79, 34.20, 14.17. HRMS $[C_{21}H_{23}BrN_2O_5S+Na]^+$: 517.04033/519.03822 calculated, 517.04044/519.03818 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((5-chloro-4-methyl-3,4-dihydro-2_H_-benzo[_b_][1,4]oxazin-7- yl)sulfonyl)glycine (24)



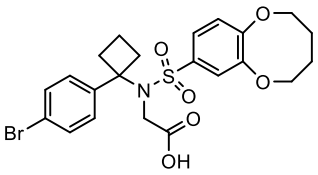
The title compound was synthesized according to the general procedure **J** using ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((5-chloro-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)sulfonyl)glycinate (**90**, 33 mg, 0.060 mmol, 1 eq) and 1 M aq. LiOH (358 µL, 0.358 mmol, 6 eq). Total time: 2 h at rt. Silica gel column chromatography (5-10% MeOH in DCM) afforded the product as a white solid (19 mg, 0.036 mmol, 61%). ^{1}H NMR (400 MHz, DMSO) δ 7.36 – 7.29 (m, 4H), 6.68 (d, *J* = 2.2 Hz, 1H), 6.62 (d, *J* = 2.2 Hz, 1H), 4.18 – 4.10 (m, 4H), 3.08 (t, *J* = 4.3 Hz, 2H), 2.85 (s, 3H), 2.75 – 2.65 (m, 2H), 2.46 – 2.38 (m, 2H), 1.75 – 1.65 (m, 1H), 1.45 – 1.36 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 171.65, 147.76, 141.28, 136.93, 134.14, 130.54, 129.26, 126.24, 120.71, 119.90, 114.07, 64.43, 60.34, 48.72, 48.30, 42.67, 34.62, 14.11. HRMS $[C_{21}H_{22}BrClN_2O_5S+H]^+$: 529.01941/531.01711 calculated, 529.01912/531.01659 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((4-methyl-3-oxo-3,4-dihydro-2_H_-benzo[_b_][1,4]oxazin-7- yl)sulfonyl)glycine (25)



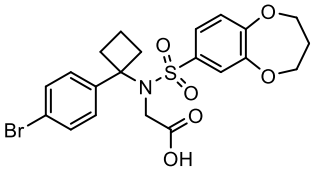
The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((4-methyl-3-oxo-3,4-dihydro-2_H_- benzo[_b_][1,4]oxazin-7-yl)sulfonyl)glycinate (**91**, 13 mg, 0.024 mmol, 1 eq) and 1 M aq. LiOH (145 µL, 0.145 mmol, 6 eq). Total time: 2 h at rt. Silica gel column chromatography (5-10% MeOH in DCM) to afford the product (6.2 mg, 0.012 mmol, 50%). ^{1}H NMR (500 MHz, DMSO) δ 7.41 – 7.34 (m, 4H), 7.20 (dd, _J_ = 8.5, 2.1 Hz, 1H), 7.07 (d, _J_ = 8.6 Hz, 1H), 6.83 (d, _J_ = 2.0 Hz, 1H), 4.69 (s, 2H), 3.97 (s, 2H), 3.28 (s, 3H), 2.82 – 2.72 (m, 2H), 2.41 – 2.34 (m, 2H), 1.71 – 1.63 (m, 1H), 1.45 – 1.38 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 172.10, 163.90, 143.74, 142.14, 136.28, 132.28, 130.55, 129.34, 121.43, 120.30, 114.82, 114.37, 66.89, 64.49, 49.18, 34.20, 27.85, 14.18. HRMS $[C_{21}H_{21}BrN_2O_6S+Na]^+$: 531.01959/533.01750 calculated, 531.01937/533.01713 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((2,3,4,5-tetrahydrobenzo[_b_][1,4]dioxocin-8-yl)sulfonyl)glycine (26)



The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((2,3,4,5-tetrahydrobenzo[_b_][1,4]dioxocin-8-yl)sulfonyl)glycinate (**92**, 33 mg, 0.061 mmol, 1 eq) and 1 M aq. LiOH (363 µL, 0.363 mmol, 6 eq). Total time: 2 h at rt. Silica gel column chromatography (5% MeOH in DCM) afforded the product (27 mg, 0.052 mmol, 86%). ^{1}H NMR (500 MHz, MeOD) δ 7.38 – 7.32 (m, 4H), 7.06 (dd, _J_ = 8.5, 2.4 Hz, 1H), 6.84 (d, _J_ = 2.4 Hz, 1H), 6.82 (d, _J_ = 8.5 Hz, 1H), 4.44 (t, _J_ = 5.5 Hz, 2H), 4.22 (t, _J_ = 5.4 Hz, 2H), 4.14 (s, 2H), 2.91 – 2.82 (m, 2H), 2.54 – 2.46 (m, 2H), 1.94 (p, _J_ = 5.8 Hz, 2H), 1.84 (p, _J_ = 5.6 Hz, 2H), 1.81 – 1.72 (m, 1H), 1.58 – 1.50 (m, 1H). ^{13}C NMR (126 MHz, MeOD) δ 173.78, 155.38, 148.71, 143.15, 136.11, 132.16, 130.41, 124.10, 123.78, 122.39, 122.31, 74.95, 72.84, 66.40, 49.13, 35.99, 28.70, 26.56, 15.30. HRMS $[C_{22}H_{24}BrNO_6S+Na]^+$: 532.03999/534.03790 calculated, 532.03995/534.03765 found.

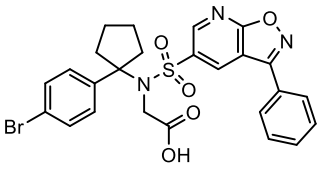
_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycine (27)



The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycinate (**93**, 20.5 mg, 39.1 µmol, 1 eq) and 1 M aq. LiOH (235 µL, 0.235 mmol, 6 eq). Total time: 2 h at rt. Silica gel column chromatography (5% MeOH in DCM) afforded the product (16.5 mg, 33.2 µmol, 85%). ^{1}H NMR (400 MHz, MeOD) δ 7.38 – 7.31 (m, 4H), 7.03 (dd, _J_ = 8.5, 2.3 Hz, 1H), 6.83 (d, _J_ = 8.5 Hz, 1H), 6.74 (d, _J_ = 2.3 Hz, 1H), 4.25 (t, _J_ = 5.6 Hz, 2H), 4.20 (t, _J_ = 5.7 Hz, 2H), 4.14 (s, 2H), 2.93 – 2.80 (m, 2H), 2.55 – 2.45 (m, 2H), 2.23 – 2.16 (m, 2H), 1.83 – 1.72 (m, 1H), 1.60 – 1.49 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ

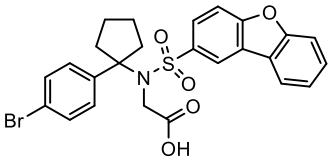
155.93, 151.71, 143.09, 136.67, 132.16, 130.45, 123.47, 122.34, 122.30, 121.86, 71.82, 71.80, 66.36, 49.21, 36.04, 32.23, 15.30. HRMS $[C_{21}H_{22}BrNO_6S+Na]^+$: 518.02434/520.02224 calculated, 518.02422/520.02196 found.

N-(1-(4-Bromophenyl)cyclopentyl)-*N*-((3-phenylisoxazolo[5,4-*b*]pyridin-5-yl)sulfonyl)glycine (28)



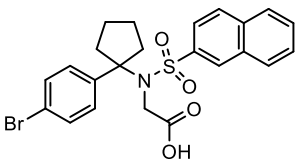
The title compound was synthesized according to the general procedure **J** using ethyl *N*-(1-(4-bromophenyl)cyclopentyl)-*N*-((3-phenylisoxazolo[5,4-*b*]pyridin-5-yl)sulfonyl)glycinate (**99a**, 20 mg, 0.034 mmol, 1 eq) and 2 M aq. NaOH (51 µL, 0.102 mmol, 3 eq). Total time: 3 h at rt. Silica gel column chromatography (6-13% MeOH in DCM) afforded the product (1.1 mg, 2.0 µmol, 6%). LC-MS $[C_{25}H_{22}BrN_3O_5S+H]^+$: 556.05/558.05 calculated, 555.93/557.80 found. HRMS $[C_{25}H_{22}BrN_3O_5S+H]^+$: 556.05363/558.05154 calculated, 556.05374/558.05152 found.

N-(1-(4-Bromophenyl)cyclopentyl)-*N*-(dibenzo[*b*,*d*]furan-2-ylsulfonyl)glycine (29)



The title compound was synthesized according to the general procedure **J** using ethyl *N*-(1-(4-bromophenyl)cyclopentyl)-*N*-(dibenzo[*b*,*d*]furan-2-ylsulfonyl)glycinate (**99b**, 19 mg, 0.035 mmol, 1 eq) and 2 M aq. NaOH (52.5 µL, 0.105 mmol, 3 eq). Total time: 4 h at rt. Silica gel column chromatography (30% EtOAc in dis. *n*-pentane with a drop of conc. HCl) afforded the product (6.5 mg, 0.012 mmol, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 1.9 Hz, 1H), 7.94 (dt, *J* = 7.5, 1.1 Hz, 1H), 7.84 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.62 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.43 (td, *J* = 7.4, 1.0 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.25 – 7.21 (m, 2H), 4.26 (s, 2H), 2.45 – 2.36 (m, 2H), 2.34 – 2.24 (m, 2H), 1.74 – 1.63 (m, 2H), 1.41 – 1.22 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.62, 158.03, 157.16, 141.25, 136.25, 131.27, 129.19, 128.59, 126.68, 124.68, 123.84, 123.26, 121.83, 121.48, 121.26, 112.14, 111.91, 73.74, 48.92, 38.10, 21.58. HRMS $[C_{25}H_{22}BrNO_5S+Na]^+$: 550.02943/552.02734 calculated, 550.02954/552.02728 found.

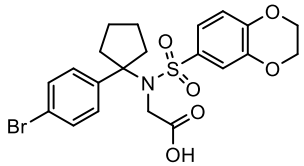
N-(1-(4-Bromophenyl)cyclopentyl)-*N*-(naphthalen-2-ylsulfonyl)glycine (30)



The title compound was synthesized according to the general procedure **J** using ethyl *N*-(1-(4-bromophenyl)cyclopentyl)-*N*-(naphthalen-2-ylsulfonyl)glycinate (**99c**, 21 mg, 0.040 mmol, 1 eq) and 2 M aq. NaOH (60 µL, 0.12 mmol, 3 eq). Total time: 3.5 h at rt. Silica gel column chromatography (2-6% MeOH in DCM) afforded the product (6.8 mg, 0.014 mmol, 35%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.85 – 7.79 (m, 2H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.19 (s, 4H), 4.25 (s, 2H), 2.45 – 2.21 (m, 4H), 1.73 – 1.59 (m, 2H), 1.39 – 1.28 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.82, 141.16, 138.57, 134.68, 132.05, 131.24, 129.61, 129.19, 128.98, 128.92, 127.88, 127.57,

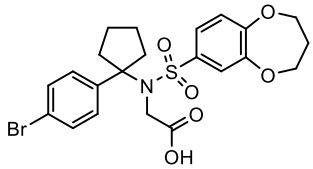
122.83, 121.80, 73.67, 49.26, 38.05, 21.54. HRMS $[C_{23}H_{22}BrNO_4S+Na]^+$: 510.03451/512.03240 calculated, 510.03497/512.03274 found.

_N_-(1-(4-Bromophenyl)cyclopentyl)-_N_-((2,3-dihydrobenzo[_b_][1,4]dioxin-6-yl)sulfonyl)glycine (31)



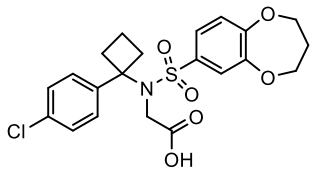
The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(4-bromophenyl)cyclopentyl)-_N_-((2,3-dihydrobenzo[_b_][1,4]dioxin-6-yl)sulfonyl)glycinate (**99d**, 16.5 mg, 31.5 µmol, 1 eq) and 1 M aq. LiOH (94 µL, 0.094 mmol, 3 eq). Silica gel column chromatography (25-30% EtOAc in dis. _n_-pentane with a drop of conc. HCl) afforded the product (1.0 mg, 2.0 µmol, 7%). LC-MS $[C_{21}H_{22}BrNO_6S+NH_4]^+$: 513.07/515.07 calculated, 512.58/514.58 found. HRMS $[C_{21}H_{22}BrNO_6S+Na]^+$: 518.02434/520.02224 calculated, 518.02369/520.02154 found.

_N_-(1-(4-Bromophenyl)cyclopentyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycine (32)



The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(4-bromophenyl)cyclopentyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycinate (**99e**, 48 mg, 0.089 mmol, 1 eq) and 1 M aq. LiOH (267 µL, 0.267 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (20-40% EtOAc in _n_-heptane with a drop of conc. HCl) afforded the product as a white solid (26 mg, 0.051 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.26 – 7.20 (m, 3H), 7.14 (d, _J_ = 2.3 Hz, 1H), 6.91 (d, _J_ = 8.5 Hz, 1H), 4.32 (t, _J_ = 5.8 Hz, 2H), 4.26 (t, _J_ = 5.8 Hz, 2H), 4.18 (s, 2H), 2.41 – 2.32 (m, 2H), 2.31 – 2.20 (m, 4H), 1.75 – 1.65 (m, 2H), 1.39 – 1.30 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.80, 154.65, 150.41, 141.32, 135.84, 131.22, 129.14, 122.89, 121.71, 121.53, 121.41, 73.53, 70.61, 70.53, 49.07, 37.94, 30.95, 21.58. HRMS $[C_{22}H_{24}BrNO_6S+Na]^+$: 532.03999/534.03790 calculated, 532.04016/534.03809 found.

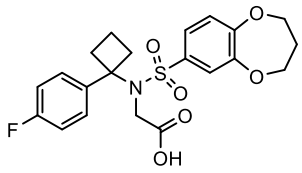
_N_-(1-(4-Chlorophenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycine (33)



The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(4-chlorophenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycinate (**105a**, 33 mg, 0.069 mmol, 1 eq) and 1 M aq. LiOH (414 µL, 0.414 mmol, 6 eq). Total time: 2 h at rt. Silica gel column chromatography (5% MeOH in DCM) afforded the product as a white powder (20 mg, 0.044 mmol, 65%). ^{1}H NMR (400 MHz, MeOD) δ 7.43 – 7.37 (m, 2H), 7.23 – 7.18 (m, 2H), 7.04 (dd, _J_ = 8.5, 2.4 Hz, 1H), 6.83 (d, _J_ = 8.5 Hz, 1H), 6.74 (d, _J_ = 2.4 Hz, 1H), 4.24 (t, _J_ = 5.8 Hz, 2H), 4.19 (t, _J_ = 5.8 Hz, 2H), 4.14 (s, 2H), 2.92 – 2.82 (m, 2H), 2.55 – 2.47 (m, 2H), 2.18 (p, _J_ = 5.8 Hz, 2H), 1.82 – 1.72 (m, 1H), 1.59 – 1.49 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 173.96, 155.93, 151.71, 142.58, 136.66, 134.18,

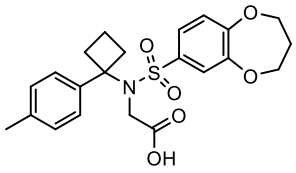
130.11, 129.15, 123.46, 122.34, 121.88, 71.76, 66.32, 49.21, 36.06, 32.22, 15.30. HRMS $[C_{21}H_{22}ClNO_6S+Na]^+$: 474.07486 calculated, 474.07469 found.

_N_-(1-(4-Fluorophenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycine (34)



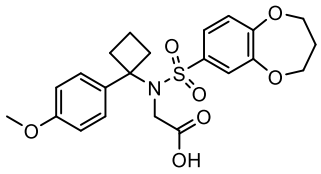
The title compound was synthesized according to the general procedure **J** using ethyl *N*-(1-(4-fluorophenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate (**105b**, 18 mg, 0.034 mmol, 1 eq) and 1 M aq. LiOH (207 µL, 0.207 mmol, 6 eq). Total time: 2 h at rt. Silica gel column chromatography (5% MeOH in DCM) afforded the product as a white powder (24 mg, 0.055 mmol, 86%). ^{1}H NMR (400 MHz, MeOD) δ 7.48 – 7.42 (m, 2H), 7.06 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.97 – 6.90 (m, 2H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 2.3 Hz, 1H), 4.23 (t, *J* = 5.8 Hz, 2H), 4.17 (t, *J* = 5.8 Hz, 2H), 4.11 (s, 2H), 2.92 – 2.81 (m, 2H), 2.56 – 2.47 (m, 2H), 2.18 (p, *J* = 5.7 Hz, 2H), 1.81 – 1.71 (m, 1H), 1.58 – 1.48 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 174.00, 163.34 (d, J_{C-F} = 245.1 Hz), 155.86, 151.71, 139.76 (d, J_{C-F} = 3.3 Hz), 136.78, 130.45 (d, J_{C-F} = 8.1 Hz), 123.48, 122.31, 121.95, 115.69 (d, J_{C-F} = 21.5 Hz), 71.72, 71.68, 66.35, 49.28, 36.13, 32.22, 15.32. HRMS $[C_{21}H_{22}FNO_6S+Na]^+$: 458.10441 calculated, 458.10419 found.

_N_-((3,4-Dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)-_N_-(1-(_p_-tolyl)cyclobutyl)glycine (35)



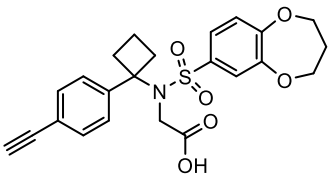
To a mixture of *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycine (**27**, 35 mg, 0.071 mmol, 1 eq), K_2CO_3 (29.2 mg, 0.212 mmol, 3 eq) and methylboronic acid (8.4 mg, 0.14 mmol, 2 eq) in degassed 1,4-dioxane/H_2O (0.5 mL/0.5 mL, 0.07 M) under N_2 was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5.8 mg, 7.1 µmol, 0.1 eq). The mixture was heated to 85 °C and stirred overnight. The reaction mixture was diluted in 0.1 M aq. HCl and extracted 3× with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered through Celite and concentrated. The residue was purified by silica gel column chromatography (20-40% EtOAc in *n*-heptane with a drop of conc. HCl) to afford the product as a white solid (15 mg, 0.035 mmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.12 – 7.06 (m, 3H), 7.02 (d, *J* = 2.3 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 4.27 (t, *J* = 5.7 Hz, 2H), 4.21 (t, *J* = 5.8 Hz, 2H), 4.01 (s, 2H), 2.85 – 2.74 (m, 2H), 2.60 – 2.51 (m, 2H), 2.34 (s, 3H), 2.22 (p, *J* = 5.7 Hz, 2H), 1.84 – 1.74 (m, 1H), 1.64 – 1.52 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.95, 154.56, 150.42, 139.04, 137.54, 135.03, 129.09, 127.12, 122.93, 121.38, 70.54, 70.44, 65.83, 47.98, 34.87, 31.03, 21.19, 14.84. HRMS $[C_{22}H_{25}NO_6S+Na]^+$: 454.12948 calculated, 454.12958 found.

_N_-(1-(4-Methoxyphenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycine (36)



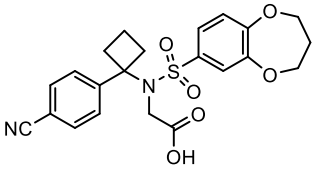
The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(4-methoxyphenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycinate (**105c**, 17 mg, 0.036 mmol, 1 eq) and 1 M aq. LiOH (214 µL, 0.214 mmol, 6 eq). Total time: 2 h at rt. Silica gel column chromatography (5% MeOH in DCM) afforded the product as a white powder (14 mg, 0.032 mmol, 89%). ^{1}H NMR (400 MHz, MeOD) δ 7.34 – 7.28 (m, 2H), 7.04 (dd, _J_ = 8.5, 2.4 Hz, 1H), 6.81 (d, _J_ = 8.5 Hz, 1H), 6.76 – 6.72 (m, 2H), 6.70 (d, _J_ = 2.4 Hz, 1H), 4.22 (t, _J_ = 5.7 Hz, 2H), 4.15 (t, _J_ = 5.7 Hz, 2H), 4.08 (s, 2H), 3.79 (s, 3H), 2.90 – 2.78 (m, 2H), 2.55 – 2.47 (m, 2H), 2.17 (p, _J_ = 5.7 Hz, 2H), 1.79 – 1.70 (m, 1H), 1.57 – 1.48 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 174.12, 160.33, 155.76, 151.68, 136.73, 135.38, 129.56, 123.53, 122.16, 122.05, 114.39, 71.65, 66.42, 55.67, 49.00, 36.17, 32.28, 15.42. HRMS $[C_{22}H_{25}NO_7S+Na]^+$: 470.12439 calculated, 470.12427 found.

_N_-(1-(4-Ethynylphenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycine (37)



The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(4-ethynylphenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycinate (**105d**, 30 mg, 0.064 mmol, 1 eq) and 1 M aq. LiOH (385 µL, 0.385 mmol, 6 eq). Total time: 2 h at rt. Silica gel column chromatography (5% MeOH in DCM) afforded the product as a white powder (28 mg, 0.063 mmol, 99%). ^{1}H NMR (400 MHz, DMSO+MeOD) δ 7.36 – 7.28 (m, 2H), 7.27 – 7.18 (m, 2H), 6.98 (dd, _J_ = 8.4, 2.3 Hz, 1H), 6.77 (d, _J_ = 8.5 Hz, 1H), 6.62 (d, _J_ = 2.3 Hz, 1H), 4.15 (t, _J_ = 5.5 Hz, 2H), 4.09 (t, _J_ = 5.6 Hz, 2H), 4.03 (s, 2H), 3.70 (s, 1H), 2.82 – 2.69 (m, 2H), 2.45 – 2.34 (m, 2H), 2.08 (p, _J_ = 5.6 Hz, 2H), 1.72 – 1.61 (m, 1H), 1.48 – 1.37 (m, 1H). ^{13}C NMR (101 MHz, DMSO+MeOD) δ 173.08, 155.21, 151.04, 144.25, 136.45, 132.22, 128.10, 123.03, 122.04, 121.85, 121.37, 84.17, 79.94, 71.37, 71.30, 65.85, 49.18, 35.49, 31.74, 14.97. HRMS $[C_{23}H_{23}NO_6S+Na]^+$: 464.11383 calculated, 464.11366 found.

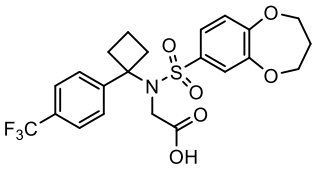
_N_-(1-(4-Cyanophenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycine (38)



_i_-PrOH (70 µL), H_2O (175 µL), Na_2CO_3 (27 mg, 0.25 mmol, 2.5 eq), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 0.1 eq), potassium hexacyanoferrate(II) trihydrate (12.5 mg, 0.300 mmol, 3 eq) and _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycine (**27**, 50 mg, 0.10 mmol, 1 eq) were ordinally added into a microtube equipped with DMF (1.2 mL, 0.08 M). The mixture was degassed under argon and heated to 100 °C and stirred overnight. The mixture was diluted in 0.1 M aq. HCl and extracted 3× with EtOAc. Combined organic layers were washed with brine, dried over

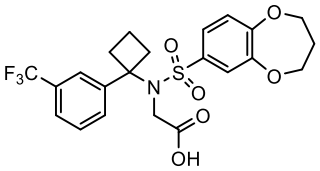
anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC to afford the product as a white solid (5.2 mg, 0.012 mmol, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 4H), 7.11 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.83 (d, *J* = 2.4 Hz, 1H), 4.30 (t, *J* = 5.8 Hz, 2H), 4.25 (t, *J* = 5.9 Hz, 2H), 4.13 (s, 2H), 2.89 – 2.78 (m, 2H), 2.59 – 2.50 (m, 2H), 2.24 (p, *J* = 5.8 Hz, 2H), 1.89 – 1.79 (m, 1H), 1.64 – 1.53 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.66, 154.73, 150.36, 147.85, 134.72, 132.13, 128.10, 122.39, 121.58, 120.91, 118.76, 111.56, 70.57, 70.52, 65.58, 48.04, 34.77, 30.78, 14.63. HRMS $[C_{22}H_{22}N_2O_6S+NH_4]^+$: 460.15368 calculated, 460.15377 found.

_N_-(1-(4-(Trifluoromethyl)phenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycine (39)



The title compound was synthesized according to the general procedure **J** using ethyl *N*-(1-(4-(trifluoromethyl)phenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate (**105e**, 18 mg, 0.034 mmol, 1 eq) and 1 M aq. LiOH (207 µL, 0.207 mmol, 6 eq). Total time: 2 h at rt. Silica gel column chromatography (5% MeOH in DCM) afforded the product as a white powder (15 mg, 0.032 mmol, 92%). ^{1}H NMR (400 MHz, MeOD) δ 7.66 – 7.61 (m, 2H), 7.55 – 7.50 (m, 2H), 6.96 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.21 (t, *J* = 5.8 Hz, 2H), 4.17 (s, 2H), 4.15 (t, *J* = 5.8 Hz, 2H), 2.98 – 2.86 (m, 2H), 2.60 – 2.51 (m, 2H), 2.17 (p, *J* = 5.7 Hz, 2H), 1.85 – 1.75 (m, 1H), 1.62 – 1.53 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 173.90, 155.94, 151.79, 148.44 (q, $J_{C\text{-}F}$ = 1.3 Hz), 136.59, 130.45 (q, $J_{C\text{-}F}$ = 32.1 Hz), 129.03, 126.00 (q, $J_{C\text{-}F}$ = 4.0 Hz), 125.67 (q, $J_{C\text{-}F}$ = 272.7 Hz), 123.52, 122.34, 121.76, 71.73, 71.64, 66.57, 49.28, 35.99, 32.18, 15.29. HRMS $[C_{22}H_{22}F_3NO_6S+Na]^+$: 508.10121 calculated, 508.10112 found.

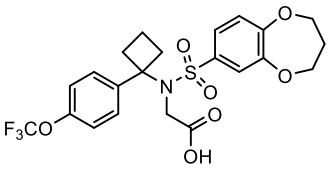
_N_-((3,4-Dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)-_N_-(1-(3-(trifluoromethyl)phenyl)cyclobutyl)glycine (40)



The title compound was synthesized according to the general procedure **J** using ethyl *N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)-*N*-(1-(3-(trifluoromethyl)phenyl)cyclobutyl)glycinate (**105f**, 19 mg, 0.037 mmol, 1 eq) and 1 M aq. LiOH (111 µL, 0.111 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (20-40% EtOAc in *n*-heptane with a drop of conc. HCl) afforded the product (15 mg, 0.031 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 1H), 7.58 (t, *J* = 2.0 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.03 – 6.96 (m, 2H), 6.83 – 6.77 (m, 1H), 4.27 (t, *J* = 5.7 Hz, 2H), 4.21 (t, *J* = 5.9 Hz, 2H), 4.14 (s, 2H), 2.93 – 2.81 (m, 2H), 2.61 – 2.52 (m, 2H), 2.21 (p, *J* = 5.7 Hz, 2H), 1.90 – 1.79 (m, 1H), 1.65 – 1.54 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.07, 154.60, 150.43, 143.47, 134.94, 130.76 (q, $J_{C\text{-}F}$ = 32.4 Hz), 130.56, 128.90, 124.51 (q, $J_{C\text{-}F}$ = 3.9 Hz), 124.17 (q, $J_{C\text{-}F}$ = 3.9 Hz), 124.11 (q, $J_{C\text{-}F}$ = 273.5

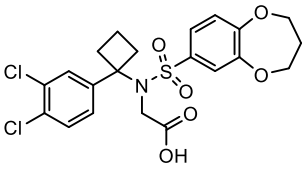
Hz), 122.47, 121.50, 120.90, 70.48, 70.30, 65.53, 48.09, 34.88, 30.86, 14.63. HRMS $[C_{22}H_{22}F_3NO_6S+NH_4]^+$: 503.14582 calculated, 503.14599 found.

_N_-((3,4-Dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)-_N_-(1-(4-(trifluoromethoxy)phenyl)cyclobutyl)glycine (41)



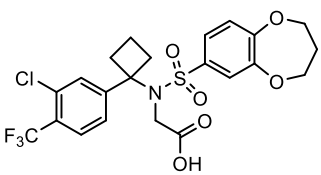
The title compound was synthesized according to the general procedure **J** using ethyl _N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)-_N_-(1-(4-(trifluoromethoxy)phenyl)cyclobutyl)glycinate (**105g**, 40 mg, 0.076 mmol, 1 eq) and 1 M aq. LiOH (227 µL, 0.227 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (20-40% EtOAc in _n_-heptane with a drop of conc. HCl) afforded the product (28 mg, 0.056 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H), 7.15 – 7.09 (m, 2H), 7.06 (d, J = 2.3 Hz, 1H), 7.03 (dd, J = 8.4, 2.4 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 4.28 (t, 2H), 4.22 (t, J = 5.8 Hz, 2H), 4.08 (s, 2H), 2.88 – 2.77 (m, 2H), 2.59 – 2.50 (m, 2H), 2.22 (p, J = 5.8 Hz, 2H), 1.87 – 1.76 (m, 1H), 1.65 – 1.51 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.29, 154.64, 150.43, 148.58 (q, J_{C-F} = 1.9 Hz), 140.95, 135.03, 128.90, 122.57, 121.50, 121.10, 120.57, 120.54 (q, J_{C-F} = 257.7 Hz), 70.53, 70.42, 65.41, 47.91, 34.90, 30.89, 14.68. HRMS $[C_{22}H_{22}F_3NO_7S+NH_4]$: 519.14073 found, 519.14031 found.

