Discovery of selective diacylglycerol lipase β inhibitors

Zhu, N.

Chapter 3

Structure-activity relationship study of glycine sulfonamides as DAGLα/β inhibitors

3.1 Introduction

Diacylglycerol lipases (DAGLα and DAGLβ) are enzymes responsible for the biosynthesis of 2-arachidonoylglycerol (2-AG) in the brain and immune system. 2-AG is the most abundant endocannabinoid in tissues which can activate cannabinoid receptors type 1 and 2 (CB_1R and CB_2R) as a full agonist.[1] Due to the important role of 2-AG in regulating physio(patho)logical processes, DAGL inhibitors have been studied as a potential therapy for metabolic disorders[2,3], addiction[4], pathological pain, and (neuro)inflammation.[5–7] The current DAGL inhibitors can be divided into three classes: 1,2,3-triazole ureas (*e.g.* KT109[8], DH376 and DO34[9]), α-ketoheterocycles (*e.g.* LEI-105[10]), and glycine sulfonamides (*e.g.* LEI-106[11]).

KT109, DH376 and DO34 are widely used to investigate the function of DAGL in cellular and animal models.[12–14] These irreversible inhibitors exhibit high potency *in vitro* and *in vivo*[15], but they show relatively moderate selectivity among the serine hydrolase family.[8,9] KT195 and DO53, serving as negative control compounds lacking DAGL inhibitory activity, are necessary to assess off-target involvement in biological studies. Importantly, triazole ureas function as dual DAGLα and DAGLβ inhibitors. LEI-105 stands as the most selective dual DAGL inhibitor to date, with no known off-targets.[10] However, it encounters challenges related to low solubility and high metabolic clearance, resulting in poor bioavailability.

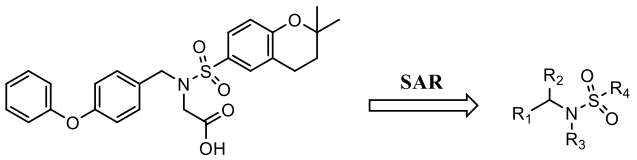
Glycine sulfonamides have been reported as DAGLα inhibitors and exhibit interactions with α/β-hydrolase domain containing 6 (ABHD6) along with a few unknown off-targets in the mouse brain membrane proteome.[11] These compounds lack an obvious serine-targeting warhead, but contain a carboxyl essential for activity.[11,15] Despite concerns about their poor cell permeability due to ionization under physiological pH, glycine sulfonamides have demonstrated good cellular activity and promising pharmacokinetics.[15] Notably, they do not easily cross the blood-brain barrier, reducing the potential for central nervous system (CNS)-mediated side effects observed with centrally acting CB_1R antagonists and DAGLα inhibitors.

Currently, subtype-selective DAGL inhibitors are still lacking, and systematic structure-activity relationships for DAGLα and DAGLβ are scarcely available. In Chapter 2, LEI-106 was identified as a hit for DAGLβ in a high-throughput screening. In this Chapter, the first structure-activity relationship (SAR) study of glycine sulfonamides and their analogs for DAGLβ, as well as their selectivity over DAGLα is described. Most of the compounds exhibited equal potency for both isoforms or slight selectivity for DAGLα, except three compounds (**49**, **51** and **52**) which demonstrated some selectivity for DAGLβ.

3.2 Results and discussion

3.2.1 Design and synthesis of DAGL inhibitors 2-52

To explore the structure-activity relationship (SAR), the scaffold of hit **1** (LEI-106) was divided into four parts, designated as R_1-R_4 (Figure 3.1), resulting in the design and synthesis of compounds **2-52**.



Hit **1** (LEI-106)

pIC_{50} (DAGLβ): 6.69 ± 0.14
pIC_{50} (DAGLα): 7.35 ± 0.06
cLogD: 1.9
LipE (DAGLβ): 4.8
Selectivity: 4-fold for DAGLα

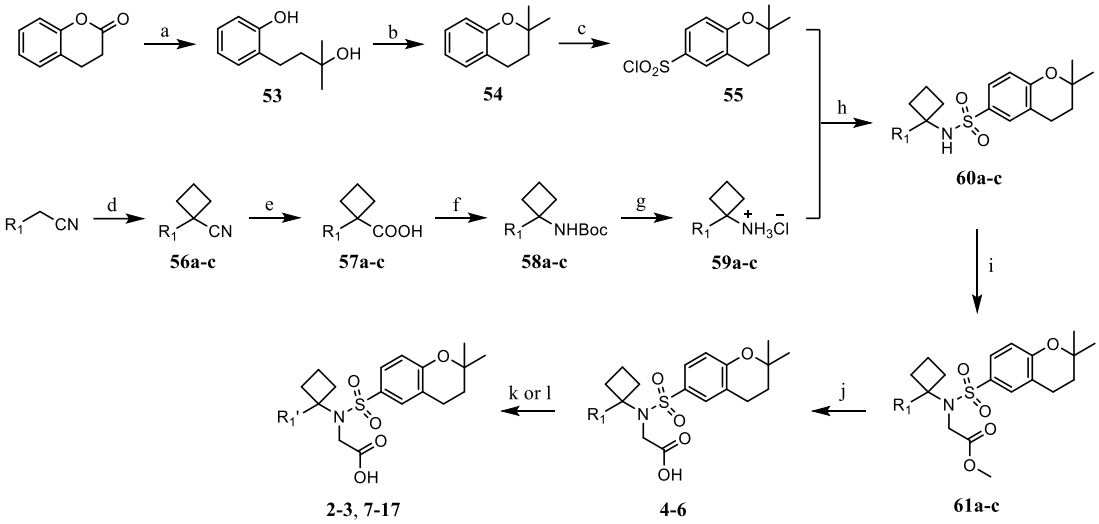
Figure 3.1 Chemical structure and biochemical activity and selectivity of Hit **1** (LEI-106) and the core structure with R_1-R_4 substituents in SAR study.

Glycine sulfonamides **2-17** featuring various modifications on R_1 were synthesized according to Scheme 3.1. The synthesis started with the addition of methyl magnesium bromide at chroman-2-one to afford diol **53**. Subsequent intramolecular ring-closure afforded ether **54**,[16] which underwent electrophilic aromatic substitution using chlorosulfonic acid to form regioselective sulfonyl chloride **55**.[17] The synthesis of amines **59a-c** started from the nitriles via sequential nucleophilic substitution[18], hydrolysis, Curtius rearrangement and *tert*-butyloxycarbamate formation[19], and finally acidolysis. Sulfonyl chloride **55** was condensed with **59a-c** to afford sulfonamides **60a-c**, which were followed by alkylating with methyl 2-bromoacetate to form sulfonamide-glycinates **61a-c**. Essential to the reaction was the use of 2-(tert-butylimino)-*N*,*N*-diethyl-1,3-dimethyl-1,3,2λ^5-diazaphosphinan-2-amine (BEMP) as a strong organic base which facilitated the alkylation.[15] Saponification of the methyl esters gave compounds **4-6**. Compounds **2-3** and **9-17** were synthesized through Suzuki-Miyaura coupling, starting from compounds **4** and **6**, respectively. A palladium-catalysed coupling in the presence of $K_4Fe(CN)_6{\cdot}3H_2O$[20] afforded final compound **7**, whose cyano group was subsequently hydrolyzed to an amide, yielding final compound **8**.

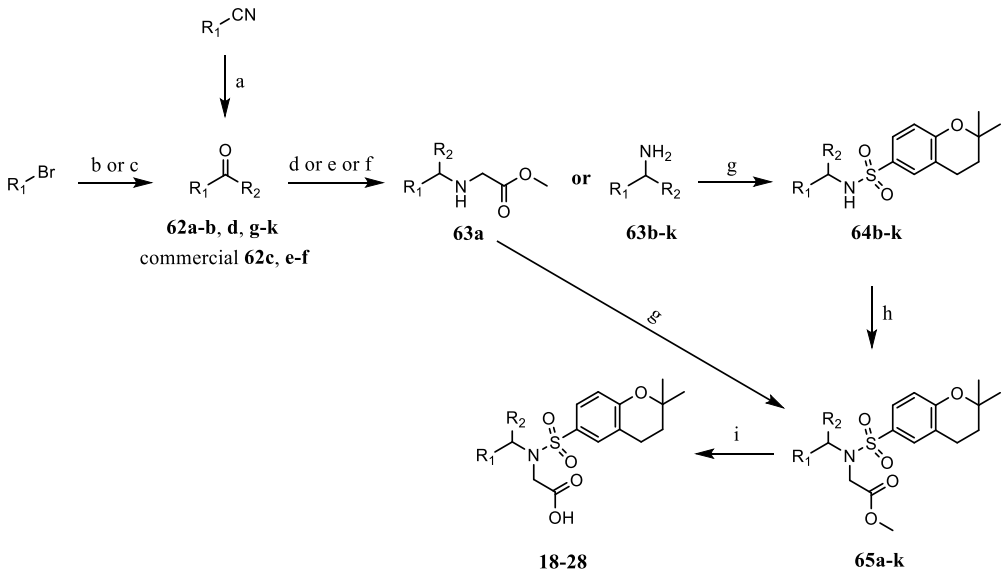
The synthesis of compounds **18-28** varying on R_2 is depicted in Scheme 3.2. When available, commercially ketones (**62c**, **e-f**) were used. Ketones not commercially available were synthesized from nitriles via nucleophilic addition and subsequent hydrolysis[21] (**62a-b**), or from bromides via nucleophilic addition of their lithium intermediates to the aldehydes and subsequent oxidation[22] (**62g-k**). Ketone **62d** was formed from 1,4-dibromobenzene and *N*-methoxy-*N*-methylcyclopropanecarboxamide via nucleophilic addition and elimination.[23] Reductive aminations[24] obtained secondary amine **63a** and primary amines **63b-k**. The final compound **18** was obtained from amine **63a** and sulfonyl chloride **55** via condensation and saponification, whereas final compounds **19-28** were obtained from amines **63b-k** and sulfonyl chloride **55** via condensation, alkylation and saponification.

Compounds **29-34**, with different substituents on R_3, were synthesized according to Scheme 3.3. Compound **60c** was *N*-alkylated with different alkyl bromides to afford compounds **34** and **66a-c** which were subsequently transformed, after saponification, into the final compounds **29**, **30**, and **32**. Compound **31** was synthesized from **30** via Jones oxidation.[25] Compound **33** was obtained through amide coupling of **6** and hydroxylamine.

Compounds **35-52** featuring various sulfonyl substituents were synthesized according to Scheme 3.4. Compound **67** was synthesized from 4-bromobenzaldehyde and glycine methyl ester via reductive amination and subsequently coupled with various sulfonyl chlorides to afford sulfonamides **68a-r**. Saponification of the methyl esters gained final compounds **35-52**.

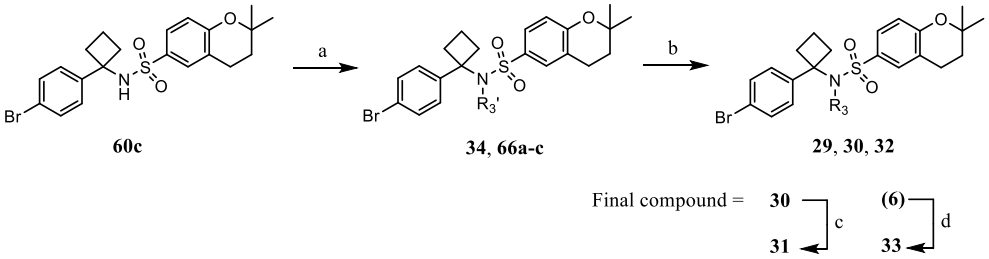


Scheme 3.1 Synthesis of glycine sulfonamides **2-17**. Reagents and conditions: a) CH_3MgBr, anhydrous THF, 0 °C-rt, 84%; b) 15% aq. H_2SO_4, toluene, reflux, 72%; c) HSO_3Cl, anhydrous DCM, 0 °C-rt, 63%; d) 1,3-dibromopropane, TBABr, KOH, toluene, H_2O, reflux, 33-61%; e) KOH, ethylene glycol, reflux, 50-92%; f) DPPA, Et_3N, anhydrous *t*-BuOH, 30 °C-reflux, 42-85%; g) 3 M aq. HCl in MeOH, rt, 93%-quant.; h) Et_3N, anhydrous DCM, rt, 46-89%; i) methyl 2-bromoacetate, BEMP, anhydrous DMF, 80 °C, 90%-quant.; j) 1 M or 2 M aq. NaOH, MeOH/THF, rt, 47-quant.; k) corresponding boronic acid, K_2CO_3, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, 1,4-dioxane/$H_2O$, 80 °C, 12-75% for **2-3**, **9-17**; l) $Pd(OAc)_2$, $K_4Fe(CN)_6 \cdot 3H_2O$, Na_2CO_3, *i*-PrOH, H_2O, DMF, 100 °C, 45% for **7**; 30% H_2O_2, 2 M aq. NaOH, MeOH, rt, 39% for **7** → **8**.

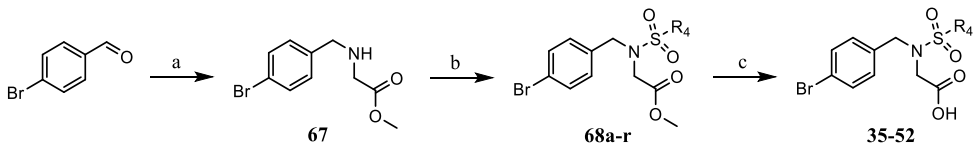


Scheme 3.2 Synthesis of glycine sulfonamides **18-28**. Reagents and conditions: a) R_2-MgX, anhydrous THF, reflux, 91% for **62a**, 86% for **62b**; b) *i.* 1,4-dibromobenzene, *n*-BuLi, anhydrous THF, -78 °C; *ii.* *N*-methoxy-*N*-methylcyclopropanecarboxamide, rt, 13% for **62d**; c) *i.* *n*-BuLi, anhydrous THF, -78 °C; *ii.* corresponding benzaldehyde, -78 °C; *iii.* I_2, K_2CO_3, *t*-BuOH, reflux, 39-54% for **62g-k**; d) 2-methoxy-2-oxoethan-1-aminium

chloride, Et_3N, AcOH, $NaBH_3CN$, anhydrous MeOH, reflux, 74% for **63a**; e) ammonium acetate, $NaBH_3CN$, anhydrous MeOH or EtOH, reflux, 15%-quant. for **63b-c**, **f-k**; f) *i. O*-methylhydroxylammonium chloride, pyridine, rt; *ii.* BH_3·THF, anhydrous THF, reflux; *iii.* aq. NaOH, 85 °C, 77% for **63d**; *i.* hydroxyl ammonium chloride, EtOH, reflux; *ii.* $LiAlH_4$, anhydrous THF, reflux, 22% for **63e**; g) 2,2-dimethylchromane-6-sulfonyl chloride (**55**), Et_3N, anhydrous DCM, 0 °C-rt, 22-99% for **64b-k**, 28% for **65a**; h) methyl 2-bromoacetate, BEMP, anhydrous DMF, 80 °C, 72%-quant. for **65b-k**; i) 1 M or 2 M aq. NaOH, THF/MeOH, rt, 22-70%.