_N_-(1-(3,4-Dichlorophenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycine (42)



The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(3,4-dichlorophenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycinate (**105h**, 9.0 mg, 0.018 mmol, 1 eq) and 1 M aq. LiOH (53 µL, 0.053 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (20-40% EtOAc in _n_-heptane with a drop of conc. HCl) afforded the product (2.5 mg, 5.1 µmol, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 1.9 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.08 (dd, J = 8.5, 2.4 Hz, 1H), 6.91 (d, J = 2.3 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 4.31 (t, J = 5.8 Hz, 2H), 4.24 (t, J = 5.9 Hz, 2H), 4.14 (s, 2H), 2.86 – 2.76 (m, 2H), 2.55 – 2.45 (m, 2H), 2.23 (p, J = 5.8 Hz, 2H), 1.87 – 1.77 (m, 1H), 1.64 – 1.54 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.51, 154.74, 150.45, 142.59, 134.66, 132.51, 131.81, 130.20, 129.76, 126.73, 122.46, 121.50, 120.85, 70.57, 70.43, 65.16, 48.08, 35.02, 30.84, 14.67. HRMS $[C_{21}H_{21}Cl_2NO_6S+NH_4]^+$: 503.08049/505.07749 calculated, 503.08045/505.07739 found.

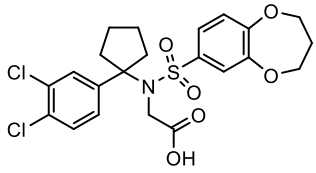
_N_-(1-(3-Chloro-4-(trifluoromethyl)phenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycine (43)



The title compound was synthesized according to the general procedure **J** using ethyl _N_-(1-(3-chrolo-4-(trifluoromethyl)phenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycinate (**105i**, 36 mg, 0.066

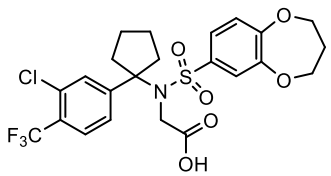
mmol, 1 eq) and 1 M aq. LiOH (197 µL, 0.197 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (20-40% EtOAc in *n*-heptane with a drop of conc. HCl) afforded the product (32 mg, 0.062 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$+MeOD) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.00 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 4.28 (t, *J* = 5.8 Hz, 2H), 4.21 (t, *J* = 5.8 Hz, 2H), 4.14 (s, 2H), 2.93 – 2.81 (m, 2H), 2.55 – 2.45 (m, 2H), 2.21 (p, *J* = 5.8 Hz, 2H), 1.88 – 1.78 (m, 1H), 1.66 – 1.54 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$+MeOD) δ 172.09, 154.46, 150.35, 148.40, 135.06, 132.07 (q, J_{C-F} = 2.1 Hz), 130.64, 127.26 (q, J_{C-F} = 5.4 Hz), 127.21 (q, J_{C-F} = 31.6 Hz), 125.34, 122.80 (q J_{C-F} = 273.3 Hz), 122.28, 121.29, 120.48, 70.41, 70.25, 65.01, 48.08, 34.76, 30.75, 14.48. HRMS $[C_{22}H_{21}ClF_3NO_6S+NH_4]^+$: 537.10685 calculated, 537.10718 found.

N-(1-(3,4-Dichlorophenyl)cyclopentyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycine (44)



The title compound was synthesized according to the general procedure **J** using ethyl *N*-(1-(3,4-dichlorophenyl)cyclopentyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate (**105j**, 44 mg, 0.083 mmol, 1 eq) and 1 M aq. LiOH (333 µL, 0.333 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (20-40% EtOAc in *n*-heptane with a drop of conc. HCl) afforded the product (33.5 mg, 66.9 µmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.23 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.19 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 4.36 – 4.30 (m, 2H), 4.27 (t, *J* = 5.9 Hz, 2H), 4.24 (s, 2H), 2.41 – 2.33 (m, 2H), 2.32 – 2.20 (m, 4H), 1.79 – 1.68 (m, 2H), 1.41 – 1.31 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.83, 154.68, 150.41, 142.75, 135.57, 132.28, 131.65, 129.90, 129.76, 126.81, 122.66, 121.54, 121.11, 73.12, 70.58, 70.42, 48.99, 38.12, 30.87, 21.56. HRMS $[C_{22}H_{23}Cl_2NO_6S+Na]^+$: 522.05153 calculated, 522.05107 found.

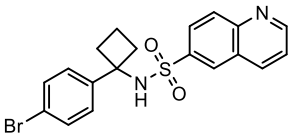
N-(1-(3-Chloro-4-(trifluoromethyl)phenyl)cyclopentyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycine (45)



The title compound was synthesized according to the general procedure **J** using ethyl *N*-(1-(3-chloro-4-(trifluoromethyl)phenyl)cyclopentyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate (**105k**, 26 mg, 0.046 mmol, 1 eq) and 1 M aq. LiOH (184 µL, 0.184 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (20-40% EtOAc in *n*-heptane with a drop of conc. HCl) afforded the product (20 mg, 0.037 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.13 – 7.06 (m, 2H), 6.87 (dt, *J* = 8.4, 1.0 Hz, 1H), 4.32 (t, *J* = 5.8 Hz, 2H), 4.25 (s, 2H), 4.25 (t, *J* = 5.8 Hz, 2H), 2.45 – 2.36 (m, 2H), 2.35 – 2.27 (m, 2H), 2.23 (p, *J* = 5.8 Hz, 2H), 1.83 – 1.70 (m, 2H), 1.45 – 1.34 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.53, 154.80, 150.54, 148.47, 135.25, 132.16 (q, J_{C-F} = 1.7 Hz), 130.62, 127.45 (q, J_{C-F} = 31.9 Hz), 127.26 (q, J_{C-F} = 5.3 Hz), 125.51, 122.85 (q, J_{C-F} = 273.7 Hz), 122.71, 121.57, 121.02, 73.27,

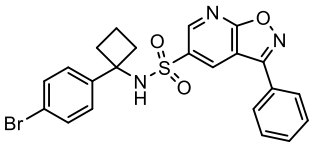
70.55, 70.37, 48.97, 38.24, 30.84, 21.68. HRMS $[C_{23}H_{23}ClF_3NO_6S+Na]^+$: 556.07789 calculated, 556.07726 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)quinoline-6-sulfonamide (46)



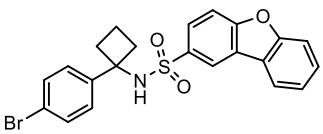
The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (53.0 mg, 0.193 mmol, 1.1 eq), quinoline-6-sulfonyl chloride (41.6 mg, 0.176 mmol, 1 eq) and DIPEA (127 µL, 0.703 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (1% MeOH in DCM) afforded the product (34 mg, 0.081 mmol, 44%). ^{1}H NMR (400 MHz, DMSO) δ 8.99 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.70 (s, 1H), 8.45 – 8.32 (m, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 1.9 Hz, 1H), 7.63 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.55 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.02 – 6.96 (m, 2H), 6.95 – 6.89 (m, 2H), 2.54 – 2.48 (m, 2H), 2.39 – 2.31 (m, 2H), 2.02 – 1.89 (m, 1H), 1.66 – 1.52 (m, 1H). ^{13}CNMR (101 MHz, DMSO) δ 152.08, 146.14, 142.35, 141.72, 135.90, 130.21, 129.07, 128.93, 128.45, 127.62, 123.29, 122.55, 119.89, 60.40, 34.06, 15.17. LC-MS $[C_{19}H_{17}BrN_2O_2S+H]^+$: 417.03/419.02 calculated, 417.17/419.00 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-3-phenylisoxazolo[5,4-*b*]pyridine-5-sulfonamide (47)



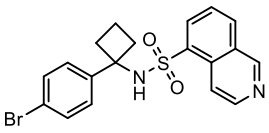
The title compound was synthesized according to general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (42.8 mg, 0.163 mmol, 1 eq), 3-phenylisoxazolo[5,4-*b*]pyridine-5-sulfonyl chloride (50 mg, 0.17 mmol, 1.04 eq) and DIPEA (123 µL, 0.707 mmol, 4.6 eq). Total time: overnight at rt. Silica gel column chromatography (10-20% EtOAc in *n*-pentane) afforded the product as a white solid (62.2 mg, 0.128 mmol, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 – 8.74 (m, 1H), 8.05 – 7.96 (m, 1H), 7.89 – 7.74 (m, 2H), 7.59 – 7.47 (m, 3H), 6.98 – 6.84 (m, 4H), 6.35 (s, 1H), 2.63 – 2.42 (m, 4H), 2.13 – 1.96 (m, 1H), 1.76 – 1.60 (m, 1H).

_N_-(1-(4-Bromophenyl)cyclobutyl)dibenzo[*b*,*d*]furan-2-sulfonamide (48)



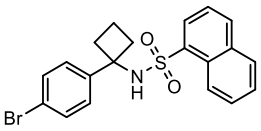
The title compound was synthesized according to general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (79.1 mg, 0.301 mmol, 1 eq), dibenzo[*b*,*d*]furan-2-sulfonyl chloride (83.6 mg, 0.314 mmol, 1.04 eq) and DIPEA (241 µL, 1.39 mmol, 4.6 eq). Total time: overnight at rt. Silica gel column chromatography (10-40% EtOAc in *n*-pentane) afforded the product (129 mg, 0.283 mmol, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.84 (m, 1H), 7.82 (d, *J* = 1.9 Hz, 1H), 7.64 – 7.49 (m, 3H), 7.47 – 7.38 (m, 2H), 7.09 – 6.97 (m, 4H), 5.40 (s, 1H), 2.67 – 2.46 (m, 4H), 2.18 – 1.95 (m, 1H), 1.82 – 1.64 (m, 1H).

***N*-(1-(4-Bromophenyl)cyclobutyl)isoquinoline-5-sulfonamide (49)**



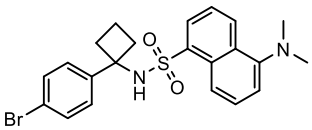
The title compound was synthesized according to general procedure **H** using 1-(4-bromophenyl)-cyclobutan-1-aminium chloride (30.0 mg, 0.114 mmol, 1 eq), isoquinoline-5-sulfonyl chloride (31.2 mg, 0.137 mmol, 1.2 eq) and Et_3N (48 µL, 0.34 mmol, 3 eq). Silica gel column chromatography (30-70% EtOAc in *n*-pentane) afforded the product (9.5 mg, 0.023 mmol, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, *J* = 1.0 Hz, 1H), 8.67 (d, *J* = 6.1 Hz, 1H), 8.25 (dt, *J* = 6.1, 1.0 Hz, 1H), 8.05 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.69 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.33 (dd, *J* = 8.2, 7.4 Hz, 1H), 6.87 – 6.79 (m, 2H), 6.78 – 6.69 (m, 2H), 5.80 (s, 1H), 2.66 – 2.48 (m, 4H), 2.13 – 1.96 (m, 1H), 1.78 – 1.64 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.33, 145.02, 140.00, 135.23, 133.45, 132.76, 130.75, 130.57, 128.67, 128.61, 125.88, 121.40, 117.15, 61.45, 35.91, 15.21. LC-MS $[C_{19}H_{17}BrN_2O_2S+H]^+$: 417.03/419.03 calculated, 417.08/419.00 found.

***N*-(1-(4-Bromophenyl)cyclobutyl)naphthalene-1-sulfonamide (50)**



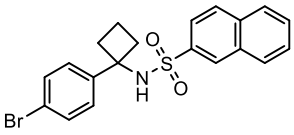
The title compound was synthesized according to general procedure **H** using 1-(4-bromophenyl)-cyclobutan-1-aminium chloride (30.0 mg, 0.114 mmol, 1 eq), naphthalene-1-sulfonyl chloride (31.1 mg, 0.137 mmol, 1.2 eq) and Et_3N (48 µL, 0.34 mmol, 3 eq). Silica gel column chromatography (5-20% EtOAc in *n*-pentane) afforded the product (37 mg, 0.088 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dq, *J* = 8.6, 0.9 Hz, 1H), 7.91 (dt, *J* = 8.3, 1.2 Hz, 1H), 7.89 – 7.85 (m, 1H), 7.67 – 7.54 (m, 3H), 7.20 (dd, *J* = 8.2, 7.4 Hz, 1H), 6.82 – 6.76 (m, 2H), 6.73 – 6.66 (m, 2H), 5.76 (s, 1H), 2.64 – 2.53 (m, 2H), 2.52 – 2.43 (m, 2H), 2.09 – 1.96 (m, 1H), 1.72 – 1.59 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.32, 135.71, 133.91, 133.53, 130.35, 129.79, 129.14, 128.31, 128.13, 127.70, 126.59, 124.29, 124.14, 121.12, 61.39, 35.63, 15.26.

***N*-(1-(4-Bromophenyl)cyclobutyl)-5-(dimethylamino)naphthalene-1-sulfonamide (51)**



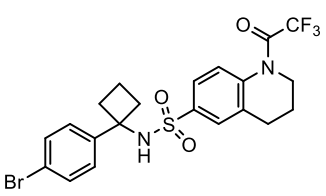
The title compound was synthesized according to general procedure **H** using 1-(4-bromophenyl)-cyclobutan-1-aminium chloride (40.0 mg, 0.152 mmol, 1 eq), 5-(dimethylamino)naphthalene-1-sulfonyl chloride (49.3 mg, 0.183 mmol, 1.2 eq) and Et_3N (64 µL, 0.46 mmol, 3 eq). Silica gel column chromatography (5-15% EtOAc in *n*-pentane) afforded the product (60.5 mg, 0.132 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dt, *J* = 8.5, 1.2 Hz, 1H), 8.14 (dt, *J* = 8.8, 1.0 Hz, 1H), 7.57 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.52 (dd, *J* = 8.6, 7.6 Hz, 1H), 7.17 (dd, *J* = 8.5, 7.4 Hz, 1H), 7.14 (dd, *J* = 7.6, 0.9 Hz, 1H), 6.85 – 6.81 (m, 2H), 6.75 – 6.71 (m, 2H), 5.66 (s, 1H), 2.89 (s, 6H), 2.63 – 2.53 (m, 2H), 2.52 – 2.42 (m, 2H), 2.08 – 1.96 (m, 1H), 1.72 – 1.61 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.99, 140.49, 135.92, 130.39, 129.77, 129.66, 129.44, 129.16, 128.49, 128.18, 123.11, 121.07, 118.68, 114.77, 61.36, 45.58, 35.73, 15.26. LC-MS $[C_{22}H_{23}BrN_2O_2S+H]^+$: 459.07/461.07 calculated, 459.00/461.00 found.

N-(1-(4-Bromophenyl)cyclobutyl)naphthalene-2-sulfonamide (52)



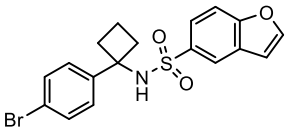
The title compound was synthesized according to general procedure **H** using 1-(4-bromophenyl)-cyclobutan-1-aminium chloride (30.0 mg, 0.114 mmol, 1 eq), naphthalene-2-sulfonyl chloride (31.1 mg, 0.137 mmol, 1.2 eq) and Et_3N (48 µL, 0.34 mmol, 3 eq). Silica gel column chromatography (5-15% EtOAc in *n*-pentane) afforded the product (36 mg, 0.086 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 1H), 7.78 – 7.76 (m, 1H), 7.75 – 7.70 (m, 2H), 7.63 – 7.55 (m, 2H), 7.52 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.02 – 6.92 (m, 4H), 5.93 (s, 1H), 2.65 – 2.46 (m, 4H), 2.11 – 2.00 (m, 1H), 1.75 – 1.64 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.81, 138.18, 134.29, 131.81, 130.85, 129.25, 128.93, 128.71, 128.35, 127.79, 127.57, 122.00, 121.36, 61.39, 35.55, 15.34.

N-(1-(4-Bromophenyl)cyclobutyl)-1-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroquinoline-6-sulfonamide (53)



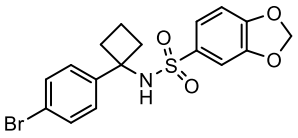
The title compound was synthesized according to general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (100 mg, 0.381 mmol, 1 eq), 1-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroquinoline-6-sulfonyl chloride (**107**, 137 mg, 0.419 mmol, 1.1 eq) and DIPEA (265 µL, 1.52 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (10-30% EtOAc in *n*-pentane) afforded the product as a white solid (196 mg, 0.379 mmol, 99%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 7.58 (bs, 1H), 7.38 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.19 – 7.10 (m, 2H), 7.03 – 6.96 (m, 2H), 6.81 (s, 1H), 3.85 (t, *J* = 5.9 Hz, 2H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.65 – 2.55 (m, 2H), 2.54 – 2.43 (m, 2H), 2.18 – 2.06 (m, 3H), 1.81 – 1.67 (m, 1H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 156.40, 141.45, 139.60, 139.27, 130.84, 128.99, 128.32, 124.89, 124.22, 120.82, 116.73 (q, $J_{C\text{-}F}$ = 288.2 Hz), 60.91, 45.47 (q, $J_{C\text{-}F}$ = 3.6 Hz), 35.20, 25.93, 23.29, 15.56.

N-(1-(4-Bromophenyl)cyclobutyl)benzofuran-5-sulfonamide (54)



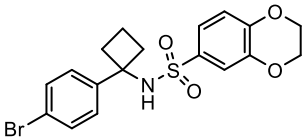
The title compound was synthesized according to general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (50 mg, 0.19 mmol, 1 eq), benzofuran-5-sulfonyl chloride (43.2 mg, 0.199 mmol, 1.05 eq) and DIPEA (133 µL, 0.760 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (20-30% EtOAc in *n*-pentane) afforded the product (22 mg, 0.054 mmol, 27%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.2 Hz, 1H), 7.53 (d, *J* = 1.9 Hz, 1H), 7.45 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.11 – 7.05 (m, 2H), 7.03 – 6.95 (m, 2H), 6.73 (dd, *J* = 2.2, 0.9 Hz, 1H), 5.67 (s, 1H), 2.60 – 2.47 (m, 4H), 2.09 – 1.99 (m, 1H), 1.76 – 1.66 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.26, 147.10, 141.10, 136.46, 130.91, 128.83, 127.25, 123.00, 121.38, 121.19, 111.59, 107.11, 61.36, 35.62, 15.30.

_N_-(1-(4-Bromophenyl)cyclobutyl)benzo[_d_][1,3]dioxole-5-sulfonamide (55)



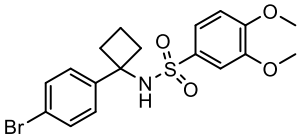
The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (287 mg, 1.09 mmol, 1.1 eq), benzo[*d*][1,3]dioxole-5-sulfonyl chloride (219 mg, 0.993 mmol, 1 eq) and DIPEA (0.69 mL, 4.0 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (20-25% EtOAc in *n*-pentane) afforded the product as an off-white solid (409 mg, 0.996 mmol, quant.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H), 7.05 – 6.99 (m, 3H), 6.68 (d, *J* = 1.8 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.04 (s, 2H), 5.60 (s, 1H), 2.63 – 2.44 (m, 4H), 2.15 – 1.99 (m, 1H), 1.80 – 1.64 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.76, 147.45, 141.34, 134.94, 130.98, 128.82, 122.51, 121.13, 107.79, 107.49, 102.34, 61.23, 35.40, 15.35.

_N_-(1-(4-Bromophenyl)cyclobutyl)-2,3-dihydrobenzo[_b_][1,4]dioxine-6-sulfonamide (56)



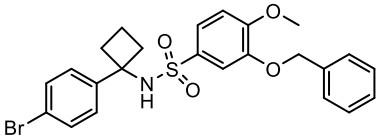
The title compound was synthesized according to general procedure **H** using 1-(4-bromophenyl)-cyclobutan-1-aminium chloride (49.2 mg, 0.188 mmol, 1 eq), 2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonyl chloride (**108**, 44.0 mg, 0.188 mmol, 1 eq) and DIPEA (0.13 mL, 0.75 mmol, 4 eq). Silica gel column chromatography (20-50% EtOAc in *n*-pentane) afforded the product as a white solid (56.6 mg, 0.133 mmol, 71%). ^{1}H NMR (400 MHz, DMSO) δ 8.31 (s, 1H), 7.26 – 7.21 (m, 2H), 7.07 – 7.01 (m, 2H), 6.88 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.60 (d, *J* = 2.2 Hz, 1H), 4.31 – 4.20 (m, 4H), 2.50 – 2.42 (m, 2H), 2.35 – 2.26 (m, 2H), 1.99 – 1.89 (m, 1H), 1.66 – 1.53 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 145.99, 142.41, 142.30, 134.70, 130.29, 128.55, 119.67, 119.57, 116.86, 115.45, 64.29, 64.03, 60.16, 34.00, 15.13.

_N_-(1-(4-Bromophenyl)cyclobutyl)-3,4-dimethoxybenzenesulfonamide (57)



The title compound was synthesized according to general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (40.0 mg, 0.152 mmol, 1 eq), 3,4-dimethoxybenzenesulfonyl chloride (43.3 mg, 0.183 mmol, 1.2 eq) and DIPEA (106 µL, 0.609 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (15-35% EtOAc in *n*-pentane) afforded the product as a colorless oil (56.7 mg, 0.133 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.13 (m, 2H), 7.06 – 6.99 (m, 2H), 6.98 – 6.91 (m, 2H), 6.62 (d, *J* = 8.2 Hz, 1H), 6.00 (s, 1H), 3.92 (s, 3H), 3.80 (s, 3H), 2.64 – 2.42 (m, 4H), 2.14 – 1.99 (m, 1H), 1.76 – 1.64 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.09, 148.59, 141.32, 133.25, 130.85, 128.76, 121.02, 120.93, 109.97, 109.17, 61.21, 56.28, 56.12, 35.36, 15.33.

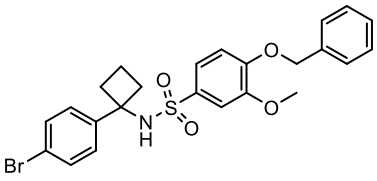
3-(Benzyloxy)-_N_-(1-(4-bromophenyl)cyclobutyl)-4-methoxybenzenesulfonamide (58)



The title compound was synthesized according to general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (92.3 mg, 0.352 mmol, 1 eq), 3-(benzyloxy)-4-methoxybenzenesulfonyl chloride (**110**, 100 mg, 0.320 mmol, 0.9 eq) and DIPEA (245 µL, 1.41

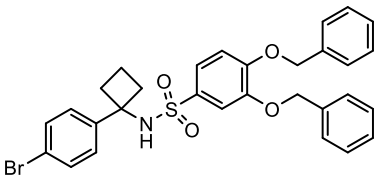
mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (10-20% EtOAc in *n*-pentane) afforded the product (83.2 mg, 0.166 mmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.43 – 7.36 (m, 2H), 7.34 – 7.28 (m, 1H), 7.10 (d, *J* = 2.2 Hz, 1H), 7.08 – 7.03 (m, 2H), 6.84 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.80 – 6.74 (m, 2H), 6.56 (d, *J* = 8.5 Hz, 1H), 6.06 (s, 1H), 5.07 (s, 2H), 3.90 (s, 3H), 2.53 – 2.33 (m, 4H), 2.08 – 1.92 (m, 1H), 1.72 – 1.57 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.67, 147.40, 141.16, 136.42, 132.98, 130.69, 128.71, 128.24, 127.76, 121.21, 120.82, 111.50, 110.27, 70.70, 61.05, 56.27, 35.19, 15.31.

4-(Benzyloxy)-*N*-(1-(4-bromophenyl)cyclobutyl)-3-methoxybenzenesulfonamide (59)



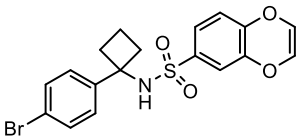
The title compound was synthesized according to general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (200 mg, 0.762 mmol, 1 eq), 4-(benzyloxy)-3-methoxybenzenesulfonyl chloride (**112**, 246 mg, 0.838 mmol, 1.1 eq) and DIPEA (531 µL, 3.05 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (10-20% EtOAc in *n*-pentane) afforded the product as a white solid (274 mg, 0.545 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$+MeOD) δ 7.48 – 7.38 (m, 4H), 7.37 – 7.31 (m, 1H), 7.18 – 7.11 (m, 2H), 6.99 (dd, *J* = 8.7, 2.2 Hz, 2H), 6.88 – 6.82 (m, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 5.18 (s, 2H), 3.79 (s, 3H), 2.60 – 2.42 (m, 4H), 2.09 – 2.00 (m, 1H), 1.77 – 1.67 (m, 1H). ^{13}C NMR (101 MHz, , $CDCl_3$+MeOD) δ 150.89, 148.72, 141.42, 136.10, 133.69, 130.65, 128.63, 128.12, 127.28, 120.72, 120.33, 112.08, 109.52, 70.87, 60.69, 55.83, 35.06, 15.14.

3,4-Bis(benzyloxy)-*N*-(1-(4-bromophenyl)cyclobutyl)benzenesulfonamide (60)



The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (228 mg, 0.869 mmol, 1.1 eq), 3,4-bis(benzyloxy)benzenesulfonyl chloride (**114**, 300 mg, 0.771 mmol, 1 eq) and DIPEA (540 µL, 3.09 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (278 mg, 0.581 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 4H), 7.43 – 7.29 (m, 6H), 7.10 – 7.05 (m, 2H), 7.03 (d, *J* = 2.2 Hz, 1H), 6.86 – 6.76 (m, 3H), 6.64 (d, *J* = 8.5 Hz, 1H), 5.60 (s, 1H), 5.18 (s, 2H), 5.07 (s, 2H), 2.51 – 2.37 (m, 4H), 2.05 – 1.92 (m, 1H), 1.72 – 1.62 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.02, 147.99, 141.12, 136.67, 136.46, 133.49, 130.82, 128.82, 128.78, 128.72, 128.23, 127.67, 127.34, 121.22, 121.00, 112.78, 112.52, 71.11, 70.96, 61.12, 35.46, 15.28.

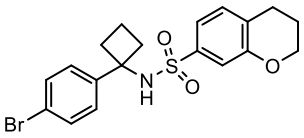
***N*-(1-(4-Bromophenyl)cyclobutyl)benzo[*b*][1,4]dioxine-6-sulfonamide (61)**



The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (34.0 mg, 0.129 mmol, 1.2 eq), benzo[*b*][1,4]dioxine-6-sulfonyl chloride (**118**, 25.0 mg, 0.107 mmol, 1 eq) and DIPEA (75 µL, 0.43 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (100% DCM) afforded the product as

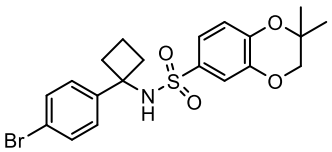
a white powder (40 mg, 0.095 mmol, 88%). ^{1}H NMR (400 MHz, DMSO) δ 8.42 (s, 1H), 7.39 – 7.26 (m, 2H), 7.13 – 7.00 (m, 2H), 6.86 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 6.21 (q, *J* = 3.6 Hz, 2H), 2.50 – 2.40 (m, 2H), 2.39 – 2.28 (m, 2H), 2.04 – 1.90 (m, 1H), 1.71 – 1.54 (m, 1H).

_N_-(1-(4-Bromophenyl)cyclobutyl)chromane-7-sulfonamide (62)



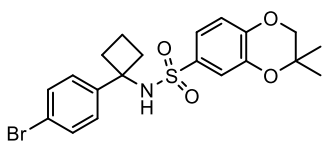
The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (40.6 mg, 0.155 mmol, 1.2 eq), chromane-7-sulfonyl chloride (**125**, 30.0 mg, 0.129 mmol, 1 eq) and DIPEA (90 µL, 0.52 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (10-20% EtOAc in *n*-pentane) afforded the product (42 mg, 0.099 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$+MeOD) δ 7.19 – 7.13 (m, 2H), 7.04 – 6.98 (m, 2H), 6.91 – 6.86 (m, 1H), 6.86 – 6.82 (m, 1H), 6.63 (d, *J* = 1.8 Hz, 1H), 4.23 – 4.16 (m, 2H), 2.78 (t, *J* = 6.4 Hz, 2H), 2.63 – 2.54 (m, 2H), 2.50 – 2.40 (m, 2H), 2.13 – 1.98 (m, 3H), 1.78 – 1.66 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$+MeOD) δ 153.90, 141.21, 139.93, 130.28, 129.52, 128.19, 126.25, 120.30, 117.51, 114.90, 66.33, 60.32, 34.34, 24.45, 21.43, 14.95.

_N_-(1-(4-Bromophenyl)cyclobutyl)-2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonamide (63)



The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (25 mg, 0.095 mmol, 1 eq), 2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonyl chloride (**134**, 35.0 mg, 0.133 mmol, 1.4 eq) and DIPEA (196 µL, 1.13 mmol, 12 eq). Total time: overnight at rt. Silica gel column chromatography (10-15% EtOAc in *n*-pentane) afforded the product as a white solid (37 mg, 0.081 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 2H), 7.10 – 7.03 (m, 2H), 6.98 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.83 (d, *J* = 2.2 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 5.71 (s, 1H), 3.88 (s, 2H), 2.62 – 2.43 (m, 4H), 2.12 – 2.00 (m, 1H), 1.76 – 1.64 (m, 1H), 1.35 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.05, 141.51, 141.39, 133.44, 130.91, 128.87, 121.04, 120.96, 117.51, 116.32, 73.44, 71.89, 61.15, 35.51, 23.39, 15.35. LC-MS $[C_{20}H_{22}BrNO_4S+H]^+$: 452.05/454.05 calculated, 451.92/453.83 found.