Scheme 3.3 Synthesis of compounds **29-34**. Reagents and conditions: a) R_3'-Br, BEMP, anhydrous DMF, 80 °C, 10-90%; b) 2 M aq. NaOH, THF/MeOH, rt, 40-99%; c) Jones reagent, acetone, 0 °C, 56%; d) NH_2OH·HCl, EDCI, HOBt, DIPEA, anhydrous DMF, rt, 27%.



Scheme 3.4 Synthesis of glycine sulfonamides **35-52**. Reagents and conditions: a) *i.* glycine methyl ester hydrochloride, Et_3N, AcOH, anhydrous MeOH, rt; *ii.* $NaBH_3CN$, rt, 76%; b) sulfonyl chlorides, Et_3N, pyridine, anhydrous DCM, rt, 19%-quant.; c) 2 M aq. NaOH, THF/MeOH, rt, 21-100%.

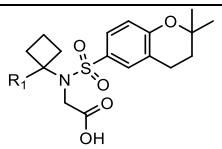
3.2.2 Biochemical evaluation and structure-activity-relationship of compounds 2-52

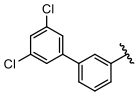
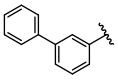
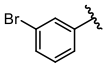
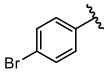
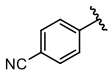
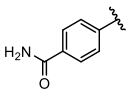
3.2.2.1 Modification on R_1

LEI-106 exhibited inhibition of both DAGLα and DAGLβ with a 4-fold selectivity for DAGLα. Additionally, compound **2** was previously reported as a potent DAGLα inhibitor with nanomolar potency and 67-fold selectivity for DAGLα over DAGLβ.[15] This compound was synthesized and its activity was confirmed with a negative logarithm half-maximal inhibitory concentration (pIC_{50}) of 7.22 ± 0.17 for DAGLβ and a pIC_{50} of 7.60 ± 0.08 for DAGLα in the EnzChek lipase substrate assay as detailed in Chapter 2 (Table 3.1). The selectivity was lower than previously reported, likely due to the utilization of different biochemical assays.[15] Although compound **2** is highly potent, it exhibits a low lipophilic efficiency (LipE) attributed to its high lipophilicity. To reduce lipophilicity, either the removal of the two chlorines in compound **2** (resulting in compound **3**) or the replacement of the 3,5-dichlorophenyl ring with a bromine (yielding compound **4**) was undertaken. Eliminating the two chlorines demonstrated no influence on potency for DAGL, whereas substituting the 3,5-dichlorophenyl ring with a bromine significantly reduced potency for DAGLα but not for DAGLβ. Both **3** and **4** exhibited higher LipE than **2**, benefiting from their decreased lipophilicity.

To investigate the impact of substituent position, compounds **5** and **6**—featuring a bromine on the *ortho* and *para* positions—were synthesized and assessed. The *para* bromine proved preferable over the *meta* and *ortho* ones for DAGL, aligning with the results of prior SAR studies involving LEI-106 counterparts.[11] Additionally, compound **6** exhibited higher potency and LipE compared to LEI-106. As a result, subsequent modifications in the SAR study primarily centered around compound **6**. Efforts to further reduce lipophilicity involved replacing the para bromine with nitrile (**7**), amide (**8**), and methyl groups (**9**). However, these analogs demonstrated lower potency than **6**. Generally, compounds tended to be less potent if the substituent introduced was less lipophilic. Compounds **7** and **8** also exhibited high topological polar surface area (tPSA), potentially resulting in reduced cellular permeability. Substituting the *para* bromine with a phenyl ring containing electron-withdrawing or donating moieties (**10-17**) maintained potency. These SAR findings strongly suggest the existence of a substantial binding pocket on DAGL for the R_1 group, with the primary determinant of potency being the compound's lipophilicity.

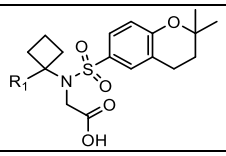
Table 3.1 Biochemical results and physicochemical properties of glycine sulfonamides **2-17**.[a]

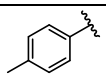
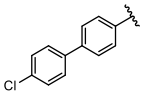
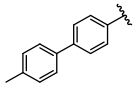
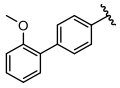
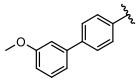
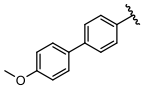
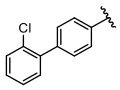
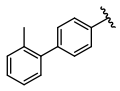
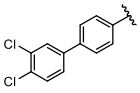


ID	R_1	pIC_{50} DAGLβ	pIC_{50} DAGLα	Apparent selectivity	cLogD	tPSA (Å^2)	LipE DAGLβ
2		7.22 ± 0.17	7.60 ± 0.08	0.4	4.5	95	2.7
3		7.24 ± 0.09	7.52 ± 0.04	0.5	3.2	95	4.0
4		7.17 ± 0.10	7.20 ± 0.03	0.9	2.3	95	4.9
5		6.66 ± 0.07	6.91 ± 0.05	0.6	2.3	95	4.4
6		7.34 ± 0.18	7.89 ± 0.11	0.3	2.3	95	5.0
7		6.14 ± 0.06	6.47 ± 0.12	0.5	1.4	119	4.7
8		< 5	5.36 ± 0.05	n.d.	0.7	138	n.d.

[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 3.1 (continued) Biochemical results and physicochemical properties of glycine sulfonamides **1-17**.[a]



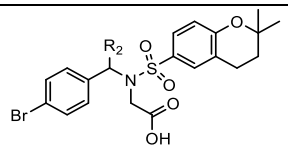
ID	R_1	pIC_{50} DAGLβ	pIC_{50} DAGLα	Apparent selectivity	cLogD	tPSA (Å^2)	LipE DAGLβ
9		6.88 ± 0.07	7.27 ± 0.14	0.4	1.9	95	5.0
10		7.22 ± 0.12	8.17 ± 0.21	0.1	3.8	95	3.4
11		7.51 ± 0.08	7.86 ± 0.04	0.4	3.6	95	3.9
12		7.15 ± 0.13	7.57 ± 0.06	0.4	3.2	104	4.0
13		7.52 ± 0.08	7.70 ± 0.06	0.7	3.2	104	4.3
14		7.36 ± 0.10	7.75 ± 0.11	0.4	3.2	104	4.2
15		7.01 ± 0.09	7.41 ± 0.09	0.4	3.8	95	3.2
16		6.94 ± 0.10	7.44 ± 0.08	0.3	3.6	95	3.3
17		7.18 ± 0.10	7.27 ± 0.05	0.8	4.5	95	2.7

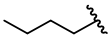
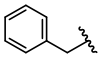
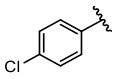
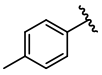
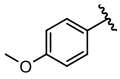
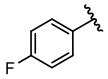
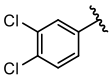
[a]The negative logarithm of the half-maximal inhibitory concentration (pIC_{50}) was determined using the EnzChek lipase substrate assay. The apparent selectivity regards the selectivity for DAGLβ over DAGLα. The calculated logarithm of the *n*-octanol-water partition coefficient at pH 7.4 (cLogD) and 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.

3.2.2.2 Modification on R_2

Exploration of the impact of the R_2 group on potency and selectivity was conducted based on compound **6**. Substituting the fused cyclobutyl ring in **6** with an ethyl group in **18** significantly reduced potency for DAGL (Table 3.2). Analogs **19-20**, featuring longer *n*-propyl and *n*-butyl groups, displayed increased potency and lipophilicity, resulting in a lower LipE. Compound **21**, with a cyclopropyl ring, demonstrated good potency and slightly higher LipE for DAGLβ compared to compound **6**.

Table 3.2 Biochemical results and physicochemical properties of glycine sulfonamides **6**, and **18-28**.[a]



ID	R_2	pIC_{50} DAGLβ	pIC_{50} DAGLα	Apparent selectivity	cLogD	tPSA (Å^2)	LipE DAGLβ
6		7.34 ± 0.18	7.89 ± 0.11	0.3	2.3	95	5.0
18		6.70 ± 0.10	6.98 ± 0.07	0.5	2.0	95	4.7
19		7.11 ± 0.09	7.44 ± 0.05	0.5	2.5	95	4.6
20		7.37 ± 0.09	7.60 ± 0.04	0.6	2.9	95	4.5
21		7.06 ± 0.09	7.23 ± 0.03	0.7	1.9	95	5.2
22		7.07 ± 0.11	7.19 ± 0.04	0.8	3.0	95	4.1
23		7.46 ± 0.11	7.64 ± 0.07	0.7	3.0	95	4.5
24		7.07 ± 0.14	7.34 ± 0.07	0.5	3.6	95	3.5
25		7.14 ± 0.11	7.29 ± 0.07	0.7	3.3	95	3.8
26		7.04 ± 0.11	7.11 ± 0.09	0.9	2.9	104	4.1
27		7.06 ± 0.11	7.24 ± 0.06	0.7	3.1	95	4.0
28		6.96 ± 0.10	7.36 ± 0.14	0.4	4.2	95	2.8

[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.

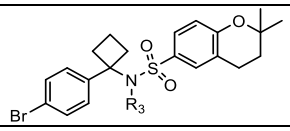
Introducing a phenyl group in **22**, a benzyl in **23**, and various substituted phenyl groups in **24-28** proved well-tolerated, indicating a substantial binding pocket for the R_2 group. Compound **23** exhibited greater potency than compound **22**, likely due to the higher lipophilicity and flexibility of the benzyl group. Analogs **24-28**, featuring electron-donating or withdrawing substituents, demonstrated similar potency, suggesting that the electronegativity

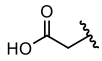
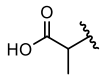
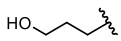
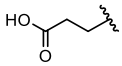
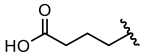
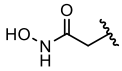
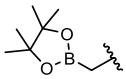
of the phenyl ring had no discernible effect on potency. Notably, these analogs were synthesized and evaluated as racemic mixtures, leaving uncertainty regarding whether the two enantiomers might differ in potency or selectivity. Since none of the variations exhibited significantly higher LipE than compound 6, further pursuit of these modifications was not undertaken.

3.2.2.3 Modification on R_3

To evaluate the significance of the acetic acid moiety, analogs **29-34** (Table 3.3) featuring different substituents on R_3 were examined. Introducing a methyl group on the Cα of the carboxyl and replacing the carboxyl with an alcohol resulted in inactive compounds **29** and **30**, respectively. The length of the linker between the carboxyl and the sulfonamide proved crucial for potency. Extended linkers led to diminished potency (**31**, **32**). Substituting the carboxyl with an *N*-hydroxylamide in **33** or a boronic acid pinacol ester in **34** drastically reduced potency. Although the analog featuring a boronic acid moiety was speculated to exhibit greater potency than its pinacol ester **34**, its synthesis was unsuccessful.

Table 3.3 Biochemical results and physicochemical properties of sulfonamides **6**, and **29-34**.[a]



ID	R_3	pIC_{50} DAGLβ	pIC_{50} DAGLα	Apparent selectivity	cLogD	tPSA (Å²)	LipE DAGLβ
6		7.34 ± 0.18	7.89 ± 0.11	0.3	2.3	95	5.0
29		< 5	< 5	n.d.	2.7	95	n.d.
30		< 5	< 5	n.d.	5.2	75	n.d.
31		5.04 ± 0.15	5.24 ± 0.10	0.6	2.8	95	2.2
32		< 5	< 5	n.d.	3.2	95	n.d.
33		5.16 ± 0.16	5.72 ± 0.06	0.3	3.9	104	1.3
34		5.41 ± 0.10	5.30 ± 0.05	1.3	6.2	73	< 0

[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.

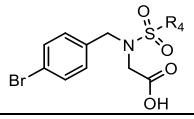
In summary, the acetic acid moiety emerged as a crucial functional group on R_3 for achieving high potency, indicating the presence of a small binding pocket in DAGL that forms specific interactions with the carboxyl, such as hydrogen bonding and/or ionic interactions.

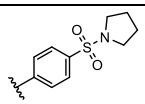
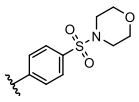
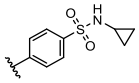
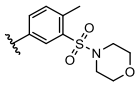
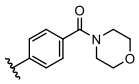
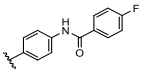
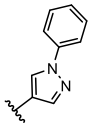
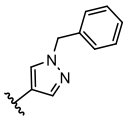
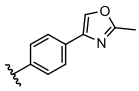
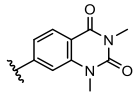
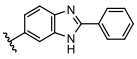
3.2.2.4 Modification on R_4

The influence of the R_4 group on potency and activity was insufficient in previous studies.[11,15] To extend the SAR study on R_4, a library containing 18 glycine sulfonamides (compounds **35-52**) was synthesized and evaluated (Table 3.4). The substituents on R_4 were selected based on the diversity, lipophilicity (cLogD < 5), polarity (tPSA < 140 $Å^2$), and molecular weight (MW < 600) of the corresponding final compounds. The cyclobutyl group on R_2 was removed to simplify the synthesis. Compound **35**, with a sulfonyl pyrrolidine on the *para* position, showed low potency, whereas the other analogs **36-38** with a sulfonamide on the phenyl ring were completely inactive. Compounds **39** and **40**, with an amide, **41** and **42** with a pyrazole, and **43-48** with different substituents on the phenyl group, were all inactive for DAGLβ, whereas compound **49**, with a quinoline ring, showed some activity for DAGLβ but not for DAGLα. Compounds **50-52** were active for both DAGL enzymes, and among them, **51** and **52** showed a selectivity of around 3-fold for DAGLβ over DAGLα. Most of the tested analogs were inactive for DAGL, indicating that the binding pocket of the R_4 substituents is quite restricted.

While most modifications on R_4 were not tolerated, the SAR analysis of this segment resulted in the development of several inhibitors (**49**, **51**, and **52**) that were the first to selectively target DAGLβ over DAGLα by a factor of ~3. Among these inhibitors, **52** exhibited the highest potency for DAGLβ, with a pIC_{50} of 6.72 ± 0.15 and a LipE of 4.9.

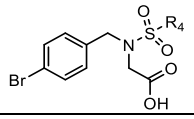
Table 3.4 Biochemical results and physicochemical properties of glycine sulfonamides **35-52**.[a]

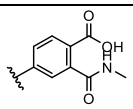
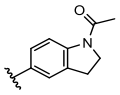
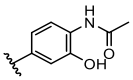
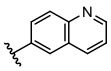
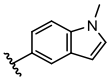
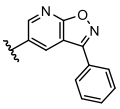
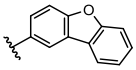


ID	R_4	pIC_{50} DAGLβ	pIC_{50} DAGLα	Apparent selectivity	cLogD	tPSA (Å^2)	LipE DAGLβ
35		5.16 ± 0.13	5.10 ± 0.08	1.1	-0.1	132	5.3
36		< 5	< 5	n.d.	-0.9	141	n.d.
37		< 5	< 5	n.d.	-0.3	140	n.d.
38		< 5	< 5	n.d.	-0.5	141	n.d.
39		< 5	< 5	n.d.	-0.3	115	n.d.
40		< 5	< 5	n.d.	1.3	115	n.d.
41		< 5	< 5	n.d.	-0.8	104	n.d.
42		< 5	< 5	n.d.	-0.5	104	n.d.
43		< 5	5.21 ± 0.07	n.d.	0.6	112	n.d.
44		< 5	< 5	n.d.	-0.5	127	n.d.
45		< 5	5.03 ± 0.36	n.d.	1.2	115	n.d.