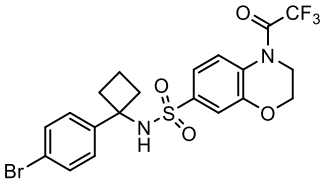
_N_-(1-(4-Bromophenyl)cyclobutyl)-3,3-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonamide (64)



The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (25 mg, 0.095 mmol, 1 eq), 3,3-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonyl chloride (**135**, 50 mg, 0.19 mmol, 2 eq) and DIPEA (196 µL, 1.13 mmol, 12 eq). Total time: overnight at rt. Silica gel column chromatography (10-15% EtOAc in *n*-pentane) afforded the product (41 mg, 0.091 mmol, 94%). ^{1}H NMR (400 MHz,

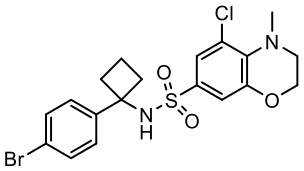
$CDCl_3$) δ 7.22 – 7.16 (m, 2H), 7.07 – 7.01 (m, 2H), 6.97 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.76 (d, *J* = 2.2 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 5.74 (s, 1H), 3.93 (s, 2H), 2.64 – 2.43 (m, 4H), 2.11 – 2.01 (m, 1H), 1.79 – 1.64 (m, 1H), 1.33 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.53, 141.90, 141.44, 134.30, 130.88, 128.81, 120.94, 119.92, 117.05, 116.76, 72.72, 72.06, 61.14, 35.44, 23.35, 15.37. LC-MS $[C_{20}H_{22}BrNO_4S+H]^+$: 452.05/454.05 calculated, 451.75/454.00 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-4-(2,2,2-trifluoroacetyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-sulfonamide (65)



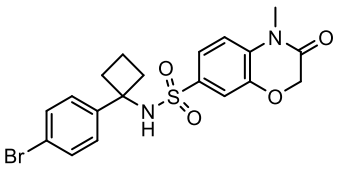
The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (35 mg, 0.13 mmol, 1 eq), 4-(2,2,2-trifluoroacetyl)-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazine-7-sulfonyl chloride (**142**, 53 mg, 0.16 mmol, 1.2 eq) and DIPEA (232 µL, 1.33 mmol, 10 eq). Total time: overnight at rt. Silica gel column chromatography (25-30% EtOAc in *n*-pentane) afforded the product (58.9 mg, 0.113 mmol, 85%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 7.76 (bs, 1H), 7.14 – 7.08 (m, 2H), 7.02 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.96 – 6.91 (m, 2H), 6.58 (d, *J* = 2.1 Hz, 1H), 4.42 – 4.36 (m, 2H), 3.97 – 3.93 (m, 2H), 2.61 – 2.49 (m, 2H), 2.49 – 2.38 (m, 2H), 2.11 – 2.01 (m, 1H), 1.75 – 1.61 (m, 1H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 146.22, 141.29, 140.18, 130.84, 128.77, 126.32, 124.08, 120.76, 118.30, 116.94, 116.24 (q, $J_{C\text{-}F}$ =289.9 Hz), 65.89, 60.82, 43.37, 34.94, 15.45.

_N_-(1-(4-Bromophenyl)cyclobutyl)-5-chloro-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-sulfonamide (66)



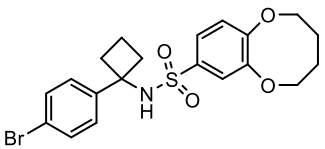
The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (68 mg, 0.26 mmol, 1 eq), 5-chloro-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-sulfonyl chloride (**148**, 66.4 mg, 0.235 mmol, 1 eq) and DIPEA (410 µL, 2.35 mmol, 10 eq). Total time: overnight at rt. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (38 mg, 0.081 mmol, 34%). ^{1}H NMR (400 MHz, $CDCl_3$+MeOD) δ 7.22 – 7.14 (m, 2H), 7.05 – 6.98 (m, 2H), 6.96 – 6.92 (m, 1H), 6.65 – 6.59 (m, 1H), 4.18 – 4.10 (m, 2H), 3.17 – 3.10 (m, 2H), 2.92 (s, 3H), 2.64 – 2.53 (m, 2H), 2.53 – 2.44 (m, 2H), 2.16 – 2.07 (m, 1H), 1.80 – 1.66 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$+MeOD) δ 147.83, 141.14, 136.50, 135.09, 130.58, 128.67, 127.29, 120.74, 120.60, 114.68, 60.68, 60.23, 49.46, 43.21, 35.04, 15.30. LC-MS $[C_{19}H_{20}BrClN_2O_3S+H]^+$: 471.01/473.01 calculated, 471.25/473.08 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-4-methyl-3-oxo-3,4-dihydro-2_H_-benzo[_b_][1,4]oxazine-7-sulfonamide (67)



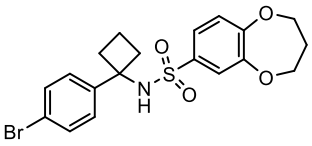
The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (43.0 mg, 0.164 mmol, 1 eq), 4-methyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-sulfonyl chloride (**145**, 51.0 mg, 0.197 mmol, 1.2 eq) and DIPEA (285 µL, 1.64 mmol, 10 eq). Total time: overnight at rt. Silica gel column chromatography (30-40% EtOAc in *n*-pentane) afforded the product (19 mg, 0.042 mmol, 25%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 7.18 – 7.12 (m, 2H), 7.03 – 6.98 (m, 3H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.64 (s, 2H), 3.37 (s, 3H), 2.61 – 2.52 (m, 2H), 2.51 – 2.45 (m, 2H), 2.15 – 2.05 (m, 1H), 1.79 – 1.66 (m, 1H). LC-MS $[C_{19}H_{19}BrN_2O_4S+H]^+$: 451.03/453.03 calculated, 451.00/453.00 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-2,3,4,5-tetrahydrobenzo[_b_][1,4]dioxocine-8-sulfonamide (68)



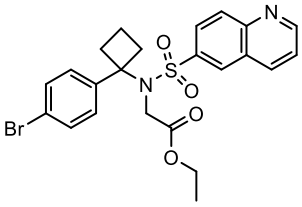
The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (101 mg, 0.184 mmol, 1.1 eq), 2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocine-8-sulfonyl chloride (**122**, 92 mg, 0.35 mmol, 1 eq) and DIPEA (0.61 mL, 3.5 mmol, 10 eq). Total time: over-weekend at rt. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product as an orange solid (38 mg, 0.084 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 2H), 7.08 – 7.01 (m, 3H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 5.79 (s, 1H), 4.45 (t, *J* = 5.5 Hz, 2H), 4.21 (t, *J* = 5.5 Hz, 2H), 2.61 – 2.45 (m, 4H), 2.09 – 2.01 (m, 1H), 1.95 (p, *J* = 5.9 Hz, 2H), 1.85 (p, *J* = 5.6 Hz, 2H), 1.77 – 1.64 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.86, 147.25, 141.39, 135.05, 130.94, 128.84, 122.79, 122.74, 121.49, 121.07, 73.87, 71.81, 61.14, 35.49, 27.69, 25.58, 15.35. LC-MS $[C_{20}H_{22}BrNO_4S+H]^+$: 452.05/454.05 calculated, 452.00/453.75 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepine-7-sulfonamide (69)



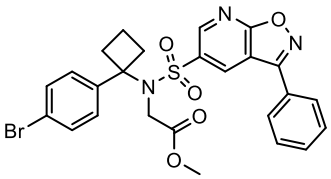
The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (43.0 mg, 0.168 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 49.0 mg, 0.197 mmol, 1.2 eq) and DIPEA (285 µL, 1.68 mmol, 10 eq). Total time: over-weekend at rt. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (73.5 mg, 0.168 mmol, quant). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 2H), 7.08 – 7.02 (m, 2H), 7.00 (dt, *J* = 8.5, 1.8 Hz, 1H), 6.88 (t, *J* = 1.8 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.54 (s, 1H), 4.28 (t, *J* = 5.8 Hz, 2H), 4.21 (t, *J* = 6.2 Hz, 2H), 2.62 – 2.47 (m, 4H), 2.22 (p, *J* = 5.9 Hz, 2H), 2.12 – 2.00 (m, 1H), 1.78 – 1.69 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.26, 150.09, 141.29, 135.60, 130.98, 128.90, 122.17, 121.36, 121.12, 120.86, 70.55, 70.47, 61.18, 35.59, 30.97, 15.35.

Ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-(quinolin-6-ylsulfonyl)glycinate (70)



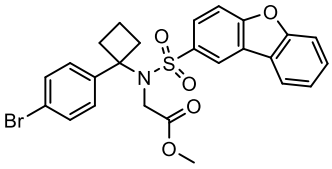
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)quinoline-6-sulfonamide (**46**, 34 mg, 0.081 mmol, 1 eq), ethyl 2-bromoacetate (18 µL, 0.16 mmol, 2 eq) and BEMP (1 M in hexane, 162 µL, 0.162 mmol, 2 eq). Total time: 12 h at 80 °C. Silica gel column chromatography (1% MeOH in DCM) afforded the product (30 mg, 0.060 mmol, 75%). ^{1}H NMR (400 MHz, MeOD) δ 8.97 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.40 (ddd, *J* = 8.4, 1.7, 0.8 Hz, 1H), 7.98 – 7.94 (m, 1H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.65 (dd, *J* = 8.4, 4.3 Hz, 1H), 7.60 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.11 – 7.04 (m, 2H), 4.39 (s, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.90 – 2.79 (m, 2H), 2.57 – 2.49 (m, 2H), 1.80 – 1.70 (m, 1H), 1.58 – 1.47 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 171.94, 153.21, 147.28, 143.60, 142.24, 138.05, 132.06, 131.20, 131.00, 130.41, 129.25, 124.76, 124.36, 122.49, 66.57, 62.64, 49.72, 36.03, 15.20, 14.46. LC-MS $[C_{23}H_{23}BrN_2O_4S+H]^+$: 503.06/505.06 calculated, 503.17/505.00 found.

Methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((3-phenylisoxazolo[5,4-*b*]pyridin-5-yl)sulfonyl)glycinate (71)



The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-3-phenylisoxazolo[5,4-*b*]pyridine-5-sulfonamide (**47**, 48 mg, 0.098 mmol, 1 eq), methyl 2-bromoacetate (19.0 µL, 0.196 mmol, 2 eq) and BEMP (1 M in hexane, 196 µL, 0.196 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (10-20% EtOAc in *n*-pentane) afforded the product (29 mg, 0.052 mmol, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (d, *J* = 2.2 Hz, 1H), 8.50 (d, *J* = 2.2 Hz, 1H), 8.00 – 7.93 (m, 2H), 7.66 – 7.57 (m, 3H), 7.38 – 7.30 (m, 2H), 7.24 – 7.17 (m, 2H), 4.30 (s, 2H), 3.80 (s, 3H), 2.83 – 2.65 (m, 2H), 2.59 – 2.42 (m, 2H), 1.84 – 1.70 (m, 1H), 1.62 – 1.49 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.77, 157.86, 149.67, 140.45, 136.00, 132.83, 131.50, 131.43, 129.56, 129.48, 127.94, 127.62, 122.22, 111.63, 65.92, 52.81, 48.00, 34.78, 14.67.

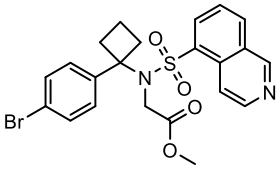
Methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-(dibenzo[*b*,*d*]furan-2-ylsulfonyl)glycinate (72)



The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)dibenzo[*b*,*d*]furan-2-sulfonamide (**48**, 61.6 mg, 0.135 mmol, 1 eq), methyl 2-bromoacetate (26 µL, 0.27 mmol, 2 eq) and BEMP (1 M in hexane, 0.27 mL, 0.27 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (10-20% EtOAc in *n*-pentane) afforded the product (39 mg, 0.074 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.0, 0.5 Hz, 1H), 7.92 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.75 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.63 – 7.41 (m, 4H), 7.37 – 7.28 (m, 4H), 4.13 (s, 2H), 3.74 (s, 3H), 2.89 – 2.73 (m, 2H), 2.74 – 2.56 (m, 2H), 1.93 – 1.76 (m, 1H), 1.64 – 1.49 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.74, 157.89, 157.13, 141.51, 136.17,

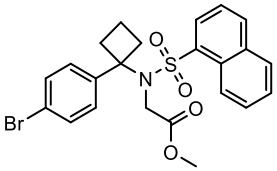
131.86, 131.31, 128.47, 126.41, 124.56, 123.77, 123.26, 121.76, 121.40, 120.94, 112.08, 111.78, 65.63, 52.58, 47.91, 34.86, 14.72.

Methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-(isoquinolin-5-ylsulfonyl)glycinate (73)



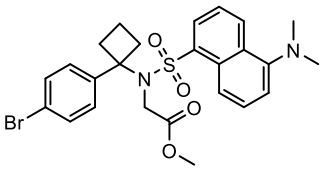
The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-isoquinoline-5-sulfonamide (**49**, 9.5 mg, 0.023 mmol, 1 eq), methyl 2-bromoacetate (4.3 µL, 0.046 mmol, 2 eq) and BEMP (1 M in hexane, 46 µL, 0.046 mmol, 2 eq). Total time: overnight at 80 °C. The product was afforded and used in the next step without purification (13.5 mg, 27.6 µmol, quant.). LC-MS $[C_{22}H_{21}BrN_2O_4S+H]^+$: 489.04/491.05 calculated, 489.00/491.00 found.

Methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-(naphthalen-1-ylsulfonyl)glycinate (74)



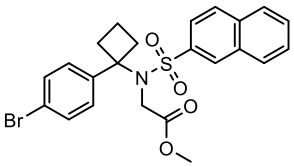
The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)-cyclobutyl)naphthalene-1-sulfonamide (**50**, 37 mg, 0.088 mmol, 1 eq), methyl 2-bromoacetate (17.0 µL, 0.176 mmol, 2 eq) and BEMP (1 M in hexane, 176 µL, 0.176 mmol, 2 eq). Total time: overnight at 80 °C. The product was afforded and used in the next step without purification (37 mg, 0.077 mmol, 87%). LC-MS $[C_{23}H_{22}BrNO_4S+Na]^+$: 510.03/512.03 calculated, 510.00/512.00 found.

Methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((5-(dimethylamino)naphthalen-1-yl)sulfonyl)glycinate (75)



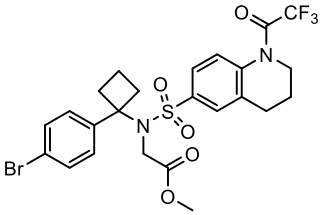
The title compound was synthesized according to general procedure **I** using *N*-(1-(4-Bromophenyl)cyclobutyl)-5-(dimethylamino)naphthalene-1-sulfonamide (**51**, 60.5 mg, 0.132 mmol, 1 eq), methyl 2-bromoacetate (25 µL, 0.263 mmol, 2 eq) and BEMP (1 M in hexane, 263 µL, 0.263 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (10-30% dist. EtOAc in *n*-heptane) afforded the product (49 mg, 0.093 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dt, *J* = 8.5, 1.1 Hz, 1H), 8.12 (dt, *J* = 8.7, 0.9 Hz, 1H), 8.04 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.47 (dd, *J* = 8.7, 7.5 Hz, 1H), 7.37 (dd, *J* = 8.5, 7.4 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.21 – 7.13 (m, 3H), 4.24 (s, 2H), 3.61 (s, 3H), 2.93 – 2.82 (m, 8H), 2.50 – 2.38 (m, 2H), 1.82 – 1.69 (m, 1H), 1.59 – 1.40 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.48, 151.74, 141.13, 137.32, 131.00, 130.07, 129.84, 129.81, 129.25, 127.97, 123.14, 121.58, 119.44, 115.13, 65.73, 52.38, 47.85, 45.55, 34.45, 14.75. LC-MS $[C_{25}H_{27}BrN_2O_4S+H]^+$: 531.09/533.09 calculated , 531.00/533.00 found.

Methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-(naphthalen-2-ylsulfonyl)glycinate (76)



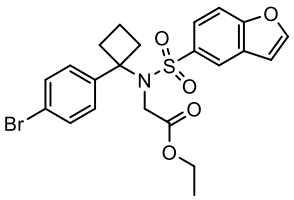
The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)-cyclobutyl)naphthalene-2-sulfonamide (**52**, 36 mg, 0.086 mmol, 1 eq), methyl 2-bromoacetate (16 µL, 0.17 mmol, 2 eq) and BEMP (1 M in hexane, 173 µL, 0.173 mmol, 2 eq). Total time: overnight at 80 °C. The product was afforded and used in the next step without purification (43 mg, 0.089 mmol, quant.). LC-MS $[C_{23}H_{22}BrNO_4S+NH_4]^+$: 505.08/507.08 calculated , 504.92/506.83 found.

Methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((1-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroquinolin-6-yl)sulfonyl)glycinate (77)



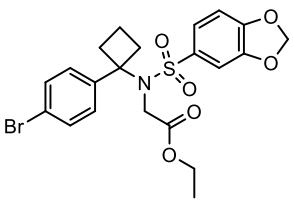
The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-1-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroquinoline-6-sulfonamide (**53**, 20 mg, 0.039 mmol, 1 eq), methyl 2-bromoacetate (7.4 µL, 0.077 mmol, 2 eq) and BEMP (1 M in hexane, 77 µL, 0.077 mmol, 2 eq). Total time: overnight at 80 °C. The product was afforded and used in the next step without purification (23 mg, 0.039 mmol, quant.).

Ethyl *N*-(benzofuran-5-ylsulfonyl)-*N*-(1-(4-bromophenyl)cyclobutyl)glycinate (78)



The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)benzofuran-5-sulfonamide (**54**, 22 mg, 0.054 mmol, 1 eq), ethyl 2-bromoacetate (11.9 µL, 0.108 mmol, 2 eq) and BEMP (1 M in hexane, 108 µL, 0.108 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (5-10% EtOAc in dis. *n*-pentane) afforded the product (10 mg, 0.021 mmol, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.2 Hz, 1H), 7.71 (dd, *J* = 2.0, 0.6 Hz, 1H), 7.60 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.47 (dt, *J* = 8.7, 0.8 Hz, 1H), 7.32 (s, 4H), 6.80 (dd, *J* = 2.2, 1.0 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.07 (s, 2H), 2.86 – 2.74 (m, 2H), 2.53 – 2.44 (m, 2H), 1.81 – 1.71 (m, 1H), 1.64 – 1.48 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.28, 156.47, 147.09, 141.63, 136.42, 131.33, 129.30, 127.46, 123.64, 122.09, 121.59, 111.61, 107.32, 65.56, 61.66, 48.03, 34.72, 14.72, 14.23. HRMS $[C_{22}H_{22}BrNO_5S+Na]^+$: 514.02943/516.02732 calculated, 514.02945/516.02724 found.

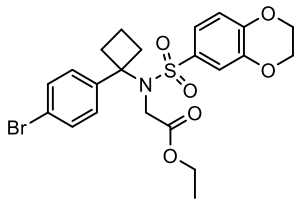
Ethyl *N*-(benzo[*d*][1,3]dioxol-5-ylsulfonyl)-*N*-(1-(4-bromophenyl)cyclobutyl)glycinate (79)



The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)benzo[*d*][1,3]dioxole-5-sulfonamide (**55**, 40 mg, 0.097 mmol, 1 eq), ethyl 2-bromoacetate (22.0 µL, 0.195 mmol, 2 eq) and BEMP (1 M in hexane, 195 µL, 0.195 mmol, 2 eq). Total

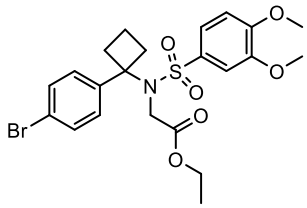
time: 12 h at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (49 mg, 0.099 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 4H), 7.19 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.93 (d, *J* = 1.9 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.06 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.06 (s, 2H), 2.84 – 2.71 (m, 2H), 2.51 – 2.41 (m, 2H), 1.83 – 1.72 (m, 1H), 1.61 – 1.51 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.27, 150.97, 147.72, 141.64, 135.26, 131.29, 129.26, 122.87, 121.60, 107.86, 107.83, 102.33, 65.45, 61.68, 48.09, 34.64, 14.68, 14.24.

Ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)glycinate (80)



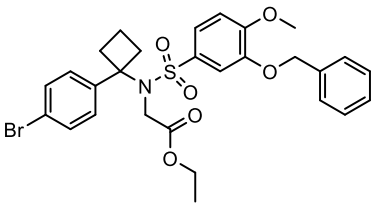
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonamide (**56**, 56.6 mg, 0.133 mmol, 1 eq), ethyl 2-bromoacetate (30.0 µL, 0.267 mmol, 2 eq) and BEMP (1 M in hexane, 267 µL, 0.267 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (20% EtOAc in dis. *n*-pentane) afforded the product as a white powder (41 mg, 0.080 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 4H), 7.12 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.96 (d, *J* = 2.2 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 4.32 – 4.25 (m, 4H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.06 (s, 2H), 2.83 – 2.72 (m, 2H), 2.50 – 2.42 (m, 2H), 1.81 – 1.72 (m, 1H), 1.60 – 1.50 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.28, 147.04, 143.03, 141.60, 134.27, 131.21, 129.22, 121.54, 120.77, 117.29, 117.10, 65.34, 64.66, 64.28, 61.62, 48.11, 34.67, 14.65, 14.22.

Ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((3,4-dimethoxyphenyl)sulfonyl)glycinate (81)



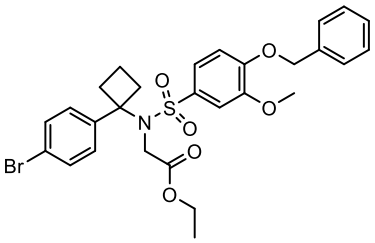
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-3,4-dimethoxybenzenesulfonamide (**57**, 56.7 mg, 0.133 mmol. 1 eq), ethyl 2-bromoacetate (29.5 µL, 0.266 mmol, 2 eq) and BEMP (1 M in hexane, 266 µL, 0.266 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (20-30% EtOAc in dis. *n*-pentane) afforded the product (53.8 mg, 0.105 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 4H), 7.27 – 7.20 (m, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.07 (s, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 2.82 – 2.72 (m, 2H), 2.48 – 2.40 (m, 2H), 1.81 – 1.71 (m, 1H), 1.59 – 1.51 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.37, 152.28, 148.74, 141.71, 133.69, 131.23, 129.32, 121.54, 121.30, 110.05, 110.02, 65.46, 61.55, 56.24, 56.22, 47.79, 34.44, 14.68, 14.20. LC-MS $[C_{22}H_{26}BrNO_6S+NH_4]^+$: 529.10/531.10 calculated, 528.75/530.67 found.

Ethyl *N*-((3-(benzyloxy)-4-methoxyphenyl)sulfonyl)-*N*-(1-(4-bromophenyl)cyclobutyl)glycinate (82)



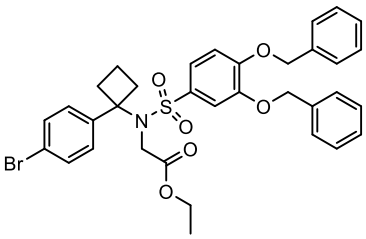
The title compound was synthesized according to the general procedure **I** using 3-(benzyloxy)-*N*-(1-(4-bromophenyl)cyclobutyl)-4-methoxybenzenesulfonamide (**58**, 85 mg, 0.17 mmol, 1 eq), ethyl 2-bromoacetate (36 µL, 0.33 mmol, 2 eq) and BEMP (1 M in hexane, 248 µL, 0.248 mmol , 1.5 eq). Total time: overnight at 80 °C. Silica gel column chromatography (15-20% EtOAc in dis. *n*-pentane) to afford the product as a light yellow oil (97 mg, 0.16 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.42 – 7.36 (m, 2H), 7.34 – 7.30 (m, 3H), 7.28 – 7.21 (m, 3H), 7.14 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 1H), 5.16 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.94 (s, 2H), 3.93 (s, 3H), 2.72 – 2.60 (m, 2H), 2.40 – 2.31 (m, 2H), 1.71 – 1.62 (m, 1H), 1.55 – 1.44 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.29, 152.84, 147.55, 141.61, 136.47, 133.54, 131.17, 129.15, 128.74, 128.20, 127.60, 121.59, 121.41, 112.18, 110.47, 70.91, 65.27, 61.53, 56.26, 48.02, 34.38, 14.59, 14.21.

Ethyl *N*-((4-(benzyloxy)-3-methoxyphenyl)sulfonyl)-*N*-(1-(4-bromophenyl)cyclobutyl)glycinate (83)



The title compound was synthesized according to the general procedure **I** using 4-(benzyloxy)-*N*-(1-(4-bromophenyl)cyclobutyl)-3-methoxybenzenesulfonamide (**59**, 274 mg, 0.545 mmol, 1 eq), ethyl 2-bromoacetate (121 µL, 1.09 mmol, 2 eq) and BEMP (1 M in hexane, 1.1 mL, 1.1 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (15-20% EtOAc in dis. *n*-pentane) afforded the product as an oil (288 mg, 0.489 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.31 (m, 9H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.17 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 5.21 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.05 (s, 2H), 3.87 (s, 3H), 2.84 – 2.71 (m, 2H), 2.49 – 2.39 (m, 2H), 1.80 – 1.70 (m, 1H), 1.63 – 1.49 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.41, 151.42, 149.27, 141.75, 136.24, 134.04, 131.28, 129.35, 128.87, 128.34, 127.40, 121.59, 121.05, 112.30, 110.51, 71.03, 65.50, 61.60, 56.30, 47.87, 34.51, 14.72, 14.24. LC-MS $[C_{28}H_{30}BrNO_6S+NH_4]^+$: 605.13/607.13 calculated, 604.67/606.50 found.

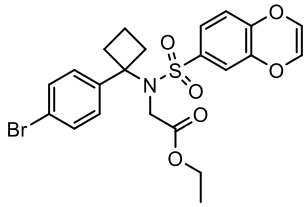
Ethyl *N*-((3,4-bis(benzyloxy)phenyl)sulfonyl)-*N*-(1-(4-bromophenyl)cyclobutyl)glycinate (84)



The title compound was synthesized according to the general procedure **I** using 3,4-bis(benzyloxy)-*N*-(1-(4-bromophenyl)cyclobutyl)benzenesulfonamide (**60**, 278 mg, 0.481 mmol, 1 eq), ethyl 2-bromoacetate (107 µL, 0.962 mmol, 2 eq) and BEMP (1 M in hexane, 962 µL, 0.962 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column

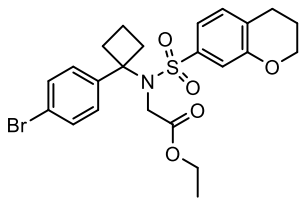
chromatography (15-20% EtOAc in *n*-pentane) afforded the product (199 mg, 0.299 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 4H), 7.41 – 7.36 (m, 4H), 7.36 – 7.26 (m, 5H), 7.25 – 7.21 (m, 2H), 7.11 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 5.21 (s, 2H), 5.15 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 2H), 2.73 – 2.62 (m, 2H), 2.40 – 2.31 (m, 2H), 1.73 – 1.58 (m, 1H), 1.55 – 1.45 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.30, 152.11, 148.16, 141.65, 136.70, 136.42, 134.05, 131.22, 129.21, 128.78, 128.71, 128.24, 128.15, 127.54, 127.30, 121.53, 121.47, 113.14, 113.01, 71.10, 71.06, 65.33, 61.58, 48.04, 34.44, 14.63, 14.23. LC-MS $[C_{34}H_{34}BrNO_6S+NH_4]^+$: 681.16/683.16 calculated, 680.67/682.50 found.

Ethyl *N*-(benzo[*b*][1,4]dioxin-6-ylsulfonyl)-*N*-(1-(4-bromophenyl)cyclobutyl)glycinate (85)



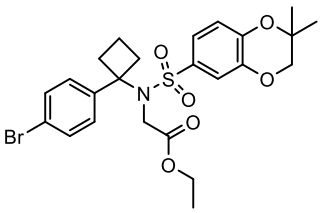
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)benzo[*b*][1,4]dioxine-6-sulfonamide (**61**, 36 mg, 0.086 mmol, 1 eq), ethyl 2-bromoacetate (19 µL, 0.17 mmol, 2 eq) and BEMP (1 M in hexane, 171 µL, 0.171 mmol, 2 eq). Total time: 6 h at 80 °C. Silica gel column chromatography (15% EtOAc in dis. *n*-pentane) afforded the product as a colorless oil (23 mg, 0.045 mmol, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.37 – 7.32 (m, 2H), 7.08 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.70 (d, *J* = 2.3 Hz, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 5.89 – 5.86 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.03 (s, 2H), 2.80 – 2.71 (m, 2H), 2.50 – 2.43 (m, 2H), 1.82 – 1.74 (m, 1H), 1.61 – 1.52 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.16, 146.26, 142.53, 141.49, 137.28, 131.38, 129.26, 127.26, 126.69, 124.00, 121.85, 116.12, 115.67, 65.50, 61.72, 48.02, 34.66, 14.70, 14.23.

Ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-(chroman-7-ylsulfonyl)glycinate (86)



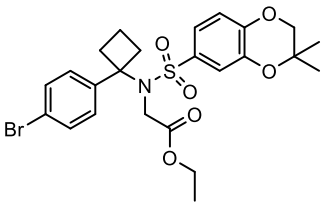
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)chromane-7-sulfonamide (**62**, 42 mg, 0.099 mmol, 1 eq), ethyl 2-bromoacetate (22 µL, 0.19 mmol, 2 eq) and BEMP (1 M in hexane, 189 µL, 0.189 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (10-20% EtOAc in dis. *n*-pentane) afforded the product as a colorless oil (34 mg, 0.067 mmol, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 4H), 7.04 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.01 – 6.97 (m, 1H), 6.92 (d, *J* = 1.9 Hz, 1H), 4.22 – 4.19 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.06 (s, 2H), 2.83 – 2.73 (m, 4H), 2.50 – 2.41 (m, 2H), 2.05 – 1.98 (m, 2H), 1.79 – 1.71 (m, 1H), 1.59 – 1.50 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.20, 154.78, 141.53, 140.53, 131.21, 130.04, 129.21, 127.05, 121.59, 118.41, 115.84, 66.79, 65.38, 61.59, 48.18, 34.62, 25.05, 21.89, 14.65, 14.19.

Ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)glycinate (87)



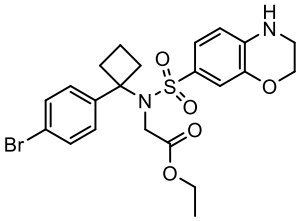
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonamide (**63**, 37 mg, 0.081 mmol, 1 eq), ethyl 2-bromoacetate (17.9 µL, 0.162 mmol, 2 eq) and BEMP (162 µL, 0.162 mmol, 2 eq). Total time: 4 h at 80 °C. Silica gel column chromatography (10-20% EtOAc in *n*-pentane) afforded the product as a pale-yellow oil (31.5 mg, 58.5 µmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 4H), 7.14 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.04 (s, 2H), 3.90 (s, 2H), 2.86 – 2.73 (m, 2H), 2.53 – 2.41 (m, 2H), 1.81 – 1.73 (m, 1H), 1.59 – 1.49 (m, 1H), 1.36 (s, 6H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.27, 146.32, 141.78, 141.70, 133.56, 131.25, 129.22, 121.59, 121.36, 117.50, 116.62, 73.53, 71.90, 65.39, 61.59, 48.08, 34.68, 23.41, 14.68, 14.21. LC-MS $[C_{24}H_{28}BrNO_6S+Na]^+$: 560.07/562.07 calculated, 560.08/562.08 found.

Ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((3,3-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)glycinate (88)



The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-3,3-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonamide (**64**, 41 mg, 0.090 mmol, 1 eq), ethyl 2-bromoacetate (19.8 µL, 0.180 mmol, 2 eq) and BEMP (180 µL, 0.180 mmol, 2 eq). Total time: 4 h at 80 °C. Silica gel column chromatography (10-20% EtOAc in *n*-pentane) afforded the product as a pale-yellow oil (42 mg, 0.078 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 4H), 7.11 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.04 (s, 2H), 3.92 (s, 2H), 2.86 – 2.74 (m, 2H), 2.52 – 2.43 (m, 2H), 1.82 – 1.72 (m, 1H), 1.61 – 1.48 (m, 1H), 1.34 (s, 6H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.25, 145.77, 142.18, 141.71, 134.42, 131.24, 129.19, 121.47, 120.38, 117.28, 116.76, 72.77, 72.12, 65.33, 61.59, 48.12, 34.71, 23.32, 14.67, 14.21. LC-MS $[C_{24}H_{28}BrNO_6S+Na]^+$: 560.07/562.07 calculated, 560.08/562.00 found.

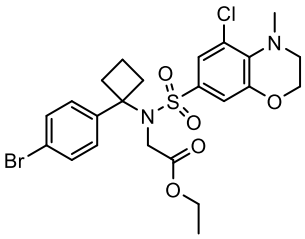
Ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-7-yl)sulfonyl)glycinate (89)



The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-4-(2,2,2-trifluoroacetyl)-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazine-7-sulfonamide (**65**, 58.9 mg, 0.113 mmol, 1 eq), ethyl 2-bromoacetate (25.0 µL, 0.227 mmol, 2 eq) and BEMP (1 M in hexane, 227 µL, 0.227 mmol, 2 eq). Total time: 4 h at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (30 mg, 0.059 mmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40

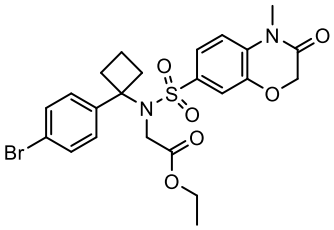
– 7.32 (m, 4H), 7.01 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.91 (d, *J* = 2.1 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 1H), 4.28 (bs, 1H), 4.23 – 4.20 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 2H), 3.48 – 3.44 (m, 2H), 2.85 – 2.74 (m, 2H), 2.48 – 2.40 (m, 2H), 1.81 – 1.70 (m, 1H), 1.61 – 1.47 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.38, 142.48, 141.99, 137.85, 131.21, 129.73, 129.15, 121.48, 121.40, 116.14, 113.64, 65.28, 64.72, 61.49, 48.04, 40.53, 34.54, 14.66, 14.19. LC-MS $[C_{22}H_{25}BrN_2O_5S+H]^+$: 509.07/511.07 calculated, 509.08/511.00 found.

Ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((5-chloro-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)sulfonyl)glycinate (90)



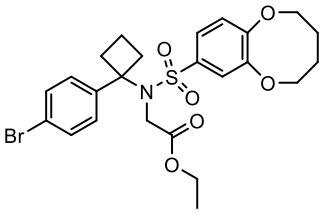
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-5-chloro-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-sulfonamide (**66**, 38 mg, 0.080 mmol, 1 eq), ethyl 2-bromoacetate (18 µL, 0.16 mmol, 2 eq) and BEMP (1 M in hexane, 161 µL, 0.161 mmol, 2 eq). Total time: 16 h at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (33 mg, 0.059 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 4H), 7.01 (d, *J* = 2.2 Hz, 1H), 6.84 (d, *J* = 2.2 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.18 – 4.14 (m, 2H), 4.11 (s, 2H), 3.17 – 3.12 (m, 2H), 2.93 (s, 3H), 2.84 – 2.74 (m, 2H), 2.52 – 2.44 (m, 2H), 1.83 – 1.74 (m, 1H), 1.60 – 1.51 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.22, 148.17, 141.27, 137.08, 135.06, 131.17, 129.24, 127.45, 121.66, 121.06, 115.07, 65.30, 61.75, 60.44, 49.69, 48.33, 43.28, 34.90, 14.65, 14.24. LC-MS $[C_{23}H_{26}BrClN_2O_5S+H]^+$: 557.05/559.05 calculated, 557.25/559.17 found.

Ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((4-methyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)sulfonyl)glycinate (91)



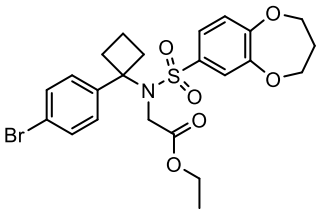
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-4-methyl-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazine-7-sulfonamide (**67**, 19 mg, 0.042 mmol, 1 eq), ethyl 2-bromoacetate (14.0 µL, 0.125 mmol, 3 eq) and BEMP (125 µL, 0.125 mmol, 3 eq). Total time: 16 h at 80 °C. Silica gel column chromatography (30-35% EtOAc in *n*-pentane) afforded the product (13 mg, 0.024 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 4H), 7.24 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 4.67 (s, 2H), 4.22 (q, *J* = 7.2 Hz , 2H), 4.11 (s, 2H), 3.38 (s, 3H), 2.82 – 2.71 (m, 2H), 2.53 – 2.44 (m, 2H), 1.83 – 1.73 (m, 1H), 1.59 – 1.51 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.27, 164.28, 144.47, 141.38, 132.77, 131.27, 129.89, 129.40, 122.20, 121.64, 115.84, 114.30, 67.54, 65.32, 61.79, 48.17, 34.79, 28.38, 14.68, 14.26.

Ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocin-8-yl)sulfonyl)glycinate (92)



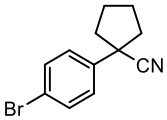
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocine-8-sulfonamide (**68**, 38 mg, 0.084 mmol, 1 eq), ethyl 2-bromoacetate (19 µL, 0.17 mmol, 2 eq) and BEMP (1 M in hexane, 169 µL, 0.169 mmol, 2 eq). Total time: 3 h at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (33 mg, 0.061 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.21 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 4.48 (t, *J* = 5.5 Hz, 2H), 4.24 (t, *J* = 5.5 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.04 (s, 2H), 2.84 – 2.73 (m, 2H), 2.51 – 2.41 (m, 2H), 1.96 (p, *J* = 5.9 Hz, 2H), 1.86 (p, *J* = 5.9 Hz, 2H), 1.82 – 1.72 (m, 1H), 1.59 – 1.50 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.20, 154.26, 147.32, 141.67, 135.17, 131.28, 129.21, 123.32, 123.25, 121.58, 121.43, 74.04, 71.66, 65.40, 61.60, 48.06, 34.63, 27.80, 25.38, 14.67, 14.21. LC-MS $[C_{24}H_{28}BrNO_6S+Na]^+$: 560.07/562.07 calculated, 560.17/562.08 found.

Ethyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate (93)



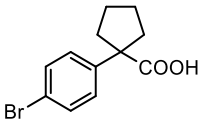
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-3,4-dihydro-*2H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**69**, 73.5 mg, 0.168 mmol, 1 eq), ethyl 2-bromoacetate (37.0 µL, 0.335 mmol, 2 eq) and BEMP (1 M in hexane, 335 µL, 0.335 mmol, 2 eq). Total time: 16 h at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (60.0 mg, 0.114 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 4H), 7.17 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 4.30 (t, *J* = 5.8 Hz, 2H), 4.24 (t, *J* = 5.9 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.05 (s, 2H), 2.83 – 2.72 (m, 2H), 2.50 – 2.43 (m, 2H), 2.23 (p, *J* = 5.8 Hz, 2H), 1.81 – 1.72 (m, 1H), 1.59 – 1.50 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.22, 154.44, 150.33, 141.61, 135.85, 131.28, 129.27, 122.58, 121.59, 121.40, 121.14, 70.54, 70.49, 65.39, 61.65, 48.12, 34.69, 30.97, 14.68, 14.22.

1-(4-Bromophenyl)cyclopentane-1-carbonitrile (94)



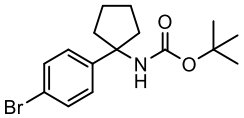
The title compound was synthesized according to the general procedure **A** using 2-(4-bromophenyl)acetonitrile (2.00 g, 10.2 mmol, 1 eq), 1,4-dibromobutane (1.2 mL 10.2 mmol, 1 eq), TBABr (33.0 mg, 0.102 mmol, 0.01 eq) and KOH (4.58 g, 81.6 mmol, 8 eq). Total time: 1 h at reflux. Silica gel column chromatography (5% Et_2O in *n*-pentane) afforded the product (2.12 g, 8.48 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.37 (m, 2H), 7.35 – 7.21 (m, 2H), 2.52 – 2.35 (m, 2H), 2.13 – 1.80 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.96, 132.00, 127.84, 123.93, 121.82, 47.42, 40.49, 24.25.

1-(4-Bromophenyl)cyclopentane-1-carboxylic acid (95)



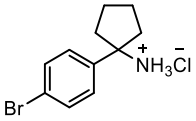
The title compound was synthesized according to the general procedure **B** using 1-(4-bromophenyl)cyclopentane-1-carbonitrile (**94**, 2.12 g, 8.48 mmol, 1 eq) and KOH (2.85 g, 50.9 mmol, 6 eq) at reflux for 3 h and then 6 M aq. HCl in 1,4-dioxane (6 mL) at reflux for 2 days. The reaction was cooled down to rt and 1 M aq. NaOH was added to pH >12. The aqueous layer was washed 2× with Et_2O. Afterwards, 3 M aq. HCl was added to pH < 2 and the aqueous layer was extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford the product (0.99 g, 3.7 mmol, 43%). ^{1}H NMR (400 MHz, MeOD) δ 7.40 (d, *J* = 7.7 Hz, 2H), 7.33 – 7.23 (m, 2H), 2.71 – 2.52 (m, 2H), 1.92 – 1.78 (m, 2H), 1.78 – 1.67 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 178.82, 143.60, 131.87, 129.49, 121.18, 59.34, 36.73, 24.13.

***tert*-Butyl (1-(4-bromophenyl)cyclopentyl)carbamate (96)**



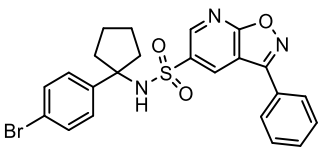
The title compound was synthesized according to the general procedure **C** using 1-(4-bromophenyl)cyclopentane-1-carboxylic acid (**95**, 989 mg, 3.68 mmol, 1 eq), diphenylphosphoryl azide (531 µL, 3.68 mmol, 1 eq) and Et_3N (567 µL, 4.04 mmol, 1.1 eq) in anhydrous *t*-BuOH (48 mL, 0.08 M). Total time: 1 h at 30 °C and overnight at reflux. Silica gel column chromatography (5% EtOAc in *n*-pentane) afforded the product (675 mg, 1.98 mmol, 54%). 1H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.36 (m, 2H), 7.31 – 7.23 (m, 2H), 4.96 (s, 1H), 2.33 – 1.91 (m, 4H), 1.90 – 1.71 (m, 4H), 1.37 (s, 9H).

1-(4-Bromophenyl)cyclopentan-1-aminium chloride (97)



The title compound was synthesized according to the general procedure **D** using *tert*-butyl (1-(4-bromophenyl)cyclopentyl)carbamate (**96**, 612 mg, 1.98 mmol) in 3 M aq. HCl in MeOH (25 mL, 0.08 M). Total time: 36 h at rt. The mixture was concentrated, washed with Et_2O and filtered to afford the product (399 mg, 1.44 mmol, 80%). ^{1}H NMR (400 MHz, MeOD) δ 7.69 – 7.57 (m, 2H), 7.52 – 7.43 (m, 2H), 2.37 – 2.21 (m, 4H), 2.08 – 1.84 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 140.84, 133.23, 129.41, 123.82, 67.13, 38.59, 23.83. LC-MS $[C_{11}H_{14}BrN–NH_2]^+$: 223.01/225.01 calculated, 222.93/224.93 found.

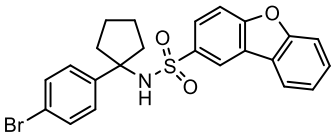
***N*-(1-(4-Bromophenyl)cyclopentyl)-3-phenylisoxazolo[5,4-*b*]pyridine-5-sulfonamide (98a)**



The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclopentan-1-aminium chloride (**97**, 80.0 mg, 0.289 mmol, 1 eq), 3-phenylisocazolo[5,4-*b*]pyridine-5-sulfonyl chloride (89.6 mg, 0.303 mmol, 1.05 eq) and DIPEA (202 µL, 1.16 mmol, 4 eq). Total time: 3 days at rt. Silica gel column chromatography (10-40% EtOAc in *n*-pentane) afforded the product (90.6 mg, 0.182 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 2.1 Hz, 1H), 8.09 (d, *J* = 2.1 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.64 –

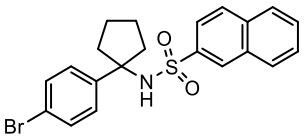
7.56 (m, 3H), 7.00 – 6.94 (m, 2H), 6.92 – 6.85 (m, 2H), 6.57 (s, 1H), 2.54 – 2.45 (m, 2H), 2.01 – 1.87 (m, 4H), 1.82 – 1.70 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.33, 157.53, 149.50, 139.72, 135.50, 131.76, 131.41, 130.86, 129.47, 129.24, 127.81, 127.52, 121.58, 111.22, 68.87, 38.91, 22.06. LC-MS $[C_{23}H_{20}BrN_3O_3S+H]^+$: 498.05/500.05 calculated, 497.92/499.83 found.

_N_-(1-(4-Bromophenyl)cyclopentyl)dibenzo[_b,d_]furan-2-sulfonamide (98b)



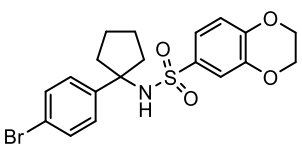
The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclopentan-1-aminium chloride (**97**, 40.0 mg, 0.145 mmol, 1 eq), dibenzo[*b*,*d*]furan-2-sulfonyl chloride (40.5 mg, 0.152 mmol, 1.05 eq) and DIPEA (101 µL, 0.578 mmol, 4 eq). Total time: 4 days at rt. Silica gel column chromatography (5-60% EtOAc in *n*-pentane) afforded the product (45 mg, 0.095 mmol, 66%). ^{1}H NMR (400 MHz, DMSO) δ 8.11 (d, *J* = 7.8, 1.3 Hz, 1H), 8.05 (s, 1H), 7.89 (t, *J* = 1.3 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.64 – 7.61 (m, 2H), 7.60 – 7.54 (m, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.02 – 6.97 (m, 2H), 6.94 – 6.89 (m, 2H), 2.47 – 2.36 (m, 2H), 1.81 – 1.51 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 156.42, 156.33, 141.59, 137.18, 129.90, 128.79, 128.36, 125.62, 123.66, 123.21, 122.73, 121.64, 120.03, 119.72, 111.80, 111.58, 67.64, 38.08, 21.81.

_N_-(1-(4-Bromophenyl)cyclopentyl)naphthalene-2-sulfonamide (98c)



The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclopentan-1-aminium chloride (**97**, 80.0 mg, 0.289 mmol, 1 eq), naphtalene-2-sulfonyl chloride (68.7 mg, 0.303 mmol, 1.05 eq) and DIPEA (202 µL, 1.16 mmol, 4 eq). Total time: 2 days at rt. Silica gel column chromatography (10-40% EtOAc in *n*-pentane) afforded the product (59.4 mg, 0.138 mmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 1H), 7.79 (d, *J* = 1.9 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.65 – 7.56 (m, 2H), 7.53 (dd, *J* = 8.7, 1.9 Hz, 1H), 6.99 – 6.91 (m, 2H), 6.89 – 6.82 (m, 2H), 5.76 (s, 1H), 2.50 – 2.38 (m, 2H), 2.01 – 1.63 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.49, 138.30, 134.24, 131.85, 131.34, 130.63, 129.26, 128.95, 128.65, 128.17, 127.79, 127.58, 121.99, 121.30, 68.75, 39.15, 22.17.

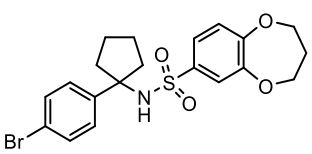
_N_-(1-(4-Bromophenyl)cyclopentyl)-2,3-dihydrobenzo[_b_][1,4]dioxine-6-sulfonamide (98d)



The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclopentan-1-aminium chloride (**97**, 61.7 mg, 0.223 mmol, 1 eq), 2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonyl chloride (**108**, 54.9 mg, 0.234 mmol, 1.05 eq) and DIPEA (156 µL, 0.892 mmol, 4 eq). Total time: 3 days at rt. Silica gel column chromatography (100% EtOAc) afforded the product (29.5 mg, 0.290 mmol, 30%). ^{1}H NMR (400 MHz, DMSO) δ 7.88 (s, 1H), 7.21 – 7.16 (m, 2H), 7.06 – 7.01 (m, 2H), 6.91 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.62 (d, *J* = 2.2 Hz, 1H), 4.33 – 4.19 (m, 4H), 2.41 – 2.29 (m, 2H), 1.79 – 1.66 (m, 4H), 1.65 – 1.53 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ

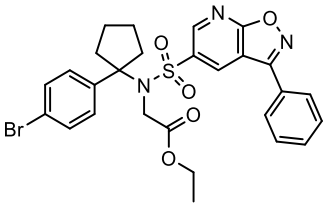
145.96, 142.33, 142.12, 134.79, 130.11, 128.85, 119.65, 119,64, 116.82, 115.42, 67.46, 64.30, 64.05, 38.11, 21.86.

_N_-(1-(4-Bromophenyl)cyclopentyl)-3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepine-7-sulfonamide (98e)



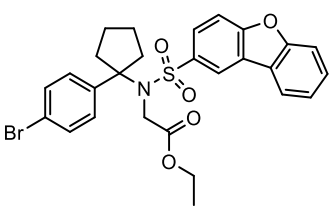
The title compound was synthesized according to the general procedure **H** using 1-(4-bromophenyl)cyclopentan-1-aminium chloride (**97**, 32.0 mg, 0.116 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 43.2 mg, 0.174 mmol, 1.5 eq) and DIPEA (61.0 µL, 0.347 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (15-25% EtOAc in *n*-pentane) afforded the product (40 mg, 0.088 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.13 (m, 2H), 7.05 – 6.99 (m, 3H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.44 (s, 1H), 4.30 (t, *J* = 5.8 Hz, 2H), 4.22 (t, *J* = 5.8 Hz, 2H), 2.46 – 2.32 (m, 2H), 2.22 (p, *J* = 5.8 Hz, 2H), 1.98 – 1.86 (m, 4H), 1.78 – 1.65 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.18, 150.13, 141.08, 135.75, 130.77, 129.09, 122.15, 121.34, 121.04, 120.74, 70.57, 70.46, 68.49, 39.16, 30.99, 22.16.

Ethyl _N_-(1-(4-bromophenyl)cyclopentyl)-_N_-((3-phenylisoxazolo[5,4-_b_]pyridin-5-yl)sulfonyl)glycinate (99a)



The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclopentyl)-3-phenylisoxazolo[5,4-*b*]pyridine-5-sulfonamide (**98a**, 90.6 mg, 0.182 mmol, 1 eq), ethyl 2-bromoacetate (40.2 µL, 0.364 mmol, 2 eq) and BEMP (1 M in hexane, 364 µL, 0.364 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (5-10% EtOAc in dis. *n*-pentane) afforded the product (26.5 mg, 45.3 µmol, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, *J* = 2.2 Hz, 1H), 8.68 (d, *J* = 2.2 Hz, 1H), 8.03 – 7.97 (m, 2H), 7.65 – 7.57 (m, 3H), 7.31 – 7.27 (m, 2H), 7.21 – 7.16 (m, 2H), 4.34 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.44 – 2.36 (m, 2H), 2.22 – 2.10 (m, 2H), 1.73 – 1.60 (m, 2H), 1.38 – 1.34 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.96, 170.77, 157.90, 150.05, 140.27, 136.62, 133.20, 131.49, 131.16, 129.60, 129.54, 127.95, 127.66, 122.20, 111.66, 73.89, 61.99, 48.71, 37.77, 21.54, 14.28. HRMS $[C_{27}H_{26}BrN_3O_5S+H]^+$: 584.08493/586.08286 calculated, 584.08474/586.08264 found.

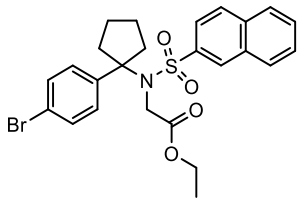
Ethyl _N_-(1-(4-bromophenyl)cyclopentyl)-_N_-(dibenzo[_b_,_d_]furan-2-ylsulfonyl)glycinate (99b)



The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclopentyl)dibenzo[*b*,*d*]furan-2-sulfonamide (**98b**, 41 mg, 0.087 mmol, 1 eq), ethyl 2-bromoacetate (19.3 µL, 0.174 mmol, 2 eq) and BEMP (1 M in hexane, 174 µL, 0.174 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (5-10% EtOAc in dis. *n*-

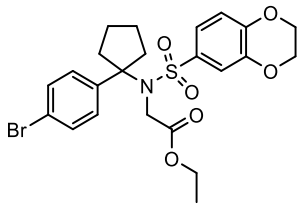
pentane) afforded the product (26 mg, 0.046 mmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 1.7 Hz, 1H), 7.98 – 7.94 (m, 2H), 7.62 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.58 (dd, *J* = 8.7, 0.5 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.43 (td, *J* = 7.5, 1.1 Hz, 1H), 7.27 (s, 4H), 4.21 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.38 – 2.22 (m, 4H), 1.70 – 1.60 (m, 2H), 1.40 – 1.30 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.82, 157.94, 157.14, 141.58, 137.00, 131.11, 129.33, 128.45, 126.82, 124.50, 123.74, 123.40, 121.63, 121.47, 121.30, 112.10, 111.85, 73.69, 61.60, 48.94, 37.81, 21.66, 14.28. HRMS $[C_{27}H_{26}BrNO_5S+Na]^+$: 578.06073/580.05865 calculated, 578.06057/580.05840 found.

Ethyl *N*-(1-(4-bromophenyl)cyclopentyl)-*N*-(naphthalen-2-ylsulfonyl)glycinate (99c)



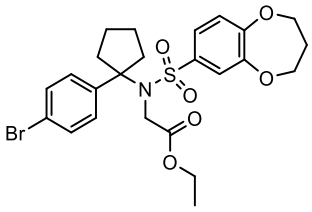
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclopentyl)naphthalene-2-sulfonamide (**98c**, 54.9 mg, 0.128 mmol, 1 eq), ethyl 2-bromoacetate (28.4 µL, 0.256 mmol, 2 eq) and BEMP (1 M in hexane, 256 µL, 0.256 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (5-10% EtOAc in dis. *n*-pentane) afforded the product (39 mg, 0.075 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 1.3 Hz, 1H), 7.91 – 7.82 (m, 4H), 7.67 – 7.56 (m, 2H), 7.30 – 7.19 (m, 4H), 4.22 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.37 – 2.21 (m, 4H), 1.69 – 1.59 (m, 2H), 1.38 – 1.29 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.73, 141.41, 139.18, 134.65, 132.05, 131.12, 129.60, 129.37, 129.32, 128.90, 128.79, 127.87, 127.45, 123.04, 121.68, 73.65, 61.57, 48.95, 37.71, 21.61, 14.24. HRMS $[C_{25}H_{26}BrNO_4S+Na]^+$: 538.06581/540.06371 calculated, 538.06572/540.06351 found.

Ethyl *N*-(1-(4-bromophenyl)cyclopentyl)-*N*-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)glycinate (99d)



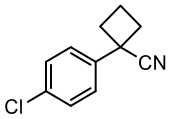
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclopentyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonamide (**98d**, 30 mg, 0.067 mmol, 1 eq), ethyl 2-bromoacetate (15.0 µL, 0.135 mmol, 2 eq) and BEMP (1 M in hexane, 135 µL, 0.135 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (10-20% EtOAc in dis. *n*-pentane) afforded the product (18.5 mg, 35.3 µmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 3H), 7.29 – 7.24 (m, 2H), 7.19 (d, *J* = 2.3 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 4.34 – 4.26 (m, 4H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.12 (s, 2H), 2.36 – 2.18 (m, 4H), 1.73 – 1.63 (m, 2H), 1.42 – 1.30 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.77, 147.10, 143.08, 141.67, 135.05, 131.05, 129.26, 121.51, 121.21, 117.44, 117.36, 73.45, 64.69, 64.29, 61.49, 48.97, 37.64, 21.66, 14.24. HRMS $[C_{23}H_{26}BrNO_6S+Na]^+$: 546.05564/548.05355 calculated, 546.05521/548.05318 found.

Ethyl *N*-(1-(4-bromophenyl)cyclopentyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate (99e)



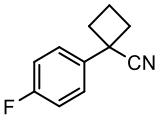
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-bromophenyl)cyclopentyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**98e**, 60.0 mg, 0.133 mmol, 1 eq), ethyl 2-bromoacetate (44 µL, 0.40 mmol, 3 eq) and BEMP (1 M in hexane, 398 µL, 0.398 mmol, 3 eq). Total time: overnight at 80 °C. Silica gel column chromatography (15-20% EtOAc in dis. *n*-pentane) afforded the product (48 mg, 0.089 mmol, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 6H), 6.93 (d, *J* = 8.5 Hz, 1H), 4.31 (t, *J* = 5.7 Hz, 2H), 4.26 (t, *J* = 5.8 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.12 (s, 2H), 2.37 – 2.15 (m, 6H), 1.74 – 1.59 (m, 2H), 1.40 – 1.31 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.65, 154.47, 150.34, 141.65, 136.53, 131.07, 129.23, 122.95, 121.50, 121.47, 121.45, 73.48, 70.55, 70.49, 61.48, 48.97, 37.63, 30.98, 21.64, 14.20.

1-(4-Chlorophenyl)cyclobutane-1-carbonitrile (100a)



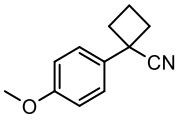
The title compound was synthesized according to the general procedure **A** using 2-(4-chlorophenyl)acetonitrile (2.00 g, 13.2 mmol, 1 eq), 1,3-dibromopropane (1.35 mL, 13.2 mmol, 1 eq), TBABr (420 mg, 1.32 mmol, 0.1 eq) and KOH (5.92 g, 106 mmol, 8 eq). Total time: 2 h at reflux. Silica gel column chromatography (4-5% Et_2O in *n*-pentane) afforded the product (790 mg, 4.13 mmol, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.21 (m, 4H), 2.86 – 2.77 (m, 2H), 2.63 – 2.53 (m, 2H), 2.49 – 2.38 (m, 1H), 2.12 – 2.01 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.34, 133.83, 129.12, 127.10, 124.00, 39.74, 34.69, 17.06.

1-(4-Fluorophenyl)cyclobutane-1-carbonitrile (100b)



The title compound was synthesized according to the general procedure **A** using 2-(4-fluorophenyl)acetonitrile (2.00 g, 14.8 mmol, 1 eq), 1,3-dibromopropane (1.51 mL, 14.8 mmol, 1 eq) and TBABr (480 mg, 1.48 mmol, 0.1 eq) and KOH (6.64 g, 118 mmol, 8 eq). Total time: 2 h at reflux. Silica gel column chromatography (4-5% Et_2O in *n*-pentane) afforded the product (1.40 g, 7.99 mmol, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 2H), 7.12 – 7.03 (m, 2H), 2.86 – 2.77 (m, 2H), 2.64 – 2.54 (m, 2H), 2.49 – 2.35 (m, 1H), 2.12 – 2.01 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.18 (d, $J_{C\text{-}F}$ = 247.3 Hz), 135.70 (d, $J_{C\text{-}F}$ = 3.3 Hz), 127.44 (d, $J_{C\text{-}F}$ = 8.2 Hz), 124.27, 115.86 (d, $J_{C\text{-}F}$ = 21.7 Hz), 39.67, 34.78, 17.03.

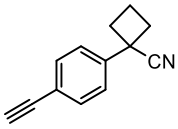
1-(4-Methoxyphenyl)cyclobutane-1-carbonitrile (100c)



The title compound was synthesized according to the general procedure **A** using 2-(4-methoxyphenyl)acetonitrile (2.00 g, 13.6 mmol, 1 eq), 1,3-dibromopropane (1.39 mL, 13.6 mmol, 1 eq), TBABr (440 mg, 1.36 mmol, 0.1 eq) and KOH (6.10 g, 109 mmol, 8 eq) and. Total time: 2 h at reflux. Silica gel column

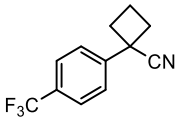
chromatography (5-10% Et_2O in *n*-pentane) afforded the product (1.27 g, 6.76 mmol, 50%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 6.94 – 6.89 (m, 2H), 3.81 (s, 3H), 2.84 – 2.76 (m, 2H), 2.63 – 2.54 (m, 2H), 2.44 – 2.36 (m, 1H), 2.10 – 2.00 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.18, 131.95, 126.87, 124.75, 114.31, 55.44, 39.71, 34.89, 17.10.

1-(4-Ethynylphenyl)cyclobutane-1-carbonitrile (100d)



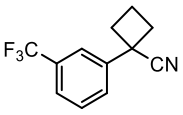
The title compound was synthesized according to the general procedure **A** using 2-(4-ethynylphenyl)acetonitrile (2.00 g, 14.2 mmol, 1 eq), 1,3-dibromopropane (1.45 mL, 14.17 mmol, 1 eq), TBABr (0.46 g, 1.42 mmol, 0.1 eq) and KOH (6.36 g, 113 mmol, 8 eq). Total time: 2 h at reflux. Silica gel column chromatography (5% Et_2O in *n*-pentane) afforded the product (1.16 g, 6.40 mmol, 45%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 2H), 7.41 – 7.35 (m, 2H), 3.11 (s, 1H), 2.88 – 2.78 (m, 2H), 2.66 – 2.55 (m, 2H), 2.50 – 2.37 (m, 1H), 2.14 – 2.02 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.41, 132.74, 125.73, 124.03, 121.89, 82.95, 78.11, 40.15, 34.70, 17.12.

1-(4-(Trifluoromethyl)phenyl)cyclobutane-1-carbonitrile (100e)



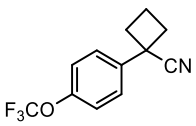
The title compound was synthesized according to the general procedure **A** using 2-(4-(trifluoromethyl)phenyl)acetonitrile (2.00 g, 10.8 mmol, 1 eq), 1,3-dibromopropane (1.10 mL, 10.8 mmol, 1 eq), TBABr (350 mg, 1.08 mmol, 0.1 eq) and KOH (4.85 g, 86.4 mmol, 8 eq). Total time: 2 h at reflux. Silica gel column chromatography (4-5% Et_2O in *n*-pentane) afforded the product (1.35 g, 5.99 mmol, 55%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 2.92 – 2.79 (m, 2H), 2.69 – 2.57 (m, 2H), 2.54 – 2.40 (m, 1H), 2.18 – 2.06 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.75 (q, $J_{C\text{-}F}$ = 1.1 Hz), 130.30 (q, $J_{C\text{-}F}$ = 33.0 Hz), 126.23, 126.08 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.94 (q, $J_{C\text{-}F}$ = 273.1 Hz), 123.73, 40.11, 34.69, 17.17.

1-(3-(Trifluoromethyl)phenyl)cyclobutane-1-carbonitrile (100f)



The title compound was synthesized according to the general procedure **A** using 2-(3-(trifluoromethyl)phenyl)acetonitrile (2.00 g, 10.8 mmol, 1 eq), 1,3-dibromopropane (1.10 mL, 10.8 mmol, 1 eq), TBABr (350 mg, 1.08 mmol, 0.1 eq) and KOH (4.85 g, 86.4 mmol, 8 eq). Total time: 2 h at reflux. Silica gel column chromatography (2-5% EtOAc in *n*-pentane) afforded the product (1.52 g, 6.74 mmol, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.49 (m, 4H), 2.95 – 2.81 (m, 2H), 2.72 – 2.58 (m, 2H), 2.57 – 2.39 (m, 1H), 2.22 – 2.04 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.93, 131.55 (q, $J_{C\text{-}F}$ = 32.6 Hz), 129.72, 129.30 (q, $J_{C\text{-}F}$ = 1.5 Hz), 124.96 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.93 (q, $J_{C\text{-}F}$ = 273.1 Hz), 123.80, 122.55 (q, $J_{C\text{-}F}$ = 3.9 Hz), 40.12, 34.73, 17.20.

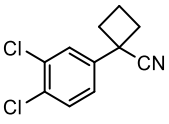
1-(4-(Trifluoromethoxy)phenyl)cyclobutane-1-carbonitrile (100g)



The title compound was synthesized according to the general procedure **A** using 2-(4-(trifluoromethoxy)phenyl)acetonitrile (2.00 g, 9.95 mmol, 1 eq), 1,3-dibromopropane(1.01 mL, 9.95 mmol , 1 eq), TBABr (350 mg, 1.08

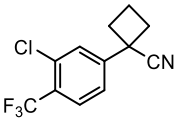
mmol, 0.1 eq) and KOH (4.85 g, 86.4 mmol, 8 eq). Total time: 3.5 h at reflux. Silica gel column chromatography (0-1% EtOAc in *n*-pentane) afforded the product as a colourless liquid (620 mg, 2.57 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.50 – 7.40 (m, 2H), 7.29 – 7.19 (m, 2H), 2.90 – 2.79 (m, 2H), 2.68 – 2.55 (m, 2H), 2.53 – 2.36 (m, 1H), 2.15 – 2.02 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.98 (q, J_{C-F} = 2.0 Hz), 138.78, 127.53, 124.24, 121.71, 120.71 (q, J_{C-F} = 258.6 Hz), 40.01, 35.00, 17.31.

1-(3,4-Dichlorophenyl)cyclobutane-1-carbonitrile (100h)



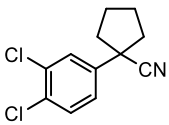
The title compound was synthesized according to the general procedure **A** using 2-(3,4-dichlorophenyl)acetonitrile (2.00 g, 10.7 mmol, 1 eq), 1,3-dibromopropane (1.09 mL, 10.7 mmol, 1 eq), TBABr (350 mg, 1.07 mmol, 0.1 eq) and KOH (4.83 g, 86.1 mmol, 8 eq). Total time: 3 h at reflux. Silica gel column chromatography (0-2% EtOAc in *n*-pentane) afforded the product as a colourless liquid (1.11 g, 4.90 mmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.3 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.26 (dd, J = 8.4, 2.3 Hz, 1H), 2.89 – 2.77 (m, 2H), 2.66 – 2.52 (m, 2H), 2.52 – 2.37 (m, 1H), 2.16 – 2.02 (m, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 139.99, 133.28, 132.31, 131.03, 127.95, 125.22, 123.53, 39.60, 34.71, 17.10.

1-(3-Chloro-4-(trifluoromethyl)phenyl)cyclobutane-1-carbonitrile (100i)



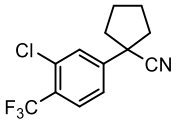
The title compound was synthesized according to the general procedure **A** using 2-(3-chloro-4-(trifluoromethyl)phenyl)acetonitrile (2.00 g, 9.11 mmol, 1 eq), 1,3-dibromopropane (930 µL, 9.11 mmol, 1 eq), TBABr (0.29 g, 0.91 mmol, 0.1 eq) and KOH (4.0 g, 73 mmol, 8 eq). Total time: 1 h at reflux. Silica gel column chromatography (2-4% EtOAc in *n*-pentane) afforded the product (1.02 g, 3.93 mmol, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.73 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 1.9 Hz, 1H), 7.43 (dd, *J* = 8.3, 1.8 Hz, 1H), 2.94 – 2.80 (m, 2H), 2.69 – 2.57 (m, 2H), 2.56 – 2.42 (m, 1H), 2.20 – 2.07 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 145.25 (q, J_{C-F} = 1.0 Hz), 133.35 (q, J_{C-F} = 2.0 Hz), 128.97, 128.40 (q, J_{C-F} = 5.1 Hz), 128.21 (q, J_{C-F} = 32.3 Hz), 124.21, 123.15, 122.69 (q, J_{C-F} = 273.7 Hz), 39.82, 34.67, 17.19.

1-(3,4-Dichlorophenyl)cyclopentane-1-carbonitrile (100j)



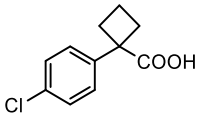
The title compound was synthesized according to the general procedure **A** using 2-(3,4-dichlorophenyl)acetonitrile (2.00 g, 10.7 mmol, 1 eq), 1,4-dibromobutane (1.28 mL, 10.7 mmol, 1 eq), TBABr (350 mg, 1.08 mmol, 0.1 eq) and KOH (4.83 g, 86.1 mmol, 8 eq). Total time: 2 h at reflux. Silica gel column chromatography (4-5% Et_2O in *n*-pentane) afforded the product (2.22 g, 9.25 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.3 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.30 (dd, *J* = 8.4, 2.3 Hz, 1H), 2.53 – 2.42 (m, 2H), 2.11 – 1.90 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.15, 133.15, 132.18, 130.89, 128.28, 125.65, 123.54, 47.27, 40.58, 24.29.

1-(3-Chloro-4-(trifluoromethyl)phenyl)cyclopentane-1-carbonitrile (100k)



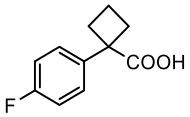
The title compound was synthesized according to the general procedure **A** using 2-(3-chloro-4-(trifluoromethyl)phenyl)acetonitrile (1.00 g, 4.55 mmol, 1 eq), 1,4-dibromobutane (0.60 mL, 5.0 mmol, 1.1 eq), TBABr (0.15 g, 0.46 mmol, 0.1 eq) and KOH (2.0 g, 36 mmol, 8 eq). Total time: 2 h at reflux. Silica gel column chromatography (4-5% Et_2O in *n*-pentane) afforded the product (1.08 g, 3.95 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 1.9 Hz, 1H), 7.48 (ddd, *J* = 8.3, 2.1, 0.9 Hz, 1H), 2.57 – 2.45 (m, 2H), 2.14 – 1.94 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.59, 133.16 (q, J_{C-F} = 1.9 Hz), 129.27, 128.24 (q, J_{C-F} = 5.3 Hz), 128.10 (q, J_{C-F} = 32.3 Hz), 124.62, 123.19, 122.70 (q, J_{C-F} = 273.7 Hz), 47.62, 40.74, 24.46.

1-(4-Chlorophenyl)cyclobutane-1-carboxylic acid (101a)



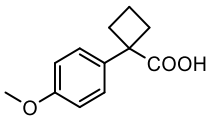
The title compound was synthesized according to the general procedure **B** using 1-(4-chlorophenyl)cyclobutane-1-carbonitrile (**100a**, 790 mg, 4.13 mmol, 1 eq) and KOH (1.39 g, 24.8 mmol, 6 eq). Total time: 16 h at reflux. Silica gel column chromatography (20% EtOAc in *n*-pentane with 0.1% TFA) afforded the product as a solid (830 mg, 3.93 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (bs, 1H), 7.33 – 7.20 (m, 4H), 2.88 – 2.79 (m, 2H), 2.53-2.43 (m, 2H), 2.13 – 2.04 (m, 1H), 1.92-1.81 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.35, 141.69, 132.93, 128.59, 128.04, 51.86, 32.37, 16.69.

1-(4-Fluorophenyl)cyclobutane-1-carboxylic acid (101b)



The title compound was synthesized according to the general procedure **B** using 1-(4-fluorophenyl)cyclobutane-1-carbonitrile (**100b**, 1.40 g, 7.99 mmol, 1 eq) and KOH (2.69 g, 47.9 mmol, 6 eq) at reflux for overnight, and 6 M aq. HCl (3.5 mL) at reflux for 6 days. The pH of the reaction mixture was adjusted by 1 M aq. NaOH to pH > 12 and the aqueous layer was extracted 2× with Et_2O. The pH of the aqueous layer was adjusted by 3 M aq. HCl to pH < 2 and extracted 3× with EtOAc. The combined EtOAc layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford the product (830 mg, 4.25 mmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.92 (bs, 1H), 7.30 – 7.23 (m, 2H), 7.05 – 6.97 (m, 2H), 2.89 – 2.79 (m, 2H), 2.55 – 2.44 (m, 2H), 2.14 – 2.01 (m, 1H), 1.93 – 1.81 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.53, 161.86 (d, J_{C-F} = 245.6 Hz), 138.94 (d, J_{C-F} = 3.1 Hz), 128.25 (d, J_{C-F} = 8.1 Hz), 115.29 (d, J_{C-F} = 21.5 Hz), 51.76, 32.45, 16.65.

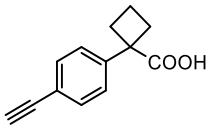
1-(4-Methoxyphenyl)cyclobutane-1-carboxylic acid (101c)



The title compound was synthesized according to the general procedure **B** using 1-(4-methoxyphenyl)cyclobutane-1-carbonitrile (**100c**, 1.26 g, 6.76 mmol, 1 eq) and KOH (2.28 g, 40.5 mmol, 6 eq). Total time: 16 h at reflux. Silica gel column chromatography (20% EtOAc in *n*-pentane with 0.1% TFA) afforded the

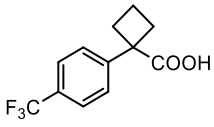
product (1.50 g, 7.27 mmol, quant.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 2H), 6.89 – 6.84 (m, 2H), 3.79 (s, 3H), 2.85 – 2.77 (m, 2H), 2.54 – 2.43 (m, 2H), 2.10 – 1.99 (m, 1H), 1.91 – 1.80 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.80, 158.58, 135.27, 127.68, 113.86, 55.41, 51.62, 32.35, 16.62.

1-(4-Ethynylphenyl)cyclobutane-1-carboxylic acid (101d)



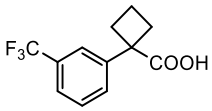
The title compound was synthesized according to the general procedure **B** using 1-(4-ethynylphenyl)cyclobutane-1-carbonitrile (**100d**, 1.16 g, 6.40 mmol, 1 eq) and KOH (2.16 g, 38.4 mmol, 6 eq). Total time: 16 h at reflux. Silica gel column chromatography (20% EtOAc in *n*-pentane with 0.1% TFA) afforded the product (730 mg, 3.63 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.85 (bs, 1H), 7.48 – 7.42 (m, 2H), 7.29 – 7.23 (m, 2H), 3.05 (s, 1H), 2.89 – 2.79 (m, 2H), 2.56 – 2.45 (m, 2H), 2.15 – 2.02 (m, 1H), 1.93 – 1.80 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.11, 143.97, 132.23, 126.61, 120.82, 83.53, 77.38, 52.28, 32.36, 16.73.

1-(4-(Trifluoromethyl)phenyl)cyclobutane-1-carboxylic acid (101e)



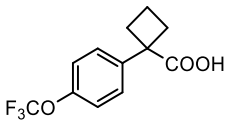
The title compound was synthesized according to the general procedure **B** using 1-(4-(trifluoromethyl)phenyl)cyclobutane-1-carbonitrile (**100e**, 1.35 g, 5.99 mmol, 1 eq) and KOH (2.0 g, 36 mmol, 6 eq). Total time: 16 h at reflux. Silica gel column chromatography (20% EtOAc in *n*-pentane with 0.1% TFA) afforded the product (1.37 g, 5.61 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 2H), 7.45 – 7.37 (m, 2H), 2.94 – 2.83 (m, 2H), 2.59 – 2.48 (m, 2H), 2.20 – 2.06 (m, 1H), 1.95 – 1.83 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.77, 147.18 (q, $J_{C\text{-}F}$ = 1.6 Hz), 129.32 (q, $J_{C\text{-}F}$ = 32.5 Hz), 127.03, 125.45 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.25 (q, $J_{C\text{-}F}$ = 272.7 Hz), 52.28, 32.46, 16.82.

1-(3-(Trifluoromethyl)phenyl)cyclobutane-1-carboxylic acid (101f)



The title compound was synthesized according to the general procedure **B** using 1-(3-(trifluoromethyl)phenyl)cyclobutane-1-carbonitrile (**100f**, 1.49 g, 6.61 mmol, 1 eq) and KOH (2.22 g, 39.6 mmol, 6 eq). Total time: 2 h at reflux. The product was afforded without purification (1.69 g, 6.93 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.40 (m, 4H), 2.99 – 2.82 (m, 2H), 2.62 – 2.49 (m, 2H), 2.22 – 2.05 (m, 1H), 1.99 – 1.83 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.41, 144.53, 130.73 (q, $J_{C\text{-}F}$ = 32.1 Hz), 130.05, 128.88, 124.21 (q, $J_{C\text{-}F}$ = 272.7 Hz), 123.75 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.31 (q, $J_{C\text{-}F}$ = 3.8 Hz), 52.14, 32.39, 16.72.

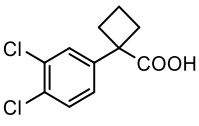
1-(4-(Trifluoromethoxy)phenyl)cyclobutane-1-carboxylic acid (101g)



The title compound was synthesized according to the general procedure **B** using 1-(4-(trifluoromethoxy)phenyl)cyclobutane-1-carbonitrile (**100g**, 620 mg, 2.57 mmol, 1 eq) and KOH (0.95 g, 17 mmol, 6.6 eq). Total time: 3.5 h at reflux. Silica gel column chromatography (20-40% EtOAc in *n*-pentane with a drop of

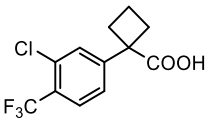
conc. HCl) afforded the product (590 mg, 2.26 mmol, 88%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 2.90 – 2.83 (m, 2H), 2.59 – 2.47 (m, 2H), 2.15 – 2.04 (m, 1H), 1.93 – 1.82 (m, 1H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 181.97, 148.15 (q, J_{C-F} = 1.8 Hz), 141.96, 128.07, 120.90, 120.59 (q, J_{C-F} = 256.8 Hz), 51.88, 32.44, 16.64.

1-(3,4-Dichlorophenyl)cyclobutane-1-carboxylic acid (101h)



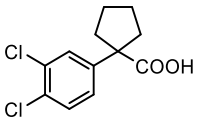
The title compound was synthesized according to the general procedure **B** using 1-(3,4-dichlorophenyl)cyclobutane-1-carbonitrile (**100h**, 1.11 g, 4.90 mmol, 1 eq) and KOH (1.65 g, 29.4 mmol, 6 eq). Total time: 4 h at reflux. Silica gel column chromatography (40% EtOAc in *n*-pentane with a drop of conc. HCl) afforded the product (1.10 g, 4.49 mmol, 91%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.6 Hz, 1H), 7.36 (d, *J* = 2.5 Hz, 1H), 7.12 (dd, *J* = 8.3, 2.3 Hz, 1H), 2.85 – 2.79 (m, 2H), 2.49 – 2.42 (m, 2H), 2.12 – 2.05 (m, 1H), 1.90 – 1.83 (m, 1H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 180.75, 143.49, 132.44, 131.04, 130.31, 128.76, 126.08, 51.64, 32.27, 16.59.

1-(3-Chloro-4-(trifluoromethyl)phenyl)cyclobutane-1-carboxylic acid (101i)



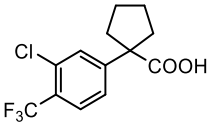
The title compound was synthesized according to the general procedure **B** using 1-(3-chloro-4-(trifluoromethyl)phenyl)cyclobutane-1-carbonitrile (**100i**, 1.02 g, 3.93 mmol, 1 eq) and KOH (1.32 g, 23.6 mmol, 6 eq). Total time: 2 h at reflux. The product was afforded without purification (1.06 g, 3.82 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.64 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 1.3 Hz, 1H), 7.28 (dd, *J* = 8.2, 1.1 Hz, 1H), 2.94 – 2.82 (m, 2H), 2.57 – 2.46 (m, 2H), 2.22 – 2.08 (m, 1H), 1.97 – 1.84 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 180.69, 148.92, 132.43 (q, J_{C-F} = 2.0 Hz), 129.77, 127.65 (q, J_{C-F} = 5.1 Hz), 126.91 (q, J_{C-F} = 31.3 Hz), 125.01, 122.95 (q, J_{C-F} = 274.7 Hz), 51.99, 32.34, 16.74.

1-(3,4-Dichlorophenyl)cyclopentane-1-carboxylic acid (101j)



The title compound was synthesized according to the general procedure **B** using 1-(3,4-dichlorophenyl)cyclopentane-1-carbonitrile (**100j**, 2.00 g, 8.33 mmol, 1 eq) in 9 M H_2SO_4 (20 mL, 0.4 M) at reflux until completion. Silica gel chromatography (30-40% EtOAc in *n*-pentane with a drop of conc. HCl) afforded the product (970 mg, 3.74 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$+MeOD) δ 7.48 (d, *J* = 2.3 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.24 (dd, *J* = 8.4, 2.3 Hz, 1H), 2.67 – 2.56 (m, 2H), 1.93 – 1.80 (m, 2H), 1.81 – 1.67 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$+MeOD) δ 177.87, 143.87, 132.12, 130.70, 130.05, 129.15, 126.60, 58.36, 36.09, 23.51.

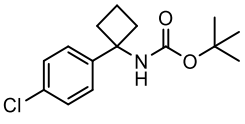
1-(3-Chloro-4-(trifluoromethyl)phenyl)cyclopentane-1-carboxylic acid (101k)



The title compound was synthesized according to the general procedure **B** using 1-(3-chloro-4-(trifluoromethyl)phenyl)cyclopentane-1-carbonitrile (**100k**, 1.08 g, 3.95 mmol, 1 eq) in 9 M H_2SO_4 (10 mL, 0.4 M) at reflux until completion. Silica gel chromatography (40-50% EtOAc in *n*-pentane with a drop of conc. HCl)

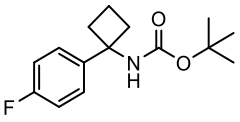
to afford the product (810 mg, 2.78 mmol, 70%). ^{1}H NMR (400 MHz, MeOD) δ 7.70 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 1.8 Hz, 1H), 7.49 (ddd, *J* = 8.3, 1.9, 0.9 Hz, 1H), 2.70 – 2.61 (m, 2H), 1.95 – 1.84 (m, 2H), 1.82 – 1.72 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 178.01, 151.50, 132.85 (q, J_{C-F} = 2.0 Hz), 131.23, 128.54 (q, J_{C-F} = 5.3 Hz), 127.48 (q, J_{C-F} = 31.5 Hz), 126.96, 124.41 (q, J_{C-F} = 272.0 Hz), 60.16, 37.11, 24.51.

tert-Butyl (1-(4-chlorophenyl)cyclobutyl)carbamate (102a)



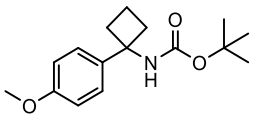
The title compound was synthesized according to the general procedure **C** using 1-(4-chlorophenyl)cyclobutane-1-carboxylic acid (**101a**, 830 mg, 3.93 mmol, 1 eq), diphenylphosphoryl azide (850 µL, 3.93 mmol, 1 eq) and Et_3N (600 µL, 4.32 mmol, 1.1 eq) in anhydrous *t*-BuOH (20 mL, 0.2 M). Total time: 2 h at 30 °C and overnight at reflux. Silica gel column chromatography (5-7% EtOAc in *n*-pentane) afforded the product (820 mg, 2.92 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.32 – 7.27 (m, 2H), 5.17 (s, 1H), 2.60 – 2.35 (m, 4H), 2.13 – 2.05 (m, 1H), 1.88 – 1.80 (m, 1H), 1.37 (s, 9H). LC-MS $[C_{15}H_{20}ClNO_2+H]^+$: 282.13 calculated, 281.83 found.

tert-Butyl (1-(4-fluorophenyl)cyclobutyl)carbamate (102b)



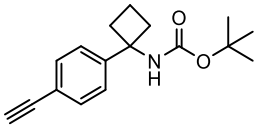
The title compound was synthesized according to the general procedure **C** using 1-(4-fluorophenyl)cyclobutane-1-carboxylic acid (**101b**, 820 mg, 4.25 mmol, 1 eq), diphenylphosphoryl azide (920 µL, 4.25 mmol, 1 eq) and Et_3N (650 µL, 4.68 mmol, 1.1 eq) in anhydrous *t*-BuOH (21 mL, 0.2 M). Total time: 2 h at 30 °C and overnight at reflux. Silica gel column chromatography (5% EtOAc in *n*-pentane) afforded the product (980 mg, 3.68 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 2H), 7.04 – 6.96 (m, 2H), 5.15 (s, 1H), 2.62 – 2.30 (m, 4H), 2.16 – 2.02 (m, 1H), 1.90 – 1.75 (m, 1H), 1.35 (s, 9H).

tert-Butyl (1-(4-methoxyphenyl)cyclobutyl)carbamate (102c)



The title compound was synthesized according to the general procedure **C** using 1-(4-methoxyphenyl)cyclobutane-1-carboxylic acid (**101c**, 1.50 g, 7.27 mmol, 1 eq), diphenylphosphoryl azide (1.57 mL, 7.27 mmol, 1 eq) and Et_3N (1.10 mL, 8.00 mmol, 1.1 eq) in anhydrous *t*-BuOH (36 mL, 0.2 M). Total time: 2 h at 30 °C and overnight at reflux. Silica gel column chromatography (5-10% EtOAc in *n*-pentane) afforded the product (760 mg, 2.74 mmol, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.3 Hz, 2H), 6.90 – 6.84 (m, 2H), 5.05 (s, 1H), 3.80 (s, 3H), 2.65 – 2.44 (m, 4H), 2.11 – 1.99 (m, 1H), 1.86 – 1.73 (m, 1H), 1.37 (s, 9H).

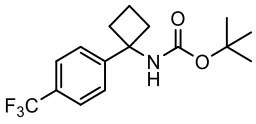
tert-Butyl (1-(4-ethynylphenyl)cyclobutyl)carbamate (102d)



The title compound was synthesized according to the general procedure **C** using 1-(4-ethynylphenyl)cyclobutane-1-carboxylic acid (**101d**, 730 mg, 3.63 mmol, 1 eq), diphenylphosphoryl azide (780 µL, 3.63 mmol, 1 eq) and Et_3N (560 µL, 3.99 mmol, 1.1 eq) in anhydrous *t*-BuOH (18 mL, 0.2 M). Total time: 2

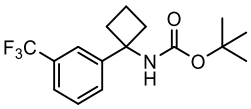
h at 30 °C and overnight at reflux. Silica gel column chromatography (5-10% EtOAc in *n*-pentane) afforded the product (520 mg, 1.90 mmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 5.16 (s, 1H), 3.05 (s, 1H), 2.59 – 2.30 (m, 4H), 2.16 – 2.06 (m, 1H), 1.91 – 1.79 (m, 1H), 1.37 (s, 9H).

tert-Butyl (1-(4-(trifluoromethyl)phenyl)cyclobutyl)carbamate (102e)



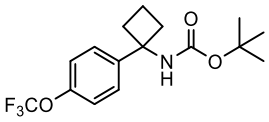
The title compound was synthesized according to the general procedure **C** using 1-(4-(trifluoromethyl)phenyl)cyclobutane-1-carboxylic acid (**101e**, 1.37 g, 5.60 mmol, 1 eq), diphenylphosphoryl azide (1.2 mL, 5.6 mmol, 1 eq) and Et_3N (860 µL, 6.15 mmol, 1.1 eq) in anhydrous *t*-BuOH (28 mL, 0.2 M). Total time: 2 h at 30 °C and overnight at reflux. Silica gel column chromatography (5-7% EtOAc in *n*-pentane) afforded the product (1.20 g, 3.81 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 2H), 7.57 – 7.50 (m, 2H), 5.22 (s, 1H), 2.60 – 2.31 (m, 4H), 2.20 – 2.08 (m, 1H), 1.96 – 1.82 (m, 1H), 1.38 (s, 9H).

tert-Butyl (1-(3-(trifluoromethyl)phenyl)cyclobutyl)carbamate (102f)



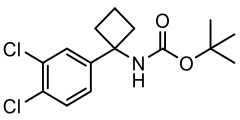
The title compound was synthesized according to the general procedure **C** using 1-(3-(trifluoromethyl)phenyl)cyclobutane-1-carboxylic acid (**101f**, 1.69 g, 6.93 mmol, 1 eq), diphenylphosphoryl azide (1.64 mL, 7.62 mmol, 1.1 eq) and Et_3N (1.93 mL, 13.9 mmol, 2.0 eq) in anhydrous *t*-BuOH (69 mL, 0.1 M). Total time: 2 h at 30 °C and overnight at reflux. Silica gel column chromatography (5-7% EtOAc in *n*-pentane) afforded the product as a white solid (890 mg, 2.82 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.18 (m, 4H), 5.19 (s, 1H), 2.68 – 2.36 (m, 4H), 2.22 – 2.10 (m, 1H), 1.97 – 1.81 (m, 1H), 1.32 (s, 9H).

tert-Butyl (1-(4-(trifluoromethoxy)phenyl)cyclobutyl)carbamate (102g)



The title compound was synthesized according to the general procedure **C** using 1-(4-(trifluoromethoxy)phenyl)cyclobutane-1-carboxylic acid (**101g**, 590 mg, 2.27 mmol, 1 eq), diphenyl phosphorazidate (520 µL, 2.38 mmol, 1.05 eq) and Et_3N (950 µL, 6.80 mmol, 3 eq) in anhydrous *t*-BuOH (27 mL, 0.1 M). Total time: 2 h at 30 °C and overnight at reflux. Silica gel column chromatography (3-4% EtOAc in *n*-pentane) afforded the product (0.21 g, 0.60 mmol, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 5.23 (s, 1H), 2.70 – 2.34 (m, 4H), 2.18 – 2.02 (m, 1H), 1.93 – 1.78 (m, 1H), 1.31 (s, 9H).