[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 3.4 (continued) Biochemical results and physicochemical properties of glycine sulfonamides **35-52**.[a]



ID	R_4	pIC_{50} DAGLβ	pIC_{50} DAGLα	Apparent selectivity	cLogD	tPSA (Å^2)	LipE DAGLβ
46		< 5	5.08 ± 0.08	n.d.	-3.1	155	n.d.
47		< 5	5.36 ± 0.14	n.d.	0.2	106	n.d.
48		< 5	< 5	n.d.	-0.6	135	n.d.
49		5.45 ± 0.14	< 5	> 2.8	0.4	99	5.1
50		5.58 ± 0.06	6.04 ± 0.04	0.3	0.3	91	5.3
51		5.55 ± 0.11	5.02 ± 0.05	3.4	0.8	125	4.7
52		6.72 ± 0.15	6.29 ± 0.07	2.7	1.8	99	4.9

[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.

3.3 Conclusion

To summarize, this Chapter explored the structure-activity relationship (SAR) of glycine sulfonamides by systematically modifying the R_1-R_4 positions. A total of 51 analogs were synthesized and assessed for their biochemical potency against both DAGL enzymes using the EnzChek lipase substrate assay.

Notably, modifications in the R_1 position significantly affected potency, revealing a preference for *para* substituents on the phenyl ring over *meta* and *ortho* counterparts. It was observed that lipophilic substitutions were better tolerated compared to hydrophilic ones. Moreover, while replacing the cyclobutyl ring on the R_2 position with alkyl groups or phenyl rings retained potency, it did not enhance it. The acetic acid moiety (at R_3) emerged as a crucial substituent, presumably due to its pivotal ionic interactions with DAGL. On the other hand, modifications on the R_4 position were only moderately accepted. However, these modifications

proved instrumental in conferring selectivity, resulting in the first selective DAGLβ inhibitors (**49**, **51**, and **52**) in the glycine sulfonamide series. Out of the 51 compounds investigated in this Chapter, compound **52** stood out as the most potent and selective DAGLβ inhibitor.

3.4 Acknowledgements

Jonathan de Ruiter and Robin van der Woude are acknowledged for their contribution to the synthesis and biochemical evaluation of final compounds. Hans van den Elst is kindly acknowledged for preparative HPLC purification and HRMS measurements.

3.5 Experimental methods

Biology

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

The membrane fractions from HEK293T cells transiently overexpressing human DAGLα and DAGLβ were diluted to 1.5 µg/mL in assay buffer 1 (50 mM HEPES pH 7.5, 5% DMSO, 0.0025% Triton X-100) and 10 µL was pipetted into the dark flat-bottom 384-well plate (Greiner Bio-One, REF 781076). The membrane fraction from HEK293T cells transfected with empty pcDNA3.1 vector was used for the negative control (mock). Inhibitors were consecutively diluted in DMSO to 600 µM and in assay buffer 2 (50 mM HEPES pH 7.5, 0.0025% Triton X-100) to 30 µM. A dilution series (8 concentrations, 5× dilution each time) was prepared in assay buffer 1. 10 µL of inhibitor solution or assay buffer 1 was transferred to the enzyme samples in the assay plate. The plate was spun down at 1000 rpm for 1 min and incubated at rt for 30 min. The EnzChek lipase substrate was consecutively diluted in DMSO to 30 µM and in assay buffer 2 to 1.5 µM. 10 µL of EnzChek solution was added to each well. The plate was spun down at 1000 rpm for 1 min and incubated at rt for 3 h in the dark. The final concentrations of protein, EnzChek lipase substrate and inhibitors were 0.5 µg/mL, 0.5 µM and 10 µM -> 0.128 nM, respectively. Endpoint fluorescence was measured in CLARIOstar® (excitation 477-14 nm, emission 525-30 nm, gain = 1600). DAGL and mock membrane fractions with DMSO were used as positive and negative controls, respectively, to calculate the assay window. The mock membrane fraction with inhibitors at each concentration was used for background correction. Assay performance was assessed using Z' factor, which was calculated with the formula: $Z' = 1 - 3(\sigma_{pc} + \sigma_{nc})/(\mu_{pc} - \mu_{nc})$, where pc represents the positive control, nc represents the negative control, σ represents the standard deviation, and µ represents the mean value. Residual activity of DAGL was calculated using the equation: Residual activity (%) = $(\mu_{DAGL} - \mu_{mock})/(\mu_{pc} - \mu_{nc}) \times 100\%$, where μ_{DAGL} and μ_{mock} represent the fluorescence intensities of DAGL and mock with inhibitors, respectively. Residual activities were used to generate the dose-response curves using GraphPad Prism 9.0.0 (log(inhibitor) vs. normalized response with variable slope). All measurements were performed three times independently (n = 1, N = 3 or n = 4, N = 3 for controls, with $Z' \geq 0.6$).

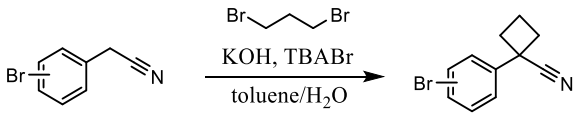
Chemistry

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.

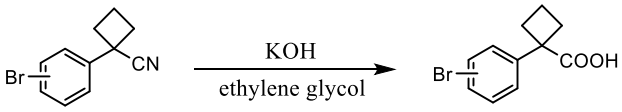
Liquid chromatography-mass spectrometry (LC-MS) analysis was performed on a Thermo Finnigan LCQ Advantage MAX ion-trap mass spectrometer (ESI^+) coupled to a Surveyor HPLC system equipped with a C18 column (50 × 4.6 mm, 3 µm particle size, Macherey-Nagel) or a Thermo Finnigan LCQ Fleet ion-trap mass 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.

General procedure A



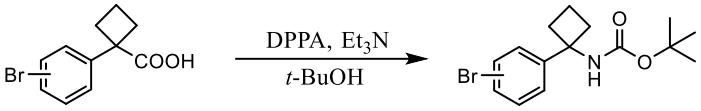
A mixture of corresponding phenyl acetonitrile (1 eq), 1,3-dibromopropane (1 eq) and TBABr (0.1 eq) in toluene (0.35 M) and solid KOH (8 eq) in H_2O (75% w/w) was heated to 100 °C with occasionally slow stirring to facilitate liquification of the aqueous phase. The reaction was then refluxed with continuous 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



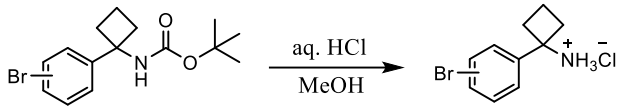
The mixture of corresponding nitrile (1 eq) and KOH (6 eq) in ethylene glycol (0.4-0.8 M) was refluxed for 2 h. The mixture was diluted in water and washed 1× with Et_2O. The pH of water layer was adjusted by 2 M aq. HCl solution to 2, which was then extracted 3× with EtOAc. Combined organic layers were dried by anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography to afford the product.

General procedure C



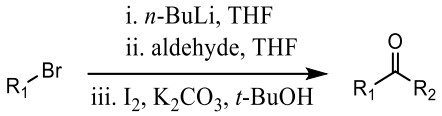
To a solution of corresponding carboxylic acid (1 eq) in anhydrous *t*-BuOH (0.08 M) with 4 Å molecular sieves was added diphenylphosphoryl azide (1 eq) and Et_3N (1.1 eq). The reaction was stirred at 30 °C for 1 h and then refluxed for overnight. The mixture was filtered and the filtrate was concentrated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

General procedure D



The corresponding Boc-protected amine (1 eq) was dissolved in 3 M aq. HCl in MeOH (0.04-0.3 M) and the reaction was stirred at rt for 24 h. The solvent was removed and the residue was washed 2× with Et_2O and filtered to afford the product.

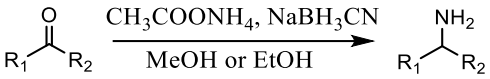
General procedure E



n-Butyllithium (2.5 M in hexane, 1.1 eq) was added dropwise to a solution of corresponding bromide (1 eq) in anhydrous THF (0.8 M) at -78 °C. The solution was allowed to stir for 30 min at -78 °C. After 30 min, corresponding aldehyde (1.05 eq) diluted in anhydrous THF (0.5 mL) was slowly added at -78 °C. The obtained mixture was warmed to rt and stirred at rt for 1 h. The mixture was concentrated under vacuum and subsequently I_2 (1.6 eq), K_2CO_3 (3 eq) and *t*-BuOH (0.67 M) were added. The mixture was allowed to reflux for 3 h. After completion, the reaction was quenched with sat. Na_2SO_3 and extracted with 3× with DCM. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The

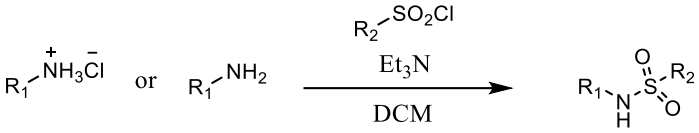
residue was purified by silica gel column chromatography to afford the product or directly used without purification.

General procedure F



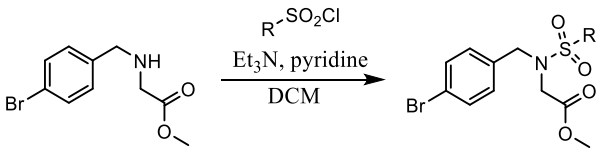
To a stirred solution of corresponding ketone (1 eq) in anhydrous MeOH or EtOH (5.0 mL) was added ammonium acetate (10-20 eq) and $NaBH_3CN$ (1.5-3 eq) at rt. The obtained mixture was refluxed for overnight. After completion, the mixture was concentrated under vacuum. The residue was quenched with 1 M aq. NaOH and extracted 3× with EtOAc. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The product was used in subsequent reactions without further purification.

General procedure G



To a solution of corresponding ammonium chloride or amine (1 eq) in anhydrous DCM at 0 °C was added Et_3N (3-5 eq) and corresponding sulfonyl chloride (1.1-2 eq). The reaction was stirred at rt for overnight. The mixture was diluted in 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 H

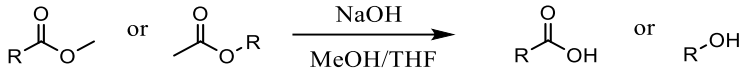


To a solution of methyl (4-bromobenzyl)glycinate (1 eq) in anhydrous DCM (0.1 M) was added Et_3N (4 eq), a drop of pyridine and corresponding sulfonyl chloride (1 eq). The reaction was stirred at rt until it was finished. The mixture was diluted in water or 0.2 M aq. HCl and extracted 3× with DCM. Combined 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

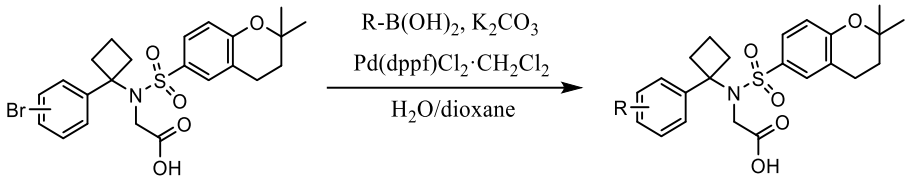
To a solution of corresponding sulfonamide (1 eq) in anhydrous DMF (0.1 M) was added corresponding alkyl bromide (1.5-3 eq) and 2-(*tert*-butylimino)-*N*,*N*-diethyl-1,3-dimethyl-1,3,2λ^5-diazaphosphinan-2-amine (BEMP, 1 M in hexane, 1.5-3 eq). The reaction was heated to 80 °C until the reaction was completed. The reaction 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 or directly used without purification.

General procedure J



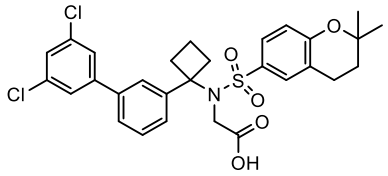
To a solution of corresponding ester (1 eq) in MeOH/THF (1:1, 0.1 M) was added 1 M or 2 M aq. NaOH (2-5 eq) and the reaction was stirred at rt until completion. The mixture was diluted in 0.1 M aq. HCl and extracted 3× with EtOAc. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography or preparative HPLC to afford the product.

General procedure K



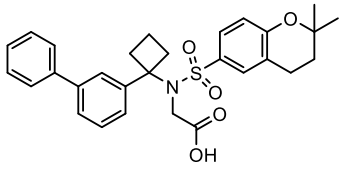
In a microwave vial containing glycine sulfonamide (1 eq) was added corresponding boronic acid (1.2-1.5 eq), K_2CO_3 (5 eq) and degassed H_2O/dioxane (1:1, 0.1 M). The mixture was degassed with N_2 and Pd(dppf)Cl_2·CH_2Cl_2 (0.05 eq) was added. The reaction was heated to 80-85 °C until completion. The 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-(3',5'-Dichloro-[1,1'-biphenyl]-3-yl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (2)



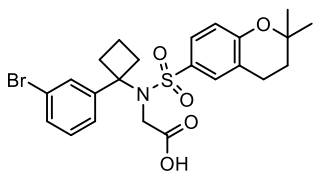
The title compound was synthesized according to general procedure **K** using _N_-(1-(3-bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**4**, 30 mg, 0.059 mmol, 1 eq), (3,5-dichlorophenyl)boronic acid (17 mg, 0.089 mmol, 1.5 eq), K_2CO_3 (40.8 mg, 0.295 mmol, 5 eq) and Pd(dppf)Cl_2·CH_2Cl_2 (2.40 mg, 2.95 µmol, 0.05 eq). Total time: 4 h at 80 °C. Silica gel column chromatography (1-7% MeOH in DCM) and preparative HPLC afforded the product as a white powder (17 mg, 0.030 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 1H), 7.47 – 7.37 (m, 3H), 7.33 (t, _J_ = 1.8 Hz, 1H), 7.24 (dd, _J_ = 8.7, 2.5 Hz, 1H), 7.22 (d, _J_ = 1.9 Hz, 2H), 6.86 (d, _J_ = 2.4 Hz, 1H), 6.65 (d, _J_ = 8.7 Hz, 1H), 4.16 (s, 2H), 2.94 – 2.82 (m, 2H), 2.66 – 2.57 (m, 2H), 2.49 (t, _J_ = 6.7 Hz, 2H), 1.91 – 1.81 (m, 1H), 1.72 – 1.57 (m, 3H), 1.23 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.62, 157.90, 143.89, 143.52, 138.77, 135.46, 130.70, 129.30, 128.95, 127.44, 127.10, 126.92, 126.49, 126.21, 125.67, 121.01, 117.46, 75.71, 65.80, 48.38, 35.28, 32.18, 26.87, 22.30, 14.85. HRMS $[C_{29}H_{29}Cl_2NO_5S+Na]^+$: 596.10357/598.10059 calculated, 596.10330/598.10039 found.