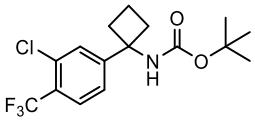
tert-Butyl (1-(3,4-dichlorophenyl)cyclobutyl)carbamate (102h)



The title compound was synthesized according to the general procedure **C** using 1-(3,4-dichlorophenyl)cyclobutane-1-carboxylic acid (**101h**, 1.10 g, 4.50 mmol, 1 eq), diphenylphosphoryl azide (0.97 mL, 4.5 mmol, 1 eq) and Et_3N (1.89 mL, 13.5 mmol, 3 eq) in anhydrous *t*-BuOH (45 mL, 0.1 M). Total time: 1 h at 30 °C and overnight at reflux. Silica gel column chromatography (3-4% EtOAc in *n*-pentane)

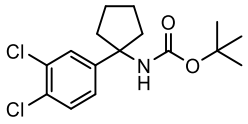
afforded the product (0.80 g, 2.6 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.3 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.30 – 7.21 (m, 1H), 5.25 (s, 1H), 2.54 – 2.25 (m, 4H), 2.17 – 2.05 (m, 1H), 1.96 – 1.81 (m, 1H), 1.38 (s, 9H).

tert-Butyl (1-(3-chloro-4-(trifluoromethyl)phenyl)cyclobutyl)carbamate (102i)



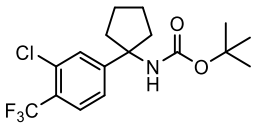
The title compound was synthesized according to the general procedure **C** using 1-(3-chloro-4-(trifluoromethyl)phenyl)cyclobutane-1-carboxylic acid (**101i**, 1.06 g, 3.82 mmol, 1 eq), diphenylphosphoryl azide (0.90 mL, 4.2 mmol, 1.1 eq) and Et_3N (1.06 mL, 7.63 mmol, 2 eq) in anhydrous *t*-BuOH (38 mL, 0.1 M). Total time: 1 h at 30 °C and overnight at reflux. Silica gel column chromatography (2-3% EtOAc in *n*-pentane) afforded the product (930 mg, 2.66 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 1.9 Hz, 1H), 7.46 – 7.34 (m, 1H), 5.28 (s, 1H), 2.61 – 2.39 (m, 4H), 2.23 – 2.09 (m, 1H), 1.98 – 1.86 (m, 1H), 1.39 (s, 9H).

tert-Butyl (1-(3,4-dichlorophenyl)cyclopentyl)carbamate (102j)



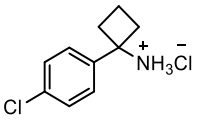
The title compound was synthesized according to the general procedure **C** using 1-(3,4-dichlorophenyl)cyclopentane-1-carboxylic acid (**101j**, 930 mg, 3.59 mmol, 1 eq), diphenylphosphoryl azide (850 µL, 3.95 mmol, 1.1 eq) and Et_3N (1.50 mL, 10.8 mmol, 3 eq) in anhydrous *t*-BuOH (36 mL, 0.1 M). Total time: 2 h at 30 °C and 2 days at reflux. Silica gel column chromatography (2-5% EtOAc in *n*-pentane) afforded the product (770 mg, 2.33 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.3 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.91 (s, 1H), 2.28 – 2.08 (m, 2H), 2.03 – 1.91 (m, 2H), 1.91 – 1.69 (m, 4H), 1.33 (s, 9H).

tert-Butyl (1-(3-chloro-4-(trifluoromethyl)phenyl)cyclopentyl)carbamate (102k)



The title compound was synthesized according to the general procedure **C** using 1-(3-chloro-4-(trifluoromethyl)phenyl)cyclopentane-1-carboxylic acid (**101k**, 810 mg, 2.78 mmol, 1 eq), diphenylphosphoryl azide (660 µL, 3.06 mmol, 1 eq) and Et_3N (1.16 mL, 8.33 mmol, 3 eq) in anhydrous *t*-BuOH (28 mL, 0.1 M). Total time: 2 h at 30 °C and 24 h at reflux. Silica gel column chromatography (5-7% EtOAc in *n*-pentane) afforded the product (940 mg, 2.58 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 1.9 Hz, 1H), 7.37 (dd, *J* = 8.2, 1.8 Hz, 1H), 4.97 (s, 1H), 2.33 – 2.08 (m, 2H), 2.06 – 1.93 (m, 2H), 1.93 – 1.75 (m, 4H), 1.30 (s, 9H).

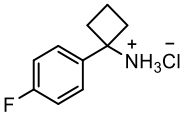
1-(4-Chlorophenyl)cyclobutan-1-aminium chloride (103a)



The title compound was synthesized according to the general procedure **D** using *tert*-butyl 1-(4-chlorophenyl)cyclobutyl)carbamate (**102a**, 820 mg, 2.92 mmol, 1 eq). Total time: over-weekend at rt. The product was afforded as a white solid (560 mg, 2.57 mmol, 88%). ^{1}H NMR (400 MHz, MeOD) δ 7.59 – 7.44 (m, 4H), 2.80 – 2.71 (m, 2H), 2.69 – 2.60 (m, 2H), 2.32 – 2.20 (m, 1H), 2.00 – 1.88 (m, 1H). ^{13}C NMR

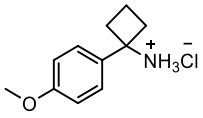
(101 MHz, MeOD) δ 140.02, 135.88, 130.24, 129.09, 59.80, 33.27, 14.79. LC-MS [$C_{10}H_{12}ClN$–NH_2]$^+$: 165.05 calculated, 165.00 found.

1-(4-Fluorophenyl)cyclobutan-1-aminium chloride (103b)



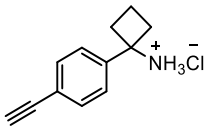
The title compound was synthesized according to the general procedure **D** using *tert*-butyl (1-(4-fluorophenyl)cyclobutyl)carbamate (**102b**, 980 mg, 3.68 mmol, 1 eq). Total time: 16 h at rt. The product was afforded as a white solid (670 mg, 3.31 mmol, 90%). ^{1}H NMR (400 MHz, MeOD) δ 7.60 – 7.53 (m, 2H), 7.26 – 7.18 (m, 2H), 2.81 – 2.72 (m, 2H), 2.70 – 2.59 (m, 2H), 2.31 – 2.19 (m, 1H), 2.01 – 1.87 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 164.19 (d, $J_{C\text{-}F}$ = 247.1 Hz), 137.35 (d, $J_{C\text{-}F}$ = 3.2 Hz), 129.65 (d, $J_{C\text{-}F}$ = 8.5 Hz), 116.88 (d, $J_{C\text{-}F}$ = 22.0 Hz), 59.83, 33.34, 14.77. LC-MS [$C_{10}H_{12}FN$+H]$^+$: 166.10 calculated, 165.83 found.

1-(4-Methoxyphenyl)cyclobutan-1-aminium chloride (103c)



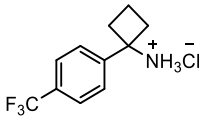
The title compound was synthesized according to the general procedure **D** using *tert*-butyl (1-(4-methoxyphenyl)cyclobutyl)carbamate (**102c**, 760 mg, 2.74 mmol, 1 eq). Total time: 16 h at rt. The product was afforded as a white solid (350 mg, 1.64 mmol, 60%). ^{1}H NMR (400 MHz, MeOD) δ 7.50 – 7.42 (m, 2H), 7.06 – 6.99 (m, 2H), 3.82 (s, 3H), 2.81 – 2.67 (m, 2H), 2.68 – 2.55 (m, 2H), 2.30 – 2.15 (m, 1H), 1.99 – 1.81 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 161.42, 133.00, 128.65, 115.36, 59.91, 55.87, 33.34, 14.82. LC-MS [$C_{11}H_{15}NO$–NH_2]$^+$: 161.10 calculated, 161.00 found.

1-(4-Ethynylphenyl)cyclobutan-1-aminium chloride (103d)



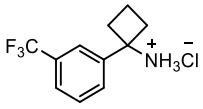
The title compound was synthesized according to the general procedure **D** using *tert*-butyl (1-(4-ethynylphenyl)cyclobutyl)carbamate (**102d**, 520 mg, 1.90 mmol, 1 eq). Total time: 16 h at rt. The product was afforded as a white solid (350 mg, 1.68 mmol, 88%). ^{1}H NMR (400 MHz, MeOD) δ 7.60 – 7.56 (m, 2H), 7.54 – 7.50 (m, 2H), 3.61 (s, 1H), 2.82 – 2.72 (m, 2H), 2.70 – 2.59 (m, 2H), 2.32 – 2.20 (m, 1H), 2.01 – 1.89 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 141.69, 133.66, 127.39, 124.41, 83.52, 79.99, 60.02, 33.23, 14.82. LC-MS [$C_{12}H_{13}N$+H]$^+$: 172.11 calculated, 171.83 found.

1-(4-(Trifluoromethyl)phenyl)cyclobutan-1-aminium chloride (103e)



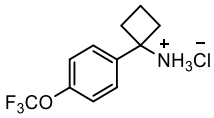
The title compound was synthesized according to the general procedure **D** using *tert*-butyl (1-(4-(trifluoromethyl)phenyl)cyclobutyl)carbamate (**102e**, 1.20 g, 3.81 mmol, 1 eq). Total time: 16 h at rt. The product was afforded as a white solid (870 mg, 3.46 mmol, 91%). ^{1}H NMR (400 MHz, MeOD) δ 7.85 – 7.71 (m, 4H), 2.88 – 2.75 (m, 2H), 2.75 – 2.63 (m, 2H), 2.37 – 2.23 (m, 1H), 2.07 – 1.91 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 145.57 (q, $J_{C\text{-}F}$ = 1.3 Hz), 131.95 (q, $J_{C\text{-}F}$ = 33.3 Hz), 128.16, 127.09 (q, $J_{C\text{-}F}$ = 3.8 Hz), 125.4 (q, $J_{C\text{-}F}$ = 271.7 Hz), 59.96, 33.30, 14.84. LC-MS [$C_{11}H_{12}F_3N$+H]$^+$: 216.10 calculated, 215.83 found.

1-(3-(Trifluoromethyl)phenyl)cyclobutan-1-aminium chloride (103f)



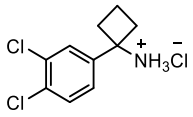
The title compound was synthesized according to the general procedure **D** using *tert*-butyl (1-(3-(trifluoromethyl)phenyl)cyclobutyl)carbamate (**102f**, 860 mg, 2.74 mmol, 1 eq). Total time: 3 days at rt. The product was afforded as a white solid (330 mg, 1.31 mmol, 48%). ^{1}H NMR (400 MHz, MeOD) δ 7.86 – 7.69 (m, 4H), 2.86 – 2.76 (m, 2H), 2.73 – 2.63 (m, 2H), 2.36 – 2.24 (m, 1H), 2.05 – 1.92 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 142.61, 132.36 (q, $J_{C\text{-}F}$ = 32.4 Hz), 131.31 (q, $J_{C\text{-}F}$ = 1.4 Hz), 131.25, 126.82 (q, $J_{C\text{-}F}$ = 3.7 Hz), 125.40 (q, $J_{C\text{-}F}$ = 273.7 Hz), 124.10 (q, $J_{C\text{-}F}$ = 3.7 Hz), 59.95, 33.23, 14.85.

1-(4-(Trifluoromethoxy)phenyl)cyclobutan-1-aminium chloride (103g)



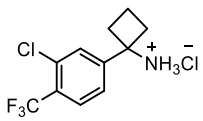
The title compound was synthesized according to the general procedure **D** using *tert*-butyl (1-(4-(trifluoromethoxy)phenyl)cyclobutyl)carbamate (**102g**, 0.20 g, 0.60 mmol, 1 eq). Total time: 24 h at rt. The product was afforded as a white solid (0.16 g, 0.60 mmol, quant.) ^{1}H NMR (400 MHz, MeOD) δ 7.68 – 7.60 (m, 2H), 7.44 – 7.36 (m, 2H), 2.85 – 2.74 (m, 2H), 2.71 – 2.59 (m, 2H), 2.33 – 2.20 (m, 1H), 2.04 – 1.90 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 151.65 (q, $J_{C\text{-}F}$ = 2.0 Hz), 140.44, 129.44, 122.60, 121.87(q, $J_{C\text{-}F}$ = 257.6 Hz), 59.77, 33.34, 14.78.

1-(3,4-Dichlorophenyl)cyclobutan-1-aminium chloride (103h)



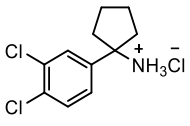
The title compound was synthesized according to the general procedure **D** using *tert*-butyl (1-(3,4-dichlorophenyl)cyclobutyl)carbamate (**102h**, 0.80 g, 2.6 mmol, 1 eq). Total time: 24 h at rt. The product was afforded as a white solid (470 mg, 1.86 mmol, 72%). ^{1}H NMR (400 MHz, MeOD) δ 7.70 (d, *J* = 2.3 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.47 (dd, *J* = 8.4, 2.3 Hz, 1H), 2.81 – 2.71 (m, 2H), 2.68 – 2.57 (m, 2H), 2.32 – 2.20 (m, 1H), 2.02 – 1.90 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 141.91, 134.07, 134.06, 132.32, 129.81, 127.39, 59.52, 33.20, 14.75.

1-(3-Chloro-4-(trifluoromethyl)phenyl)cyclobutan-1-aminium chloride (103i)



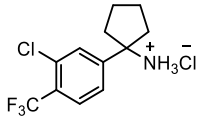
The title compound was synthesized according to the general procedure **D** using *tert*-butyl (1-(3-chloro-4-(trifluoromethyl)phenyl)cyclobutyl)carbamate (**102i**, 930 mg, 2.66 mmol, 1 eq). Total time: over-weekend at rt. The product was afforded as a white solid (0.28 g, 0.99 mmol, 38%). ^{1}H NMR (400 MHz, MeOD) δ 7.90 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 1.9 Hz, 1H), 7.66 (dd, *J* = 8.2, 1.9 Hz, 1H), 2.85 – 2.74 (m, 2H), 2.73 – 2.62 (m, 2H), 2.36 – 2.24 (m, 1H), 2.07 – 1.94 (m, 1H). ^{13}C NMR (101 MHz, MeOD) *δ* 147.21, 133.87 (q, $J_{C\text{-}F}$ = 2.0 Hz), 130.67, 129.53 (q, $J_{C\text{-}F}$ = 5.2 Hz), 129.51 (q, $J_{C\text{-}F}$ = 32.0 Hz), 126.34, 124.02 (q, $J_{C\text{-}F}$ = 272.3 Hz), 59.48, 33.15, 14.77.

1-(3,4-Dichlorophenyl)cyclopentan-1-aminium chloride (103j)



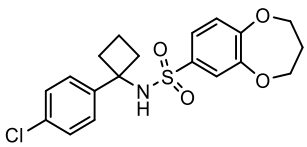
The title compound was synthesized according to the general procedure **D** using *tert*-butyl (1-(3,4-dichlorophenyl)cyclopentyl)carbamate (**102j**, 770 mg, 2.33 mmol, 1 eq). Total time: 16 h at rt. The product was afforded as a white solid (520 mg, 1.95 mmol, 84%). ^{1}H NMR (400 MHz, MeOD) δ 7.72 (d, *J* = 2.3 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.48 (dd, *J* = 8.5, 2.3 Hz, 1H), 2.36 – 2.22 (m, 4H), 2.04 – 1.88 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 142.22, 134.02, 133.95, 132.24, 129.84, 127.49, 66.85, 38.57, 23.81.

1-(3-Chloro-4-(trifluoromethyl)phenyl)cyclopentan-1-aminium chloride (103k)



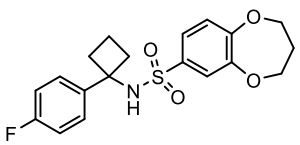
The title compound was synthesized according to the general procedure **D** using *tert*-butyl (1-(3-chloro-4-(trifluoromethyl)phenyl)cyclopentyl)carbamate (**102k**, 940 mg, 2.58 mmol, 1 eq). Total time: 2 days at rt. The product was afforded as a white solid (720 mg, 2.39 mmol, 93%). ^{1}H NMR (400 MHz, MeOD) δ 7.89 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 1.6 Hz, 1H), 7.68 (ddd, *J* = 8.3, 1.9, 0.9 Hz, 1H), 2.38 – 2.27 (m, 4H), 2.07 – 1.90 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 147.83, 133.81 (q, J_{C-F} = 2.0 Hz), 130.76, 129.51 (q, J_{C-F} = 5.3 Hz), 129.40 (q, J_{C-F} = 31.3 Hz), 126.52, 124.11 (q, J_{C-F} = 273.7 Hz), 66.95, 38.84, 24.01.

***N*-(1-(4-Chlorophenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (104a)**



The title compound was synthesized according to the general procedure **H** using 1-(4-chlorophenyl)cyclobutan-1-aminium chloride (**103a**, 35 mg, 0.16 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 48 mg, 0.19 mmol, 1.2 eq) and DIPEA (0.28 mL, 1.6 mmol, 10 eq). Total time: overnight at rt. Silica gel column chromatography (20-25% EtOAc in *n*-pentane) afforded the product (37 mg, 0.093 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$+MeOD) δ 7.13 – 7.02 (m, 4H), 6.98 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.27 (t, *J* = 5.7 Hz, 2H), 4.19 (t, *J* = 5.8 Hz, 2H), 2.66 – 2.53 (m, 2H), 2.53 – 2.42 (m, 2H), 2.21 (p, *J* = 5.7 Hz, 2H), 2.14 – 2.02 (m, 1H), 1.79 – 1.65 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$+MeOD) δ 153.79, 149.72, 140.99, 135.77, 132.25, 128.15, 127.58, 121.70, 121.02, 120.34, 70.31, 70.19, 60.41, 34.79, 30.75, 15.09.

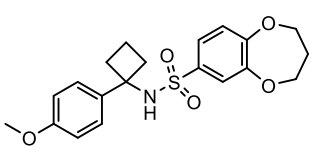
***N*-(1-(4-Fluorophenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (104b)**



The title compound was synthesized according to the general procedure **H** using 1-(4-fluorophenyl)cyclobutan-1-aminium chloride (**103b**, 34 mg, 0.17 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 50 mg, 0.20 mmol, 1.2 eq) and DIPEA (290 µL, 1.69 mmol, 10 eq). Total time: overnight at rt. Silica gel column

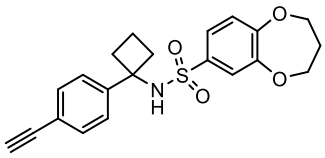
chromatography (20-25% EtOAc in *n*-pentane) afforded the product (36 mg, 0.097 mmol, 57%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 7.15 – 7.04 (m, 2H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.79 – 6.67 (m, 4H), 4.20 (t, *J* = 5.7 Hz, 2H), 4.14 (t, *J* = 5.9 Hz, 2H), 2.61 – 2.36 (m, 4H), 2.16 (p, *J* = 5.8 Hz, 2H), 2.09 – 1.96 (m, 1H), 1.75 – 1.61 (m, 1H).

_N_-(1-(4-Methoxyphenyl)cyclobutyl)-3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepine-7-sulfonamide (104c)



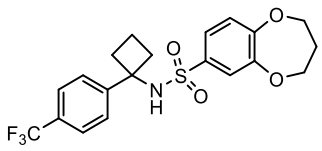
The title compound was synthesized according to the general procedure **H** using 1-(4-methoxyphenyl)cyclobutan-1-aminium chloride (**103c**, 36 mg, 0.17 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 50 mg, 0.20 mmol, 1.2 eq) and DIPEA (290 µL, 1.68 mmol, 10 eq). Total time: overnight at rt. Silica gel column chromatography (20-25% EtOAc in *n*-pentane) afforded the product (42.0 mg, 0.108 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 7.06 (m, 2H), 7.02 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.65 – 6.59 (m, 2H), 5.61 (s, 1H), 4.24 (t, 2H), 4.17 (t, *J* = 5.8 Hz, 2H), 3.76 (s, 3H), 2.59 – 2.49 (m, 4H), 2.18 (p, *J* = 5.7 Hz, 2H), 2.06 – 1.98 (m, 1H), 1.73 – 1.64 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.48, 153.94, 150.00, 136.02, 134.24, 128.23, 122.19, 121.17, 120.98, 113.18, 70.33, 70.25, 61.22, 55.25, 35.62, 31.07, 15.31.

_N_-(1-(4-Ethynylphenyl)cyclobutyl)-3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepine-7-sulfonamide (104d)



The title compound was synthesized according to the general procedure **H** using 1-(4-ethynylphenyl)cyclobutan-1-aminium chloride (**103d**, 35 mg, 0.17 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 50 mg, 0.20 mmol, 1.2 eq) and DIPEA (290 µL, 1.68 mmol, 10 eq). Total time: overnight at rt. Silica gel column chromatography (20-25% EtOAc in *n*-pentane) afforded the product (37 mg, 0.097 mmol, 58%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 7.23 – 7.18 (m, 2H), 7.14 – 7.09 (m, 2H), 6.99 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.80 (d, *J* = 2.3 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 4.26 (t, *J* = 5.8 Hz, 2H), 4.19 (t, *J* = 5.8 Hz, 2H), 3.12 (s, 1H), 2.64 – 2.55 (m, 2H), 2.54 – 2.45 (m, 2H), 2.20 (p, *J* = 5.8 Hz, 2H), 2.12 – 2.04 (m, 1H), 1.77 – 1.68 (m, 1H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 154.14, 150.00, 143.44, 135.95, 131.62, 126.94, 122.03, 121.37, 120.76, 120.67, 83.61, 77.47, 70.64, 70.47, 61.02, 35.05, 31.10, 15.47.

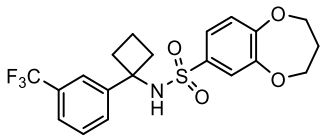
_N_-(1-(4-(Trifluoromethyl)phenyl)cyclobutyl)-3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepine-7-sulfonamide (104e)



The title compound was synthesized according to the general procedure **H** using 1-(4-(trifluoromethyl)phenyl)cyclobutan-1-aminium chloride (**103e**, 42.0 mg, 0.167 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 50 mg, 0.20 mmol, 1.2 eq) and DIPEA (290 µL, 1.67 mmol, 10 eq). Total time: overnight at rt. Silica gel

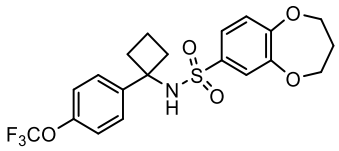
column chromatography (20-25% EtOAc in *n*-pentane) afforded the product (52.1 mg, 0.122 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 4H), 6.96 – 6.89 (m, 2H), 6.70 (d, *J* = 8.3 Hz, 1H), 5.50 (s, 1H), 4.23 (t, *J* = 5.8 Hz, 2H), 4.16 (t, *J* = 5.8 Hz, 2H), 2.65 – 2.51 (m, 4H), 2.19 (p, *J* = 5.8 Hz, 2H), 2.13 – 2.05 (m, 1H), 1.78 – 1.70 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.27, 150.20, 146.22 (q, J_{C-F} = 1.1 Hz), 135.53, 129.34 (q, J_{C-F} = 32.4 Hz), 127.43, 124.93 (q, J_{C-F} = 3.8 Hz), 122.18, 121.34, 120.62, 70.41, 70.32, 61.33, 35.62, 30.89, 15.39 (missing ^{13}C peak of the CF_3 group).

_N_-(1-(3-(Trifluoromethyl)phenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (104f)



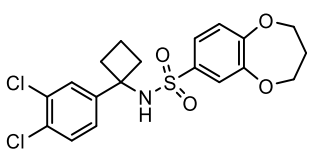
The title compound was synthesized according to the general procedure **H** using 1-(3-(trifluoromethyl)phenyl)cyclobutan-1-aminium chloride (**103f**, 40 mg, 0.16 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 43.5 mg, 0.175 mmol, 1.1 eq) and DIPEA (140 µL, 0.795 mmol, 5 eq). Total time: overnight at rt. Silica gel column chromatography (20-25 % EtOAc in *n*-pentane) afforded the product (31 mg, 0.073 mmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.26 – 7.18 (m, 1H), 6.89 – 6.80 (m, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 5.76 (s, 1H), 4.15 (t, *J* = 5.8 Hz, 2H), 4.09 (t, *J* = 5.9 Hz, 2H), 2.63 – 2.41 (m, 4H), 2.11 (p, *J* = 5.9 Hz, 2H), 2.07 – 1.92 (m, 1H), 1.77 – 1.62 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.11, 150.16, 143.26, 135.54, 130.46 (q, J_{C-F} = 1.1 Hz), 130.35 (q, J_{C-F} = 32.3 Hz), 128.48, 124.07 (q, J_{C-F} = 273.7 Hz), 123.99 (q, J_{C-F} = 3.9 Hz), 123.89 (q, J_{C-F} = 3.7 Hz), 122.02, 121.28, 120.52, 70.31, 70.16, 61.27, 35.64, 30.88, 15.35.

_N_-(1-(4-(Trifluoromethoxy)phenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (104g)



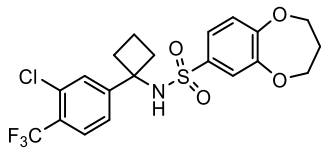
The title compound was synthesized according to the general procedure **H** using 1-(4-(trifluoromethoxy)phenyl)cyclobutan-1-aminium chloride (**103g**, 40 mg, 0.15 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 40.8 mg, 0.164 mmol, 1.1eq) and DIPEA (78 µL, 0.45 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (15-20% EtOAc in *n*-pentane) afforded the product (58 mg, 0.13 mmol, 88%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 7.22 – 7.16 (m, 2H), 6.95 – 6.86 (m, 4H), 6.71 – 6.67 (m, 1H), 4.19 (t, *J* = 5.7 Hz, 2H), 4.14 (t, *J* = 5.8 Hz, 2H), 2.62 – 2.52 (m, 2H), 2.50 – 2.40 (m, 2H), 2.16 (p, *J* = 5.8 Hz, 2H), 2.10 – 1.98 (m, 1H), 1.76 – 1.63 (m, 1H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 154.51, 150.61, 148.31 (q, J_{C-F} = 1.8 Hz), 142.24, 136.71, 128.88, 122.30, 121.64, 120.99 (q, J_{C-F} = 257.6 Hz), 120.81, 120.48, 70.89, 70.84, 61.12, 35.45, 31.42, 15.76.

_N_-(1-(3,4-Dichlorophenyl)cyclobutyl)-3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepine-7-sulfonamide (104h)



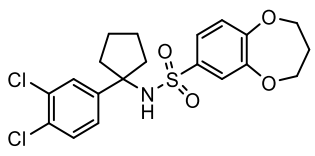
The title compound was synthesized according to the general procedure **H** using 1-(3,4-dichlorophenyl)cyclobutan-1-aminium chloride (**103h**, 60 mg, 0.24 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 65 mg, 0.26 mmol, 1.1 eq) and DIPEA (124 µL, 0.714 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (15% EtOAc in *n*-pentane) afforded the product (40 mg, 0.093 mmol, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.3 Hz, 1H), 7.14 (d, *J* = 2.2 Hz, 1H), 7.10 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 5.34 (s, 1H), 4.29 (t, *J* = 5.9 Hz, 2H), 4.21 (t, *J* = 5.9 Hz, 2H), 2.60 – 2.44 (m, 4H), 2.21 (p, *J* = 5.8 Hz, 2H), 2.14 – 2.01 (m, 1H), 1.80 – 1.67 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.35, 150.18, 142.35, 135.29, 132.12, 131.14, 129.87, 129.61, 126.54, 122.15, 121.33, 120.66, 70.48, 70.41, 60.84, 35.75, 30.91, 15.29.

_N_-(1-(3-Chloro-4-(trifluoromethyl)phenyl)cyclobutyl)-3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepine-7-sulfonamide (104i)



The title compound was synthesized according to the general procedure **H** using 1-(3-chloro-4-(trifluoromethyl)phenyl)cyclobutan-1-aminium chloride (**103i**, 40 mg, 0.14 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 38.2 mg, 0.154 mmol, 1.1 eq) and DIPEA (70 µL, 0.42 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (46 mg, 0.096 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.1 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.86 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 5.91 (s, 1H), 4.19 (t, *J* = 5.8 Hz, 2H), 4.12 (t, *J* = 5.9 Hz, 2H), 2.60 – 2.40 (m, 4H), 2.12 (p, *J* = 5.8 Hz, 2H), 2.08 – 1.99 (m, 1H), 1.74 – 1.62 (m, 1H). ^{13}C NMR (101MHz, $CDCl_3$) *δ* 154.40, 150.31, 147.83, 135.21, 131.96 (q, $J_{C\text{-}F}$ = 2.0 Hz), 130.38, 127.19 (q, $J_{C\text{-}F}$ = 5.1 Hz), 126.96 (q, $J_{C\text{-}F}$ = 31.3 Hz), 125.23, 122.83 (q, $J_{C\text{-}F}$ = 273.7 Hz), 122.12, 121.30, 120.37, 70.45, 70.22, 60.87, 35.42, 30.85, 15.36.

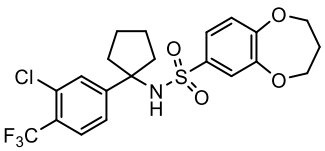
_N_-(1-(3,4-Dichlorophenyl)cyclopentyl)-3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepine-7-sulfonamide (104j)



The title compound was synthesized according to the general procedure **H** using 1-(3,4-dichlorophenyl)cyclopentan-1-aminium chloride (**103j**, 40 mg, 0.15 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 45 mg, 0.18 mmol, 1.2 eq) and DIPEA (105 µL, 0.600 mmol, 4 eq). Total time: 3 days at rt. Silica gel column chromatography (20-25% EtOAc in *n*-pentane) afforded the product (54 mg, 0.12 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.3 Hz, 1H), 7.13 (d, *J* = 2.1 Hz, 1H), 7.07 (td, *J* = 8.1, 2.3 Hz, 2H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 5.85 (s, 1H), 4.30 (t, *J* = 5.7

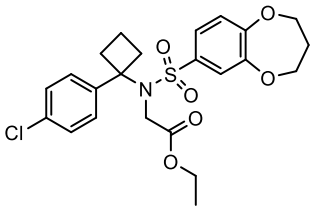
Hz, 2H), 4.21 (t, *J* = 5.8 Hz, 2H), 2.49 – 2.35 (m, 2H), 2.21 (p, *J* = 5.8 Hz, 2H), 2.01 – 1.82 (m, 4H), 1.79 – 1.65 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.21, 150.20, 142.25, 135.49, 131.71, 130.88, 129.73, 129.66, 126.83, 122.04, 121.32, 120.48, 70.44, 70.40, 68.06, 39.05, 30.93, 22.09.

_N_-(1-(3-Chloro-4-(trifluoromethyl)phenyl)cyclopentyl)-3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepine-7-sulfonamide (104k)



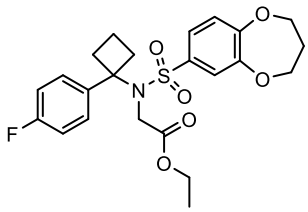
The title compound was synthesized according to the general procedure **H** using 1-(3-chloro-4-(trifluoromethyl)phenyl)cyclopentan-1-ammonium chloride (**103k**, 40 mg, 0.13 mmol, 1 eq), 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (**137**, 39.8 mg, 0.160 mmol, 1.2 eq) and DIPEA (93 µL, 0.53 mmol, 4 eq). Total time: 2 days at rt. Silica gel column chromatography (20-25% EtOAc in *n*-pentane) afforded the product (42 mg, 0.089 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.20 (m, 2H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.97 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 5.89 (s, 1H), 4.28 (t, *J* = 5.7 Hz, 2H), 4.21 (t, *J* = 5.8 Hz, 2H), 2.49 – 2.38 (m, 2H), 2.20 (p, *J* = 5.8 Hz, 2H), 1.97 – 1.85 (m, 4H), 1.80 – 1.69 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.31, 150.44, 147.64, 135.42, 131.69 (q, J_{C-F} = 2.0 Hz), 130.57, 127.03 (q, J_{C-F} = 5.1 Hz), 126.91 (q, J_{C-F} = 30.3 Hz), 125.54, 122.83 (q, J_{C-F} = 273.7 Hz), 122.02, 121.34, 120.30, 70.47, 70.22, 68.19, 39.07, 30.88, 22.11.