_N_-(1-([1,1'-Biphenyl]-3-yl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (3)



The title compound was synthesized according to general procedure **K** using _N_-(1-(3-bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**4**, 37 mg, 0.073 mmol, 1 eq)**,** phenylboronic acid (13.3 mg, 0.109 mmol, 1.5 eq), K_2CO_3 (50.5 mg, 0.365 mmol, 5 eq) and Pd(dppf)Cl_2·CH_2Cl_2 (2.98 mg, 3.65 µmol, 0.05 eq). Total time: 4 h at 80 °C. Silica gel column chromatography (1-7% MeOH in DCM) and preparative HPLC afforded the product as a white powder (12 mg, 0.024 mmol, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (t, _J_ = 1.8 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.44 – 7.31 (m, 6H), 7.23 (dd, _J_ = 8.7, 2.5 Hz, 1H), 6.80 (d, _J_ = 2.4 Hz, 1H), 6.61 (d, _J_ = 8.7 Hz, 1H), 4.10 (s, 2H), 2.94 – 2.80 (m, 2H), 2.73 – 2.57 (m, 2H), 2.45 (t, _J_ = 6.7 Hz, 2H), 1.92 – 1.77 (m, 1H), 1.71 – 1.61 (m, 1H), 1.58 (t, _J_ = 6.7 Hz, 2H), 1.19 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.14, 157.90, 142.96, 141.41, 140.81, 130.14, 129.43, 128.96, 128.70, 127.60, 127.17, 127.11, 126.37, 126.32, 125.92, 121.15, 117.29, 75.68, 65.95, 48.48, 35.40, 32.13, 26.90, 22.24, 14.95. HRMS $[C_{29}H_{31}NO_5S+Na]^+$: 528.18151 calculated, 528.18139 found.

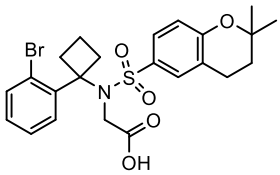
_N_-(1-(3-Bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (4)



The title compound was synthesized according to general procedure **J** using methyl _N_-(1-(3-bromophen-yl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (**61a**, 68 mg, 0.13 mmol, 1 eq) and 2 M aq. NaOH (0.26 mL, 0.52 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (1-10% MeOH in DCM) afforded the product as a white powder (43 mg, 0.085 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.36

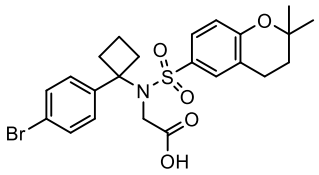
(d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 6.88 (s, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 4.10 (s, 2H), 2.98 – 2.81 (m, 2H), 2.66 – 2.42 (m, 4H), 1.87 – 1.69 (m, 3H), 1.64 – 1.49 (m, 1H), 1.31 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.76, 157.74, 145.15, 130.83, 130.60, 130.34, 129.74, 129.21, 126.88, 125.83, 122.45, 121.07, 117.35, 75.69, 65.31, 48.65, 35.16, 32.36, 27.03, 22.30, 14.82. HRMS $[C_{23}H_{26}BrNO_5S+Na]^+$: 530.06073/532.05863 calculated, 530.06064/532.05847 found.

_N_-(1-(2-Bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (5)



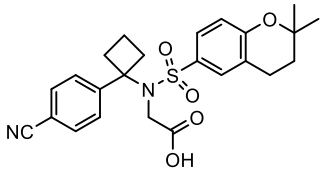
The title compound was synthesized according to general procedure **J** using methyl *N*-(1-(2-bromophenyl)cyclobutyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (**61b**, 22 mg, 0.042 mmol, 1 eq) and 2 M aq. NaOH (83.0 µL, 0.166 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (1-7% MeOH in DCM) afforded the product as a white powder (10 mg, 0.020 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.9 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.58 (s, 1H), 6.49 (d, *J* = 8.7 Hz, 1H), 4.46 (s, 2H), 3.19 – 2.99 (m, 2H), 2.78 (bs, 2H), 2.49 (t, *J* = 6.6 Hz, 2H), 1.90 – 1.78 (m, 1H), 1.72 (t, *J* = 6.7 Hz, 2H), 1.54 – 1.41 (m, 1H), 1.30 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.36, 157.27, 139.45, 134.43, 130.98, 128.76, 128.51, 126.82, 126.29, 124.85, 120.37, 116.97, 75.42, 66.85, 51.62 (br), 35.41, 32.41, 26.83, 22.27, 15.16. HRMS $[C_{23}H_{26}BrNO_5S+Na]^+$: 530.06073/532.05863 calculated, 530.06062/532.05844 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (6)



The title compound was synthesized according to general procedure **J** using methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (**61c**, 438 mg, 0.838 mmol, 1 eq) and 1 M aq. NaOH (3 mL, 3 mmol, 3.6 eq). Total time: 30 min at 90 °C. The product was afforded as a white solid (426 mg, 0.838 mmol, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.34 – 7.24 (m, 3H), 6.86 (d, *J* = 2.3 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 4.06 (s, 2H), 2.87 – 2.76 (m, 2H), 2.62 (t, *J* = 6.7 Hz, 2H), 2.57 – 2.49 (m, 2H), 1.88 – 1.77 (m, 3H), 1.65 – 1.52 (m, 1H), 1.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.85, 157.89, 141.51, 131.35, 130.69, 129.31, 129.22, 126.89, 121.64, 121.30, 117.50, 75.88, 65.41, 48.12, 35.14, 32.37, 26.97, 22.34, 14.76. HRMS $[C_{23}H_{26}BrNO_5S+NH_4]^+$: 525.10533/527.10323 calculated, 525.10553/527.10339 found.

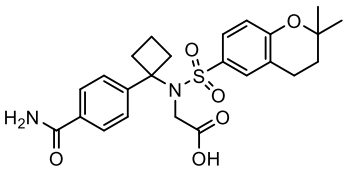
_N_-(1-(4-Cyanophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (7)



i-PrOH (0.14 mL), H_2O (0.35 mL), Na_2CO_3 (52 mg, 0.49 mmol, 2.5 eq), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 0.1 eq), Potassium hexacyanoferrate(II) trihydrate (25 mg, 0.059 mmol, 0.3 eq) and *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**6**, 100 mg, 0.197 mmol, 1 eq) were sequentially added to a microwave tube

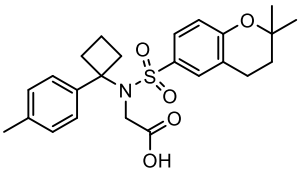
equipped with DMF (2.4 mL, 0.08 M). The mixture was degassed under argon and heated to 100 °C overnight. The mixture was diluted in 0.1 M aq. HCl and extracted 3× with EtOAc. Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC to afford the product as a white solid (40 mg, 0.088 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 4H), 7.26 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 4.13 (s, 2H), 2.90 – 2.80 (m, 2H), 2.62 (t, *J* = 6.7 Hz, 2H), 2.58 – 2.49 (m, 2H), 1.90 – 1.77 (m, 3H), 1.65 – 1.53 (m, 1H), 1.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.97, 158.05, 148.11, 132.01, 130.93, 129.19, 128.16, 126.71, 121.20, 118.67, 117.71, 111.23, 75.98, 65.50, 48.09, 34.82, 32.26, 26.93, 22.35, 14.63. HRMS $[C_{24}H_{26}N_2O_5S+Na]^+$: 477.14546 calculated, 477.14539 found.