Ethyl _N_-(1-(4-chlorophenyl)cyclobutyl)-_N_-((3,4-dihydro-2_H_-benzo[_b_][1,4]dioxepin-7-yl)sulfonyl)glycinate (105a)



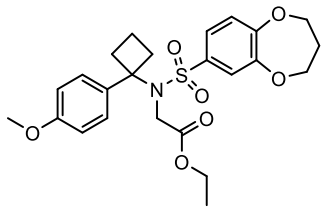
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-chlorophenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**104a**, 37 mg, 0.093 mmol, 1 eq), ethyl 2-bromoacetate (21.0 µL, 0.187 mmol, 2 eq) and BEMP (1 M in hexane, 187 µL, 0.187 mmol, 2 eq). Total time: 16 h at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (33 mg, 0.069 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.24 – 7.19 (m, 2H), 7.17 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 4.29 (t, *J* = 5.8 Hz, 2H), 4.24 (t, *J* = 5.9 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.05 (s, 2H), 2.84 – 2.73 (m, 2H), 2.51 – 2.42 (m, 2H), 2.22 (p, *J* = 5.8 Hz, 2H), 1.81 – 1.72 (m, 1H), 1.59 – 1.50 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.20, 154.41, 150.31, 141.05, 135.85, 133.34, 128.91, 128.29, 122.55, 121.37, 121.14, 70.49, 70.45, 65.33, 61.62, 48.09, 34.71, 30.95, 14.66, 14.21.

Ethyl *N*-(1-(4-fluorophenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate (105b)



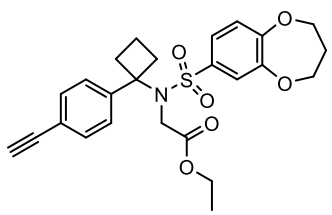
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-fluorophenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**104b**, 36 mg, 0.097 mmol, 1 eq), ethyl 2-bromoacetate (21 µL, 0.18 mmol, 2 eq) and BEMP (1 M in hexane, 184 µL, 0.184 mmol, 2 eq). Total time: 16 h at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (31 mg, 0.067 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 2H), 7.19 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 6.97 – 6.90 (m, 2H), 6.88 (d, *J* = 8.5 Hz, 1H), 4.28 (t, *J* = 5.8 Hz, 2H), 4.23 (t, *J* = 5.8 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.04 (s, 2H), 2.83 – 2.73 (m, 2H), 2.52 – 2.44 (m, 2H), 2.22 (p, *J* = 5.8 Hz, 2H), 1.81 – 1.71 (m, 1H), 1.59 – 1.50 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.22, 162.05 (d, $J_{C\text{-}F}$ = 246.6 Hz), 154.35, 150.31, 138.21 (d, $J_{C\text{-}F}$ = 3.3 Hz), 135.99, 129.27 (d, $J_{C\text{-}F}$ = 8.1 Hz), 122.56, 121.36, 121.20, 114.94 (d, $J_{C\text{-}F}$ = 21.3 Hz), 70.46, 70.40, 65.34, 61.58, 47.99, 34.79, 30.96, 14.68, 14.21.

Ethyl *N*-(1-(4-methoxyphenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate (105c)



The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-methoxyphenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**104c**, 42.0 mg, 0.108 mmol, 1 eq), ethyl 2-bromoacetate (24 µL, 0.22 mmol, 2 eq) and BEMP (1 M in hexane, 216 µL, 0.216 mmol, 2 eq). Total time: 16 h at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (44 mg, 0.093 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2H), 7.21 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.11 (d, *J* = 2.3 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.81 – 6.75 (m, 2H), 4.27 (t, *J* = 5.8 Hz, 2H), 4.21 (t, *J* = 5.8 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 2H), 3.81 (s, 3H), 2.82 – 2.71 (m, 2H), 2.52 – 2.44 (m, 2H), 2.21 (p, *J* = 5.8 Hz, 2H), 1.79 – 1.69 (m, 1H), 1.59 – 1.49 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.37, 158.91, 154.27, 150.32, 136.20, 134.29, 128.67, 122.73, 121.33, 121.29, 113.48, 70.43, 70.40, 65.46, 61.51, 55.34, 47.98, 34.75, 31.09, 14.79, 14.23.

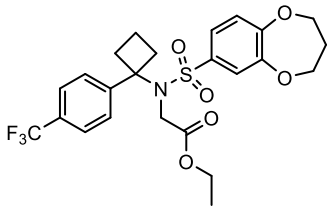
Ethyl *N*-(1-(4-ethynylphenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate(105d)



The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-ethynylphenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**104d**, 37 mg, 0.097 mmol, 1 eq), ethyl 2-bromoacetate (22 µL, 0.19 mmol, 2 eq) and BEMP (1 M in hexane, 194 µL, 0.194 mmol, 2 eq). Total time: 16 h at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (30 mg, 0.064 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 4H), 7.16 (dd, *J* =

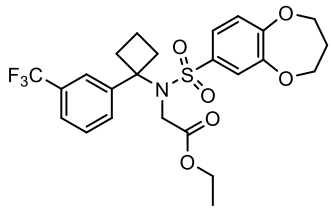
8.5, 2.3 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 4.29 (t, *J* = 5.4 Hz, 2H), 4.24 (t, *J* = 5.8 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.05 (s, 2H), 3.08 (s, 1H), 2.87 – 2.73 (m, 2H), 2.54 – 2.43 (m, 2H), 2.21 (p, *J* = 5.8 Hz, 2H), 1.83 – 1.70 (m, 1H), 1.62 – 1.49 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.22, 154.40, 150.27, 143.31, 135.78, 131.95, 127.33, 122.53, 121.36, 121.26, 121.19, 83.49, 77.60, 70.46, 70.44, 65.57, 61.61, 48.21, 34.68, 30.96, 14.69, 14.21.

Ethyl *N*-(1-(4-(trifluoromethyl)phenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7- yl)sulfonyl)glycinate (105e)



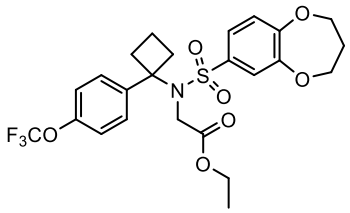
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-(trifluoromethyl)phenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**104e**, 52.1 mg, 0.122 mmol, 1 eq), ethyl 2-bromoacetate (27 µL, 0.24 mmol, 2 eq) and BEMP (1 M in hexane, 244 µL, 0.244 mmol, 2 eq). Total time: 16 h at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (47 mg, 0.092 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.50 (m, 4H), 7.11 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 4.27 (t, *J* = 5.8 Hz, 2H), 4.21 (t, *J* = 5.8 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.07 (s, 2H), 2.89 – 2.78 (m, 2H), 2.55 – 2.47 (m, 2H), 2.25 – 2.17 (m, 2H), 1.85 – 1.76 (m, 1H), 1.62 – 1.53 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.11, 154.48, 150.39, 146.74 (q, $J_{C\text{-}F}$ = 1.3 Hz), 135.69, 129.69 (q, $J_{C\text{-}F}$ = 32.3 Hz), 127.74, 125.20 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.19 (q, $J_{C\text{-}F}$ = 273.7 Hz), 122.61, 121.42, 121.04, 70.48, 70.40, 65.56, 61.69, 48.18, 34.69, 30.93, 14.67, 14.20.

Ethyl *N*-(1-(3-(trifluoromethyl)phenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7- yl)sulfonyl)glycinate (105f)



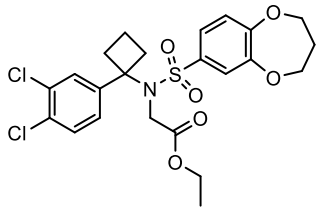
The title compound was synthesized according to the general procedure **I** using *N*-(1-(3-(trifluoromethyl)phenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**104f**, 25 mg, 0.056 mmol, 1 eq), ethyl 2-bromoacetate (13 µL, 0.12 mmol, 2 eq) and BEMP (1 M in hexane, 117 µL, 0.117 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (19 mg, 0.037 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.61 (t, *J* = 2.0 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.45 – 7.38 (m, 1H), 7.11 – 7.04 (m, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 4.27 (t, *J* = 5.8 Hz, 2H), 4.21 (t, *J* = 5.9 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.10 (s, 2H), 2.90 – 2.78 (m, 2H), 2.56 – 2.45 (m, 2H), 2.21 (p, *J* = 5.8 Hz, 2H), 1.85 – 1.74 (m, 1H), 1.65 – 1.51 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.09, 154.41, 150.37, 143.76, 135.72, 130.76, 130.60 (q, $J_{C\text{-}F}$ = 32.2 Hz), 128.78, 124.34 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.18 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.15 (q, $J_{C\text{-}F}$ = 273.7 Hz), 122.48, 121.41, 120.94, 70.45, 70.28, 65.48, 61.69, 48.21, 34.70, 30.91, 14.62, 14.19.

Ethyl *N*-(1-(4-(trifluoromethoxy)phenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7- yl)sulfonyl)glycinate (105g)



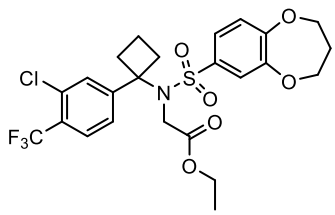
The title compound was synthesized according to the general procedure **I** using *N*-(1-(4-(trifluoromethoxy)phenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**104g**, 58 mg, 0.13 mmol, 1 eq), ethyl 2-bromoacetate (29 µL, 0.26 mmol, 2 eq) and BEMP (1 M in hexane, 262 µL, 0.262 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (40 mg, 0.076 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H), 7.10 (d, *J* = 2.3 Hz, 1H), 7.07 – 7.00 (m, 3H), 6.78 (d, *J* = 8.5 Hz, 1H), 4.20 (t, 2H), 4.15 (t, *J* = 5.8 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 2H), 2.79 – 2.66 (m, 2H), 2.47 – 2.37 (m, 2H), 2.14 (p, *J* = 5.8 Hz, 2H), 1.76 – 1.64 (m, 1H), 1.55 – 1.41 (m, 1H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.13, 154.44, 150.37, 148.44 (q, J_{C-F} = 1.9 Hz), 141.25, 135.89, 128.99, 122.57, 121.41, 121.12, 120.54 (q, J_{C-F} = 258.6 Hz), 120.44, 70.49, 70.39, 65.36, 61.61, 48.02, 34.69, 30.94, 14.64, 14.17.

Ethyl *N*-(1-(3,4-dichlorophenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate (105h)



The title compound was synthesized according to the general procedure **I** using *N*-(1-(3,4-dichlorophenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**104h**, 29 mg, 0.068 mmol, 1 eq), ethyl 2-bromoacetate (15 µL, 0.14 mmol, 2 eq) and BEMP (1 M in hexane, 136 µL, 0.136 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (28 mg, 0.054 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 2.0 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.13 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 4.30 (t, *J* = 5.8 Hz, 2H), 4.24 (t, *J* = 5.8 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.12 (s, 2H), 2.85 – 2.73 (m, 2H), 2.50 – 2.39 (m, 2H), 2.22 (p, *J* = 5.8 Hz, 2H), 1.84 – 1.73 (m, 1H), 1.61 – 1.51 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.16, 154.46, 150.32, 142.92, 135.61, 132.28, 131.51, 130.01, 129.93, 126.87, 122.40, 121.38, 120.84, 70.51, 70.39, 65.02, 61.75, 48.19, 34.79, 30.89, 14.61, 14.23. HRMS $[C_{23}H_{25}Cl_2NO_6S+Na]^+$: 536.06718/538.06419 calculated, 536.06655/538.06343 found.

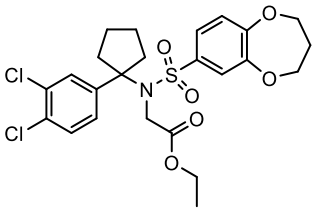
Ethyl *N*-(1-(3-chloro-4-(trifluoromethyl)phenyl)cyclobutyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate (105i)



The title compound was synthesized according to the general procedure **I** using *N*-(1-(3-chloro-4-(trifluoromethyl)phenyl)cyclobutyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**104i**, 46 mg, 0.10 mmol, 1 eq), ethyl 2-bromoacetate (22 µL, 0.20 mmol, 2 eq) and BEMP (1 M in hexane, 0.20 mL, 0.20 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column

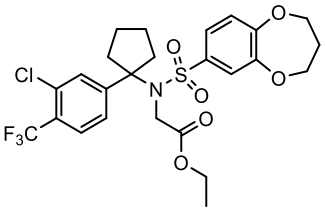
chromatography (20% EtOAc in *n*-pentane) afforded the product (36 mg, 0.066 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.7 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.09 – 7.03 (m, 2H), 6.86 – 6.81 (m, 1H), 4.29 (t, *J* = 5.8 Hz, 2H), 4.23 (t, *J* = 5.8 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.15 (s, 2H), 2.88 – 2.76 (m, 2H), 2.54 – 2.43 (m, 2H), 2.21 (p, *J* = 5.8 Hz, 2H), 1.87 – 1.77 (m, 1H), 1.66 – 1.53 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.05, 154.56, 150.47, 148.52, 135.40, 132.20 (q, J_{C-F} = 2.0 Hz), 130.74, 127.37 (q, J_{C-F} = 5.2 Hz), 127.35 (q, J_{C-F} = 32.3 Hz), 125.50, 122.87 (q, J_{C-F} = 274.7 Hz), 122.42, 121.39, 120.72, 70.47, 70.30, 65.16, 61.81, 48.26, 34.74, 30.84, 14.58, 14.21. HRMS $[C_{24}H_{25}ClF_3NO_6S+NH_4]^+$: 565.13815 calculated, 565.13779 found.

Ethyl *N*-(1-(3,4-dichlorophenyl)cyclopentyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate (105j)



The title compound was synthesized according to the general procedure **I** using *N*-(1-(3,4-dichlorophenyl)cyclopentyl)-3,4-dihydro-*2H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**104j**, 54 mg, 0.12 mmol, 1 eq), ethyl 2-bromoacetate (27 µL, 0.24 mmol, 2 eq) and BEMP (1 M in hexane, 244 µL, 0.244 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (50 mg, 0.095 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 2.1 Hz, 1H), 7.31 – 7.25 (m, 3H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 4.32 (t, *J* = 5.8 Hz, 2H), 4.26 (t, *J* = 5.8 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.18 (s, 2H), 2.36 – 2.28 (m, 2H), 2.27 – 2.19 (m, 4H), 1.76 – 1.63 (m, 2H), 1.42 – 1.32 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.60, 154.51, 150.33, 143.06, 136.19, 132.11, 131.43, 129.90, 129.77, 126.93, 122.71, 121.45, 121.18, 73.09, 70.52, 70.38, 61.63, 48.90, 37.83, 30.91, 21.62, 14.23. HRMS $[C_{24}H_{27}Cl_2NO_6S+Na]^+$: 550.08283/552.07984 calculated, 550.08267/552.07949 found.

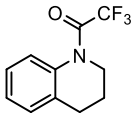
Ethyl *N*-(1-(3-chloro-4-(trifluoromethyl)phenyl)cyclopentyl)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)glycinate (105k)



The title compound was synthesized according to the general procedure **I** using *N*-(1-(3-chloro-4-(trifluoromethyl)phenyl)cyclopentyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide (**104k**, 42 mg, 0.089 mmol, 1 eq), ethyl 2-bromoacetate (19.7 µL, 0.178 mmol, 2 eq) and BEMP (1 M in hexane, 178 µL, 0.178 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (20% EtOAc in *n*-pentane) afforded the product (36 mg, 0.064 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 1.8 Hz, 1H), 7.43 (ddd, *J* = 8.1, 1.8, 0.9 Hz, 1H), 7.22 – 7.15 (m, 2H), 6.88 (d, *J* = 8.4 Hz, 1H), 4.31 (t, *J* = 5.9 Hz, 2H), 4.25 (t, *J* = 5.9 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.19 (s, 2H), 2.40 – 2.18 (m, 6H), 1.78 – 1.67 (m, 2H), 1.44 – 1.33 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.48, 154.62, 150.48, 148.86, 135.88, 132.00 (q, J_{C-F} = 1.9 Hz), 130.74, 127.25 (q, J_{C-F} = 32.3 Hz), 127.12 (q, J_{C-F} = 5.2 Hz), 125.60, 122.88 (q, J_{C-F} = 273.7 Hz), 122.75, 121.47, 121.11, 73.27,

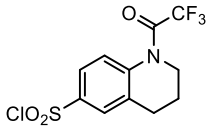
70.50, 70.33, 61.71, 48.93, 37.96, 30.89, 21.76, 14.22. HRMS $[C_{25}H_{27}ClF_3NO_6S+NH_4]^+$: 579.15380 calculated, 579.15333 found.

1-(3,4-Dihydroquinolin-1(2*H*)-yl)-2,2,2-trifluoroethan-1-one (106)



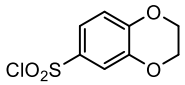
To a solution of 1,2,3,4-tetrahydroquinoline (1.00 g, 7.51 mmol, 1 eq) and Et_3N (3.14 mL, 22.5 mmol, 3 eq) in Et_2O (10 mL, 0.75 M) at 0 °C was added 2,2,2-trifluoroacetic anhydride (2.1 mL, 15 mmol, 2 eq) in Et_2O (3 mL) dropwise. The reaction was warmed to rt and stirred for overnight. The reaction mixture was diluted in water and extracted 3× with Et_2O. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (5-20% Et_2O in *n*-pentane) to afford the product (1.50 g, 6.54 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (bs, 1H), 7.25 – 7.04 (m, 3H), 3.84 (t, *J* = 6.2 Hz, 2H), 2.88 (bs, 2H), 2.08 (p, *J* = 6.7 Hz, 2H).

1-(2,2,2-Trifluoroacetyl)-1,2,3,4-tetrahydroquinoline-6-sulfonyl chloride (107)



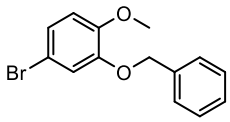
1-(3,4-Dihydroquinolin-1(2*H*)-yl)-2,,2,2-trifluoroethan-1-one (**106**, 0.50 g, 2.2 mmol, 1 eq) was dissolved in anhydrous DCM (10 mL, 0.2 M) and chlorosulfonic acid (150 µL, 2.18 mmol, 1 eq) was added dropwise at 0 °C. The mixture was stirred for 2 h and chlorosulfonic acid (150 µL, 2.18 mmol, 1 eq) was added dropwise at 0 °C. The reaction mixture was slowly warmed to rt and stirred for another 2 h. The reaction was quenched with cool water and extracted 3× with DCM. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford the product (370 mg, 1.13 mmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.97 (m, 1H), 7.94 – 7.87 (m, 2H), 3.97 – 3.90 (m, 2H), 3.05 (t, *J* = 6.9 Hz, 2H), 2.25 – 2.13 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.35 (q, $J_{C\text{-}F}$ = 37.0 Hz), 142.95, 141.15, 132.70, 128.31, 125.79, 125.07, 116.39 (q, $J_{C\text{-}F}$ = 288.3 Hz), 45.26 (q, $J_{C\text{-}F}$ = 3.6 Hz), 26.48, 22.92.

2,3-Dihydrobenzo[*b*][1,4]dioxine-6-sulfonyl chloride (108)



The title compound was synthesized according to general procedure **E** using 6-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine (150 mg, 0.698 mmol, 1 eq) and *n*-BuLi (1.6 M in hexane, 910 µL, 1.46 mmol, 2.1 eq) at -78 °C for 1.5 h, and subsequently SO_2 (0.5 M in hexane, 2.8 mL, 1.4 mmol, 2 eq) at -78 °C to -40 °C for 1 h and *N*-chlorosuccinimide (112 mg, 0.837 mmol, 1.2 eq) at 0 °C for 1 h. Silica gel column chromatography (0-15% EtOAc in *n*-pentane) afforded the product (44.0 mg, 0.188 mmol, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.50 (m, 2H), 7.03 (d, *J* = 8.5 Hz, 1H), 4.40 – 4.36 (m, 2H), 4.36 – 4.31 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.85, 143.80, 136.56, 121.14, 118.26, 116.90, 64.85, 64.23.

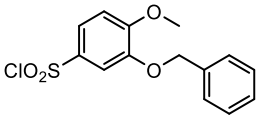
2-(Benzyloxy)-4-bromo-1-methoxybenzene (109)



To a solution of 5-bromo-2-methoxyphenol (2.00 g, 9.80 mmol, 1 eq) in anhydrous DMF (35 mL, 0.28 M) was added K_2CO_3 (2.70 g, 19.6 mmol, 2

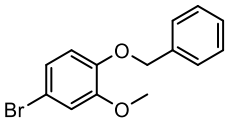
eq) and benzyl bromide (1.40 mL, 11.8 mmol, 1.2 eq). The mixture was heated to 106 °C and stirred overnight. The mixture was cooled down and diluted in EtOAc and water and the aqueous layer was extracted 2× with EtOAc. The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (5% EtOAc in *n*-pentane) to afford the product as a white solid (1.9 g, 6.6 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.45 (m, 2H), 7.44 – 7.39 (m, 2H), 7.38 – 7.33 (m, 1H), 7.10 – 7.05 (m, 2H), 6.81 – 6.77 (m, 1H), 5.14 (s, 2H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.08, 149.03, 136.50, 128.72, 128.17, 127.50, 124.05, 117.29, 113.13, 112.61, 71.26, 56.22.

3-(Benzyloxy)-4-methoxybenzenesulfonyl chloride (110)



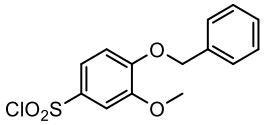
The title compound was synthesized according to general procedure **E** using 2-(benzyloxy)-4-bromo-1-methoxybenzene (**109**, 960 mg, 3.29 mmol, 1 eq) and *n*-BuLi (2.5 M in hexane, 1.58 mL, 3.95 mmol, 1.2 eq) at -78 °C for 1 h, SO_2 (1.2 M in THF, 5.48 mL, 6.58 mmol, 2 eq) at -78 °C to -40 °C for 1 h and then at rt for 1 h, and subsequently *N*-chlorosuccinimide (660 mg, 4.94 mmol. 1.5 eq) at 0 °C for 1 h and at rt for 1 h. Silica gel column chromatography (5-20% EtOAc in *n*-pentane) afforded the product (390 mg, 1.26 mmol, 39%). ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.66 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.41 – 7.29 (m, 3H), 6.98 (d, *J* = 8.7 Hz, 1H), 5.16 (s, 2H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.42, 148.40, 135.72, 135.48, 128.80, 128.52, 127.78, 122.03, 111.26, 110.92, 71.40, 56.50.

1-(Benzyloxy)-4-bromo-2-methoxybenzene (111)



To a solution of 4-bromo-2-methoxyphenol (1.45 g, 7.14 mmol, 1 eq) in anhydrous DMF (20 mL, 0.36 M) was added K_2CO_3 (2.80 g, 20.3 mmol, 2.84 eq) and the mixture was stirred at rt for 10 min. Benzyl bromide (1.02 mL, 8.57 mmol, 1.2 eq) was added and the mixture was then stirred at rt for overnight. The mixture was diluted in EtOAc and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (3-10% EtOAc in *n*-pentane) to afforded the product as a white solid (1.93 g, 6.58 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 5H), 6.98 (d, *J* = 2.3 Hz, 1H), 6.93 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 5.09 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.51, 147.41, 136.75, 128.65, 128.04, 127.34, 123.37, 115.36, 115.27, 113.39, 71.19, 56.18.

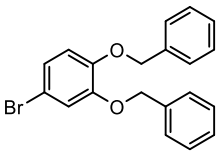
4-(Benzyloxy)-3-methoxybenzenesulfonyl chloride (112)



The title compound was synthesized according to general procedure **E** using 1-(benzyloxy)-4-bromo-2-methoxybenzene (**111**, 800 mg, 2.73 mmol, 1 eq) and *n*-BuLi (2.5 M in hexane, 1.10 mL, 2.73 mmol, 1 eq) at -78 °C for 1 h, and SO_2 (1.2 M in THF, 3.40 mL, 4.09 mmol, 1.5 eq) at -78 °C to -40 °C for 1 h and then at rt for 1 h, and subsequently *N*-chlorosuccinimide (440 mg, 3.27 mmol, 1.2 eq) at

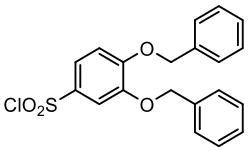
0 °C for 1 h and at rt for 1 h. Silica gel column chromatography (5-20% EtOAc in *n*-pentane) afforded the product as a light yellow solid (610 mg, 1.93 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.48 – 7.31 (m, 6H), 7.00 (d, *J* = 8.7 Hz, 1H), 5.24 (s, 2H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.96, 149.85, 136.18, 135.44, 128.95, 128.59, 127.38, 121.59, 112.41, 109.44, 71.25, 56.53.

(((4-Bromo-1,2-phenylene)bis(oxy))bis(methylene))dibenzene (113)



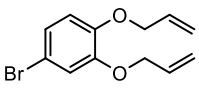
To a solution of 2-bromobenzene-1,2-diol (1.03 g, 5.43 mmol, 1 eq) in anhydrous DMF (22 mL, 0.25 M) was added K_2CO_3 (1.88 g, 13.6 mmol, 2.5 eq) and the mixture stirred at rt for 30 min. Benzyl bromide (1.60 mL, 13.6 mmol, 2.5 eq) was then added dropwise at rt. The reaction mixture was stirred at 90 °C for overnight. The reaction was quenched with sat. NH_4Cl and extracted 3× with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (2-5% EtOAc in *n*-pentane) to afford the product as a white crystalline solid (1.49 g, 4.05 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.27 (m, 10H), 7.06 (d, *J* = 2.3 Hz, 1H), 6.98 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.11 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.93, 148.24, 136.99, 136.70, 128.70, 128.65, 128.15, 128.05, 127.47, 127.40, 124.28, 118.20, 116.54, 113.54, 71.56, 71.47.

3,4-Bis(benzyloxy)benzenesulfonyl chloride (114)



The title compound was synthesized according to general procedure **E** using (((4-bromo-1,2-phenylene)bis(oxy))bis(methylene))dibenzene (**113**, 760 mg, 2.05 mmol, 1 eq) and *n*-BuLi (2.5 M in hexane, 0.82 mL, 2.05 mmol, 1 eq) at -78 °C for 1 h, SO_2 (1.2 M in THF, 2.60 mL, 3.12 mmol, 1.5 eq) at -78 °C to -40 °C for 1 h and at rt for 2 h, and subsequently *N*-chlorosuccinimide (330 mg, 2.46 mmol, 1.2 eq) at 0 °C for 1 h and at rt for 1 h. Silica gel column chromatography (5-10% EtOAc in *n*-pentane) afforded the product as a white crystalline solid (300 mg, 0.783 mmol, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.53 (d, *J* = 2.3 Hz, 1H), 7.48 – 7.31 (m, 10H), 7.01 (d, *J* = 8.7 Hz, 1H), 5.25 (s, 2H), 5.20 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.66, 148.89, 136.14, 135.77, 135.67, 128.91, 128.83, 128.50, 128.48, 127.63, 127.20, 122.00, 113.01, 112.19, 71.57, 71.19.

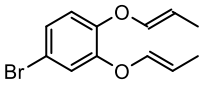
1,2-Bis(allyloxy)-4-bromobenzene (115)



To a mixture of 4-bromobenzene-1,2-diol (1.00 g, 5.29 mmol, 1 eq) in anhydrous DMF (10.6 mL, 0.5 M) was added K_2CO_3 (2.20 g, 15.9 mmol, 3 eq) and allyl bromide (1.37 mL, 15.9 mmol, 3 eq). The mixture was heated to 60 °C and stirred overnight. The mixture was diluted in water and extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (2-10% EtOAc in *n*-pentane) to afford the product (362 mg, 1.35 mmol, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.93 (m,

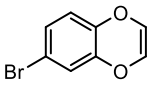
2H), 6.79 – 6.71 (m, 1H), 6.13 – 5.95 (m, 2H), 5.43 (dq, *J* = 8.5, 1.6 Hz, 1H), 5.38 (dq, *J* = 8.6, 1.6 Hz, 1H), 5.30 (dq, *J* = 7.7, 1.3 Hz, 1H), 5.27 (dq, *J* = 7.7, 1.3 Hz, 1H), 4.62 – 4.49 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.39, 147.82, 133.17, 132.87, 123.85, 118.12, 117.95, 117.35, 115.47, 113.12, 70.16, 70.10.

4-Bromo-1,2-bis((prop-1-en-1-yl)oxy)benzene (116)



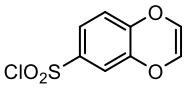
To a solution of 1,2-bis(allyloxy)-4-bromobenzene (**115**, 1.00 g, 3.72 mmol, 1 eq) in anhydrous benzene (12.4 mL, 0.3 M) was added $RuClH(CO)(PPh_3)_3$ (35 mg, 0.037 µmol, 1%) under argon and the mixture was heated to 80 °C for 24 h. The reaction mixture was purified by silica gel column chromatography (1% EtOAc in *n*-pentane) to afford the product (460 mg, 1.71 mmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 2.3 Hz, 1H), 7.09 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.36 – 6.21 (m, 2H), 5.00 – 4.85 (m, 2H), 1.73 (d, *J* = 1.8 Hz, 3H), 1.72 (d, *J* = 1.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.29, 146.83, 141.43, 140.98, 125.68, 120.15, 118.42, 114.87, 109.13, 108.28, 9.56, 9.54.

6-Bromobenzo[*b*][1,4]dioxine (117)



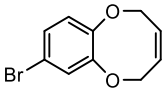
A solution of 4-bromo-1,2-bis((prop-1-en-1-yl)oxy)benzene (**116**, 460 mg, 1.71 mmol, 1 eq) in anhydrous DCM (17 mL, 0.1 M) was degassed under argon. Grubbs catalyst (II) (73 mg, 0.085 mmol, 5%) was added and the mixture was degassed again under argon. The mixture was heated to reflux for overnight. The mixture was diluted in DCM and concentrated. The residue was purified by silica gel column chromatography (100% *n*-pentane) to afford the product (320 mg, 1.50 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.76 (d, *J* = 2.3 Hz, 1H), 6.48 (d, *J* = 8.5 Hz, 1H), 5.86 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.55, 142.14, 127.01, 126.77, 119.57, 117.62, 115.57.

Benzo[*b*][1,4]dioxine-6-sulfonyl chloride (118)



The title compound was synthesized according to general procedure **E** using 6-bromobenzo[*b*][1,4]dioxine (**117**, 0.15 g, 0.70 mmol, 1 eq) and *n*-BuLi (2.5 M in hexane, 0.28 mL, 0.70 mmol, 1 eq) at -78 °C for 1 h, SO_2 (1.2 M in THF, 880 µL, 1.06 mmol, 1.5 eq) at -78 °C to -40 °C for 1 h and at rt for 1 h, and subsequently *N*-chlorosuccinimide (113 mg, 0.850 mmol, 1.2 eq) at 0 °C for 1 h and at rt for 1 h. Silica gel column chromatography (6% EtOAc in *n*-pentane) afforded the product (80 mg, 0.34 mmol, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.24 (d, *J* = 2.3 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 5.93 (q, *J* = 3.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.03, 143.49, 139.52, 127.45, 126.87, 124.52, 117.09, 115.38.

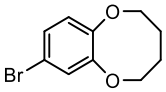
8-Bromo-2,5-dihydrobenzo[*b*][1,4]dioxocine (119)



A solution of 1,2-bis(allyloxy)-4-bromobenzene (**115**, 730 mg, 2.71 mmol, 1 eq) in anhydrous DCM (27 mL, 0.1 M) was degassed with argon. Grubbs catalyst (II) (115 mg, 0.140 mmol, 5%) was added. The mixture was degassed again with argon and refluxed for overnight. The reaction mixture was diluted in DCM and concentrated. The residue

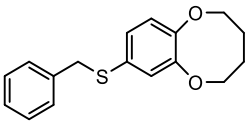
was purified by silica gel column chromatography(0-15% EtOAc in *n*-pentane) to afford the product (0.11 g, 0.46 mmol, 17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 2.4 Hz, 1H), 7.04 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 5.92 – 5.83 (m, 2H), 4.93 – 4.89 (m, 2H), 4.88 – 4.85 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.14, 147.48, 129.97, 129.00, 126.64, 125.46, 124.24, 115.41, 70.81, 69.97.

8-Bromo-2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocine (120)



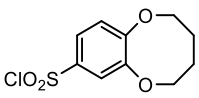
To a solution of 8-bromo-2,5-dihydrobenzo[*b*][1,4]dioxocine (**119**, 54.9 mg, 0.228 mmol, 1 eq) in degassed EtOH (1.9 mL, 0.12 M) was added $RhCl(PPh_3)_3$ (6.1 mg, 6.6 µmol, 0.03 eq). The mixture was degassed with N_2. Subsequently, the N_2 was changed to H_2 and the reaction was bubbled for 2 h at 50 °C. The mixture was filtered through Celite and washed with methanol. The filtrate was concentrated and the residue was purified by silica gel column chromatography (100% *n*-pentane) to afford the product (35.0 mg, 0.144 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 2.5 Hz, 1H), 7.03 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 4.34 (t, *J* = 5.2 Hz, 2H), 4.29 (t, *J* = 5.2 Hz, 2H), 1.94 – 1.84 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.54, 148.71, 126.35, 125.40, 123.96, 115.03, 72.99, 72.79, 27.00, 26.66.

8-(Benzylthio)-2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocine (121)



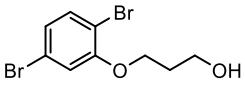
The title compound was synthesized according to the general procedure **F** using 8-bromo-2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocine (**120**, 63.2 mg, 0.260 mmol, 1 eq), benzyl mercaptan (31 µL, 0.26 mmol, 1 eq), DIPEA (91 µL, 0.52 mmol, 2 eq), xantphos (15 mg, 0.026 mmol, 0.1 eq) and $Pd_2(dba)_3$ (12 mg, 0.013 mmol, 0.05 eq). Total time: 4 h at 100 °C. Silica gel column chromatography (100% *n*-pentane) afforded the product (55.8 mg, 0.195 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 5H), 6.93 (d, *J* = 2.2 Hz, 1H), 6.89 (d, *J* = 2.3 Hz, 1H), 6.86 (s, 1H), 4.34 – 4.25 (m, 4H), 4.03 (s, 2H), 1.91 – 1.84 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.32, 149.04, 137.80, 129.70, 129.00, 128.53, 127.20, 126.67, 125.49, 122.67, 73.02, 72.66, 40.31, 27.06, 26.70.

2,3,4,5-Tetrahydrobenzo[*b*][1,4]dioxocine-8-sulfonyl chloride (122)



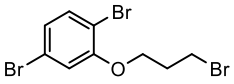
The title compound was synthesized according to the general procedure **G** using 8-(benzylthio)-2,3,4,5-tetrahydrobenzo[*b*][1,4]dioxocine (**121**, 55.8 mg, 0.195 mmol, 1 eq) and *N*-chlorosuccinimide (104 mg, 0.779 mmol, 4 eq). Total time: 2 h at rt. The product was afforded without purification (91.7 mg, 0.164 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 2.5 Hz, 1H), 7.64 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 4.62 (t, *J* = 5.7 Hz, 2H), 4.30 (t, *J* = 5.8 Hz, 2H), 2.07 – 2.00 (m, 2H), 1.90 – 1.84 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.74, 147.07, 136.98, 124.04, 123.81, 121.94, 75.12, 71.29, 28.19, 24.49.

3-(2,5-Dibromophenoxy)propan-1-ol (123)



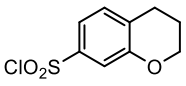
To a mixture of 1,4-dibromo-2-fluorobenzene (520 mg, 2.05 mmol, 1 eq) in propane-1,3-diol (2.7 mL) and 1-methylpyrrolidin-2-one (0.26 mL) was added *t*-BuOK (800 mg, 7.17 mmol, 3.5 eq) portion-wise under N_2 at rt. The resulting dark mixture was stirred at 100 °C for overnight. The mixture was poured into water and extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (5-20% EtOAc in *n*-pentane) to afford the product (510 mg, 1.64 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 2.1 Hz, 1H), 6.97 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.16 (t, *J* = 5.8 Hz, 2H), 3.90 (t, *J* = 5.7 Hz, 2H), 2.33 (s, 1H), 2.10 (p, *J* = 5.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.76, 134.10, 125.03, 121.67, 116.41, 110.93, 67.59, 60.44, 31.72.

1,4-Dibromo-2-(3-bromopropoxy)benzene (124)



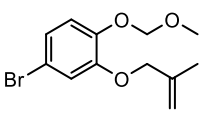
To a solution of 3-(2,5-dibromophenoxy)propan-1-ol (**123**, 500 mg, 1.61 mmol, 1 eq) in toluene (6.5 mL, 0.25 M) was added PBr_3 (0.22 g, 0.81 mmol, 0.5 eq) at 0 °C. The mixture was heated to 100 °C for 2 h. The mixture was poured into ice-water and extracted 3× with EtOAc. Combined organic layers were washed with sat. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (0-1% EtOAc in *n*-pentane) to afford the product (430 mg, 1.14 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.3 Hz, 1H), 7.03 (d, *J* = 2.1 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.14 (t, *J* = 5.7 Hz, 2H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.36 (p, *J* = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.72, 134.24, 125.17, 121.65, 116.72, 111.19, 66.73, 32.16, 29.93.

Chromane-7-sulfonyl chloride (125)



The title compound was synthesized according to general procedure **E** using 1,4-dibromo-2-(3-bromopropoxy)benzene (**124**, 0.20 g, 0.54 mmol, 1 eq) and *n*-BuLi (2.5 M in hexane, 430 µL, 1.07 mmol, 1 eq) at -78 °C for 2 h, SO_2 (1.2 M in THF, 670 µL, 0.805 mmol, 1.5 eq) at -78 °C to -40 °C for 1 h and at rt for 1 h, and subsequently *N*-chlorosuccinimide (86 mg, 0.64 mmol, 1.2 eq) at 0 °C for 1 h and at rt for 1 h. Silica gel column chromatography (6% EtOAc in *n*-pentane) afforded the product (62.0 mg, 0.266 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.38 (m, 2H), 7.28 – 7.21 (m, 1H), 4.30 – 4.24 (m, 2H), 2.89 (t, *J* = 6.5 Hz, 2H), 2.10 – 2.02 (m, 2H).

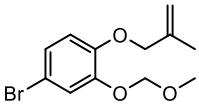
4-Bromo-1-(methoxymethoxy)-2-((2-methylallyl)oxy)benzene (126)



To a stirred solution of 2-methylprop-2-en-1-ol (2.06 g, 28.5 mmol, 2 eq) in anhydrous DMF (27 mL, 0.5 M) was added NaH (60% w/w in mineral oil, 1.14 g, 15.3 mmol, 2 eq) portion-wise under N_2 at 0 °C. The mixture was stirred at 0 °C for 30 min. To the mixture was added 4-bromo-2-fluoro-1-

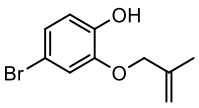
(methoxymethoxy)benzene (3.35 g, 14.3 mmol, 1 eq) in anhydrous DMF (2 mL) and the mixture was stirred at rt for 24 h. The reaction was quenched with ice cold water and extracted 3× with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (1-3% EtOAc in *n*-pentane) to afford the product (2.48 g, 8.64 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 3H), 5.18 (s, 2H), 5.09 (p, *J* = 1.3 Hz, 1H), 5.00 (p, *J* = 1.3 Hz, 1H), 4.48 (s, 2H), 3.51 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.04, 146.08, 140.22, 123.99, 118.80, 117.38, 114.72, 113.22, 95.83, 72.87, 56.38, 19.42.

4-Bromo-2-(methoxymethoxy)-1-((2-methylallyl)oxy)benzene (127)



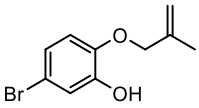
To a stirred solution of 2-methylprop-2-en-1-ol (1.10 g, 15.3 mmol, 2 eq) in anhydrous DMF (15 mL, 0.5 M) was added NaH (60% w/w in mineral oil, 610 mg, 15.3 mmol, 2 eq) portion-wise under N_2 at 0 °C. The mixture was stirred at 0 °C for 30 min. To the mixture was added 4-bromo-1-fluoro-2-(methoxymethoxy)benzene (1.80 g, 7.66 mmol, 1 eq) in anhydrous DMF (0.4 mL) and the mixture was stirred at rt for 3 days. The reaction was quenched with water and extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (2-5% EtOAc in *n*-pentane) to afford the product (1.12 g, 3.90 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 2.4 Hz, 1H), 7.05 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 1H), 5.20 (s, 2H), 5.08 – 5.04 (m, 1H), 5.00 – 4.95 (m, 1H), 4.47 (s, 2H), 3.51 (s, 3H), 1.81 (dd, *J* = 1.5, 0.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.41, 147.64, 140.46, 125.23, 120.48, 115.34, 113.00, 112.94, 95.72, 72.83, 56.36, 19.33.

4-Bromo-2-((2-methylallyl)oxy)phenol (128)



To a solution of 4-bromo-1-(methoxymethoxy)-2-((2-methylallyl)oxy)benzene (**126**, 2.44 g, 8.50 mmol, 1 eq) in anhydrous DCM (28.3 mL, 0.25 M) was added TFA (5.66 mL, 8.7 eq) at 0 °C. The reaction was stirred at 0 °C until completion. The mixture was diluted in DCM and washed with cold water, cold sat. $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (1-5% EtOAc in *n*-pentane) to afford the product (1.88 g, 7.72 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.95 (m, 2H), 6.81 (d, *J* = 8.3 Hz, 1H), 5.61 (s, 1H), 5.10 – 5.06 (m, 1H), 5.06 – 5.02 (m, 1H), 4.48 (t, *J* = 1.2 Hz, 2H), 1.83 (dd, *J* = 1.5, 0.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.40, 145.15, 139.86, 124.52, 116.00, 115.61, 113.99, 111.58, 73.06, 19.49.

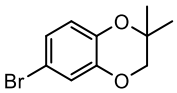
5-Bromo-2-((2-methylallyl)oxy)phenol (129)



To a solution of 4-bromo-2-(methoxymethoxy)-1-((2-methylallyl)oxy)benzene (**127**, 1.00 g, 3.48 mmol, 1 eq) in anhydrous DCM (17 mL, 0.16 M) was added TFA (5 mL, 18.8 eq) slowly at 0 °C. The reaction was stirred at 0 °C until completion. The mixture was diluted in DCM and washed with cold

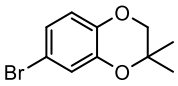
water, cold sat. $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (1-5% EtOAc in *n*-pentane) to afford the product (670 mg, 2.77 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 2.4 Hz, 1H), 6.93 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 5.71 (s, 1H), 5.08 – 5.05 (m, 1H), 5.04 – 5.01 (m, 1H), 4.48 (s, 2H), 1.82 (dd, *J* = 1.5, 0.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.80, 145.01, 140.09, 122.87, 118.10, 113.84, 113.61, 113.46, 73.00, 19.47.

6-Bromo-2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine (130)



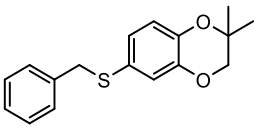
The solution of 4-bromo-2-((2-methylallyl)oxy)phenol (**128**, 1.85 g, 7.61 mmol, 1 eq) in formic acid (15 mL, 0.5 M) was refluxed for 30 min. The reaction mixture was diluted in EtOAc and washed with sat. $NaHCO_3$, water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (0-4% EtOAc in *n*-pentane) to afford the product (650 mg, 2.68 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 2.3 Hz, 1H), 6.94 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 3.86 (s, 2H), 1.33 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.14, 142.04, 124.71, 119.98, 118.98, 112.26, 72.60, 71.97, 23.37.

7-Bromo-2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine (131)



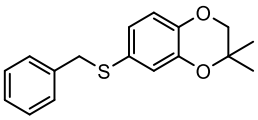
The solution of 5-bromo-2-((2-methylallyl)oxy)phenol (**129**, 674 mg, 2.77 mmol, 1 eq) in formic acid (14 mL, 0.2 M) was refluxed for 30 min. The reaction mixture was diluted in EtOAc and washed with sat. $NaHCO_3$, water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (0-2% EtOAc in *n*-pentane) to afford the product (276 mg, 1.14 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 2.3 Hz, 1H), 6.92 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 1H), 3.86 (s, 2H), 1.33 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.65, 141.64, 123.74, 120.65, 118.27, 113.29, 72.83, 71.93, 23.39.

6-(Benzylthio)-2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine (132)



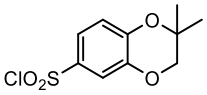
The title compound was synthesized according to the general procedure **F** using 6-bromo-2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine (**130**, 620 mg, 2.55 mmol, 1 eq), benzyl mercaptan (299 µL, 2.55 mmol, 1 eq), DIPEA (888 µL, 5.10 mmol, 2 eq), xantphos (148 mg, 0.26 mmol, 0.1 eq) and $Pd_2(dba)_3$ (116 mg, 0.130 mmol, 0.05 eq). Total time: 4 h at 100 °C. Silica gel column chromatography (1-5% EtOAc in *n*-pentane) afforded the product (547 mg, 1.91 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.18 (m, 5H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.82 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.00 (s, 2H), 3.83 (s, 2H), 1.31 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.29, 142.25, 138.00, 128.97, 128.48, 127.13, 126.77, 125.67, 120.43, 117.96, 72.58, 71.92, 40.90, 23.39.

7-(Benzylthio)-2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine (133)



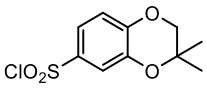
The title compound was synthesized according to the general procedure **F** using 7-bromo-2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine (**131**, 250 mg, 1.03 mmol, 1 eq), benzyl mercaptan (121 µL, 1.03 mmol, 1 eq), DIPEA (358 µL, 2.03 mmol, 2 eq), xantphos (59.5 mg, 0.100 mmol, 0.1 eq) and $Pd_2(dba)_3$ (47 mg, 0.050 mmol, 0.05 eq). Total time: 4 h at 100 °C. Silica gel column chromatography (1-5% EtOAc in *n*-pentane) afforded the product (257 mg, 0.897 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.17 (m, 5H), 6.86 (d, *J* = 1.7 Hz, 1H), 6.78 – 6.76 (m, 2H), 4.01 (s, 2H), 3.84 (s, 2H), 1.32 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.77, 141.74, 137.92, 128.98, 128.49, 127.92, 127.13, 124.42, 120.80, 117.25, 72.52, 71.99, 40.69, 23.39.

2,2-Dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonyl chloride (134)



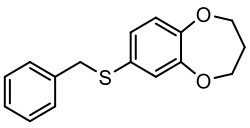
The title compound was synthesized according to the general procedure **G** using 6-(benzylthio)-2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine (**132**, 537 mg, 1.88 mmol, 1 eq) and *N*-chlorosuccinimide (1.00 g, 7.50 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (1-5% EtOAc in *n*-pentane) afforded the product (472 mg, 1.80 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.51 (m, 2H), 6.98 (d, *J* = 8.5 Hz, 1H), 3.96 (s, 2H), 1.40 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.24, 142.47, 136.07, 121.61, 118.44, 116.59, 74.48, 71.87, 23.45.

3,3-Dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonyl chloride (135)



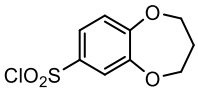
The title compound was synthesized according to the general procedure **G** using 7-(benzylthio)-2,2-dimethyl-2,3-dihydrobenzo[*b*][1,4]dioxine (**133**, 257 mg, 0.900 mmol, 1 eq) and *N*-chlorosuccinimide (479 mg, 3.58 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (1-5% EtOAc in *n*-pentane) afforded the product (244 mg, 0.929 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.47 (m, 2H), 7.09 – 6.99 (m, 1H), 3.99 (s, 2H), 1.38 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.55, 143.00, 137.05, 120.60, 117.78, 117.15, 73.36, 72.29, 23.35.

7-(Benzylthio)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine (136)



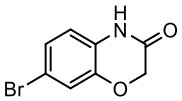
The title compound was synthesized according to the general procedure **F** using 7-bromo-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine (250 mg, 1.09 mmol, 1 eq), benzyl mercaptan (128 µL, 1.09 mmol, 1 eq), DIPEA (380 µL, 2.18 mmol, 2 eq), xantphos (63 mg, 0.11 mmol, 0.1 eq) and $Pd_2(dba)_3$ (50 mg, 0.060 mmol, 0.05 eq). Total time: 4 h at 100 °C. Silica gel column chromatography (1-5% EtOAc in *n*-pentane) afforded the product (219 mg, 0.804 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 5H), 6.96 (d, *J* = 2.2 Hz, 1H), 6.89 – 6.83 (m, 2H), 4.19 – 4.15 (m, 4H), 4.03 (s, 2H), 2.16 (p, *J* = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.30, 150.48, 137.69, 129.97, 128.95, 128.54, 127.22, 126.17, 124.19, 122.00, 70.67, 70.64, 40.14, 31.83.

3,4-Dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonyl chloride (137)



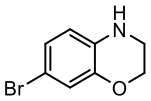
The title compound was synthesized according to the general procedure **G** using 7-(benzylthio)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine (**136**, 219 mg, 0.810 mmol, 1 eq) and *N*-chlorosuccinimide (430 mg, 3.22 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (1-5% EtOAc in *n*-pentane) afforded the product as a white solid (181 mg, 0.728 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.4 Hz, 1H), 7.58 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 4.41 (t, *J* = 6.0 Hz, 2H), 4.35 (t, *J* = 6.0 Hz, 2H), 2.29 (p, *J* = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.01, 150.77, 137.86, 122.65, 122.25, 121.12, 70.72, 70.42, 30.36.

7-Bromo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (138)



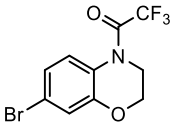
To a solution of 2-amino-5-bromophenol (300 mg, 1.60 mmol, 1 eq) in anhydrous DMF (6.4 mL, 0.25 M) was added K_2CO_3 (440 mg, 3.19 mmol, 2 eq) at rt and the mixture was stirred for 30 min. 2-chloroacetyl chloride (127 µL, 1.60 mmol, 1 eq) was then added dropwise and the reaction was heated to 80 °C for 3 h. The reaction mixture was diluted in water and extracted 3× with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (40% EtOAc in *n*-pentane) to afford the product (290 mg, 1.29 mmol, 81%). ^{1}H NMR (400 MHz, DMSO) δ 10.82 (s, 1H), 7.17 (d, *J* = 2.1 Hz, 1H), 7.13 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 4.60 (s, 2H).

7-Bromo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (139)



To a solution of 7-bromo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**138**, 270 mg, 1.19 mmol, 1 eq) in anhydrous THF (7.4 mL, 0.16 M) under argon was added borane-THF complex (1 M in THF, 2.38 mL, 2.38 mmol, 2 eq). The mixture was refluxed for 1 h. The reaction was quenched with water and 2 M aq. NaOH and extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (20% EtOAc in *n*-pentane) to afford the product (220 mg, 1.04 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, *J* = 2.2 Hz, 1H), 6.84 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 4.24 – 4.19 (m, 2H), 3.76 (bs, 1H), 3.41 – 3.36 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.84, 132.96, 124.05, 119.72, 116.58, 109.73, 65.26, 40.75.

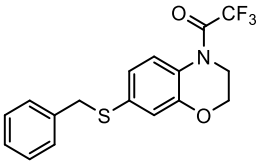
1-(7-Bromo-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)-2,2,2-trifluoroethan-1-one (140)



To a solution of 7-bromo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (**139**, 220 mg, 1.04 mmol, 1 eq) and Et_3N (440 µL, 3.13 mmol, 3 eq) in Et_2O (2.9 mL, 0.25 M) at 0 °C was added 2,2,2-trifluoroacetic anhydride (290 µL, 2.09 mmol, 2 eq) in Et_2O (1.25 mL) dropwise. The reaction was warmed to rt and stirred overnight. The mixture was diluted in water and extracted 3× with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified

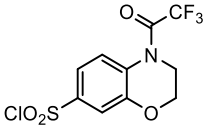
by silica gel column chromatography (10% EtOAc in *n*-pentane) to afford the product (0.30 g, 0.96 mmol, 92%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (bs, 1H), 7.11 (d, *J* = 2.2 Hz, 1H), 7.07 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.42 – 4.35 (m, 2H), 3.98 (t, *J* = 4.7 Hz, 2H).

1-(7-(Benzylthio)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)-2,2,2-trifluoroethan-1-one (141)



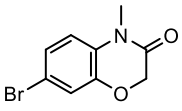
The title compound was synthesized according to the general procedure **F** using 1-(7-bromo-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)-2,2,2-trifluoroethan-1-one (**140**, 0.27 g, 0.87 mmol, 1 eq), benzyl mercaptan (0.10 mL, 0.87 mmol, 1 eq), DIPEA (300 µL, 1.73 mmol, 2 eq), xantphos (50 mg, 0.087 mmol, 0.1 eq) and $Pd_2(dba)_3$ (40 mg, 0.043 mmol, 0.05 eq). Total time: 4 h at 100°C. Silica gel column chromatography (5-10% EtOAc in *n*-pentane) afforded the product (0.27 g, 0.76 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.35 – 7.19 (m, 5H), 6.90 – 6.84 (m, 2H), 4.37 – 4.32 (m, 2H), 4.11 (s, 2H), 3.95 (t, *J* = 4.6 Hz, 2H).

4-(2,2,2-Trifluoroacetyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-sulfonyl chloride (142)



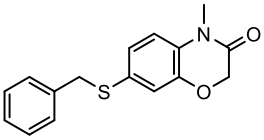
The title compound was synthesized according to the general procedure **G** using 1-(7-(benzylthio)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)-2,2,2-trifluoroethan-1-one (**141**, 268 mg, 0.597 mmol, 1 eq) and *N*-chlorosuccinimide (406 mg, 3.04 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (10-15% EtOAc in *n*-pentane) afforded the product (186 mg, 0.565 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 1H), 7.65 – 7.59 (m, 2H), 4.51 – 4.46 (m, 2H), 4.09 – 4.04 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.08 (q, $J_{C\text{-}F}$ = 37.5 Hz), 147.30, 142.02, 129.90, 125.01, 119.13, 116.86, 116.05 (q, $J_{C\text{-}F}$ = 288.9 Hz), 65.92, 43.27 (q, $J_{C\text{-}F}$ = 3.9 Hz).

7-Bromo-4-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (143)



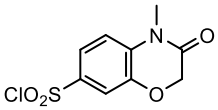
To a solution of 7-bromo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**138**, 300 mg, 1.32 mmol, 1 eq) in anhydrous DMF (5.3 mL, 0.25 M) under N_2 was added *t*-BuOK (295 mg, 2.63 mmol, 2 eq) and the mixture was stirred at rt for 30 min. CH_3I (160 µL, 2.63 mmol, 2 eq) was added drop-wise and stirred at rt for overnight. The reaction was quenched with water and extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (25% EtOAc in *n*-pentane) to afford the product (183 mg, 0.756 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.14 (d, *J* = 2.1 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 4.62 (s, 2H), 3.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.08, 145.83, 128.98, 125.73, 120.17, 116.08, 116.00, 67.64, 28.21.

7-(Benzylthio)-4-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (144)



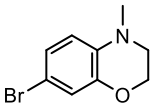
The title compound was synthesized according to the general procedure **F** using 7-bromo-4-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**143**, 160 mg, 0.660 mmol, 1 eq), benzyl mercaptan (78 µL, 0.66 mmol, 1 eq), DIPEA (230 µL, 1.62 mmol, 2 eq), xantphos (38 mg, 0.066 mmol, 0.1 eq) and $Pd_2(dba)_3$ (30 mg, 0.033 mmol, 0.05 eq). Total time: 4 h at 100 °C. Silica gel column chromatography (20-25% EtOAc in *n*-pentane) afforded the product (0.11 g, 0.39 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.20 (m, 5H), 6.99 – 6.93 (m, 2H), 6.87 – 6.77 (m, 1H), 4.58 (s, 2H), 4.07 (s, 2H), 3.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.28, 145.22, 137.39, 131.34, 128.91, 128.63, 128.43, 127.38, 125.04, 118.85, 115.08, 67.65, 39.73, 28.15. LC-MS $[C_{16}H_{15}NO_2S+H]^+$: 286.09 calculated, 286.17 found.

4-Methyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-sulfonyl chloride (145)



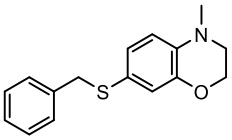
The title compound was synthesized according to the general procedure **G** using 7-(benzylthio)-4-methyl-2*H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (**144**, 115 mg, 0.400 mmol, 1 eq) and *N*-chlorosuccinimide (214 mg, 1.61 mmol, 4 eq). Total time: 2 h at rt. The product was afforded without purification (110 mg, 0.420 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 1H), 4.75 (d, *J* = 0.6 Hz, 2H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.21, 145.02, 138.77, 135.53, 122.29, 115.59, 115.18, 67.29, 28.47.

7-Bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (146)



To a solution of 7-bromo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (**139**, 230 mg, 1.07 mmol, 1 eq) in anhydrous DMF (4.7 mL, 0.23 M) under N_2 at 0 °C was added NaH (60% w/w in mineral oil, 86.0 mg, 2.15 mmol, 2 eq). The mixture was stirred at 0 °C for 20 min. Subsequently, CH_3I (74.0 µL, 1.18 mmol, 1.1 eq) was added and the mixture was stirred at 0 °C for 30 min. More CH_3I (74.0 µL, 1.18 mmol, 1.1 eq) was added and the mixture was stirred at rt for another 4 h. The mixture was diluted in water and extracted 3× with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (10% EtOAc in *n*-pentane) to afford the product (185 mg, 0.811 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), , 6.49 (d, *J* = 8.5 Hz, 1H), 4.30 – 4.22 (m, 2H), 3.26 – 3.19 (m, 2H), 2.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.08, 135.89, 124.08, 118.82, 113.56, 109.31, 65.07, 48.90, 38.79. LC-MS $[C_9H_{10}BrNO+H]^+$: 228.00 calculated, 228.08 found.

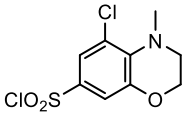
7-(Benzylthio)-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (147)



The title compound was synthesized according to the general procedure **F** using 7-bromo-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (**146**, 185 mg, 0.810 mmol, 1 eq), benzyl mercaptan (95 µL, 0.81 mmol, 1 eq), DIPEA

(280 µL, 1.62 mmol, 2 eq), xantphos (47 mg, 0.081 mmol, 0.1 eq) and $Pd_2(dba)_3$ (37 mg, 0.041 mmol, 0.05 eq). Total time: 4 h at 100 °C. Silica gel column chromatography (5-10% EtOAc in *n*-pentane) afforded the product (123 mg, 0.453 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.16 (m, 5H), 6.84 – 6.79 (m, 2H), 6.51 (d, *J* = 8.8 Hz, 1H), 4.27 – 4.20 (m, 2H), 3.97 (s, 2H), 3.26 – 3.19 (m, 2H), 2.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.21, 138.40, 136.29, 134.86, 128.96, 128.50, 126.97, 126.22, 120.04, 112.51, 64.86, 49.01, 41.49, 38.69. LC-MS $[C_{16}H_{17}NOS+H]^+$: 272.11 calculated, 272.17 found.

5-Chloro-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine-7-sulfonyl chloride (148)



The title compound was synthesized according to the general procedure **G** using 7-(benzylthio)-4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (**147**, 123 mg, 0.450 mmol, 1 eq) and *N*-chlorosuccinimide (242 mg, 1.81 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (5-10% EtOAc in *n*-pentane) afforded the product (88 mg, 0.31 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 2.3 Hz, 1H), 7.42 (d, *J* = 2.3 Hz, 1H), 4.23 – 4.18 (m, 2H), 3.27 – 3.23 (m, 2H), 3.07 (s, 3H). LC-MS $[C_9H_9Cl_2NO_3S+H]^+$: 281.98 calculated, 282.00 found.

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