_N_-(1-(4-Carbamoylphenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (8)



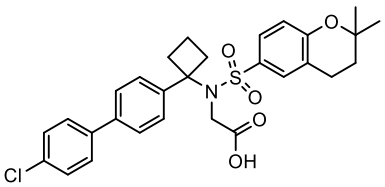
A solution of *N*-(1-(4-cyanophenyl)cyclobutyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**7**, 20 mg, 0.044 mmol, 1 eq) in MeOH (3.0 mL, 0.015 M) was treated with 30% H_2O_2 (13 µL, 0.12 mmol, 2.7 eq) and 2 M aq. NaOH (50 µL, 0.10 mmol, 2.3 eq). The reaction was stirred at rt until completion. 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 preparative HPLC to afford the product as a white solid (8.0 mg, 0.017 mmol, 39%). ^{1}H NMR (400 MHz, DMSO) δ 7.94 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.35 (s, 1H), 7.17 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.64 – 6.58 (m, 2H), 4.05 (s, 2H), 2.81 – 2.70 (m, 2H), 2.49 – 2.41 (m, 4H), 1.78 – 1.61 (m, 3H), 1.48 – 1.37 (m, 1H), 1.23 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 171.74, 167.38, 156.65, 145.64, 132.77, 131.10, 128.58, 127.00, 126.84, 126.22, 120.86, 116.57, 75.50, 64.66, 48.03, 34.68, 31.49, 26.54, 21.40, 14.25. HRMS $[C_{24}H_{28}N_2O_6S+Na]^+$: 495.15603 calculated, 495.15569 found.

_N_-((2,2-Dimethylchroman-6-yl)sulfonyl)-_N_-(1-(*p*-tolyl)cyclobutyl)glycine (9)



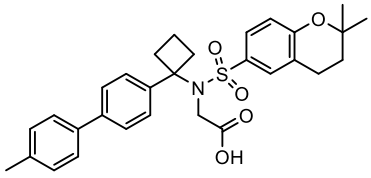
The title compound was synthesized according to general procedure **K** using *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**6**, 38 mg, 0.075 mmol, 1 eq), methylboronic acid (6.7 mg, 0.12 mmol, 1.5 eq), K_2CO_3 (31 mg, 0.22 mmol, 3 eq) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (6.0 mg, 7.4 µmol, 0.098 eq). Total time: overnight at 80 °C. Silica gel column chromatography (20-40% EtOAc in *n*-pentane) afforded the product as a white solid (25 mg, 0.056 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.24 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 3.98 (s, 2H), 2.87 – 2.75 (m, 2H), 2.64 – 2.53 (m, 4H), 2.34 (s, 3H), 1.85 – 1.75 (m, 3H), 1.63 – 1.53 (m, 1H), 1.33 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.62, 157.78, 139.29, 137.32, 130.65, 129.59, 129.05, 127.21, 127.19, 121.12, 117.35, 75.71, 65.77, 48.12, 35.12, 32.37, 26.93, 22.30, 21.21, 14.92. HRMS $[C_{24}H_{29}NO_5S+Na]^+$: 466.16586 calculated, 466.16591 found.

_N_-(1-(4'-Chloro-[1,1'-biphenyl]-4-yl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (10)



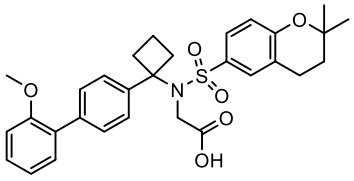
The title compound was synthesized according to general procedure **K** using _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**6**, 40 mg, 0.079 mmol, 1 eq), (4-chlorophenyl)boronic acid (15 mg, 0.094 mmol, 1.2 eq), K_2CO_3 (54.4 mg, 0.393 mmol, 5 eq) and Pd(dppf)Cl_2·CH_2Cl_2 (3.2 mg, 3.9 µmol, 0.05 eq). Total time: 2 h at 85 °C. Preparative HPLC afforded the product as a white solid (12 mg, 0.022 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.35 (m, 8H), 7.21 (d, _J_ = 8.1 Hz, 1H), 7.00 (s, 1H), 6.61 (d, _J_ = 8.6 Hz, 1H), 4.06 (s, 2H), 2.97 – 2.80 (m, 2H), 2.60 (t, _J_ = 8.7 Hz, 2H), 2.51 (t, _J_ = 6.2 Hz, 2H), 1.91 – 1.74 (m, 1H), 1.70 – 1.54 (m, 3H), 1.24 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.83, 157.72, 141.86, 138.96, 138.86, 133.71, 130.85, 129.44, 129.14, 128.31, 127.90, 127.04, 126.65, 121.11, 117.40, 75.70, 65.62, 48.39, 35.15, 32.21, 26.86, 22.28, 14.93. HRMS $[C_{29}H_{30}ClNO_5S+Na]^+$: 562.14254 calculated, 562.14264 found.

_N_-((2,2-Dimethylchroman-6-yl)sulfonyl)-_N_-(1-(4'-methyl-[1,1'-biphenyl]-4-yl)cyclobutyl)glycine (11)



The title compound was synthesized according to general procedure **K** using _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**6**, 40 mg, 0.079 mmol, 1 eq), _p_-tolylboronic acid (13 mg, 0.094 mmol, 1.2 eq), K_2CO_3 (54.4 mg, 0.393 mmol, 5 eq) and Pd(dppf)Cl_2·CH_2Cl_2 (3.2 mg, 3.9 µmol, 0.05 eq). Total time: 2 h at 85 °C. Preparative HPLC afforded the product as a white solid (19 mg, 0.037 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.42 (m, 6H), 7.31 – 7.23 (m, 2H), 7.21 (dd, _J_ = 8.6, 2.1 Hz, 1H), 6.97 (d, _J_ = 2.4 Hz, 1H), 6.62 (d, _J_ = 8.7 Hz, 1H), 4.05 (s, 2H), 2.85 (q, _J_ = 10.6 Hz, 2H), 2.61 (t, _J_ = 8.4 Hz, 2H), 2.51 (t, _J_ = 6.6 Hz, 2H), 2.40 (s, 3H), 1.84 (q, _J_ = 9.8 Hz, 1H), 1.70 – 1.59 (m, 3H), 1.24 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.83, 157.74, 140.98, 140.23, 137.48, 137.42, 130.64, 129.68, 129.51, 127.71, 127.06, 126.92, 126.61, 121.19, 117.36, 75.69, 65.70, 48.27, 35.21, 32.19, 26.86, 22.26, 21.27, 14.94. HRMS $[C_{30}H_{33}NO_5S+Na]^+$: 542.19716 calculated, 542.19702 found.

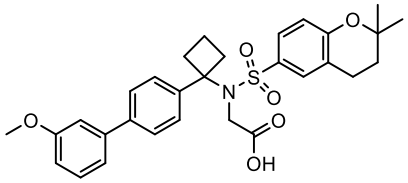
_N_-((2,2-Dimethylchroman-6-yl)sulfonyl)-_N_-(1-(2'-methoxy-[1,1'-biphenyl]-4-yl)cyclobutyl)glycine (12)



The title compound was synthesized according to general procedure **K** using _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**6**, 40 mg, 0.079 mmol, 1 eq), (2-methoxyphenyl)boronic acid (17.9 mg, 0.118 mmol, 1.5 eq), K_2CO_3 (54.4 mg, 0.393 mmol, 5 eq) and Pd(dppf)Cl_2·CH_2Cl_2 (3.2 mg, 3.9 µmol, 0.05 eq). Total time: 2 h at 85 °C. Preparative HPLC afforded the product as a white solid (14 mg, 0.026 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.42 (m, 4H), 7.38 – 7.30 (m, 2H), 7.15 – 7.09 (m, 2H), 7.04 (td, _J_ = 7.5, 1.0 Hz, 1H), 7.00 (d, _J_ = 8.6 Hz, 1H), 6.66 – 6.59 (m, 1H), 4.03

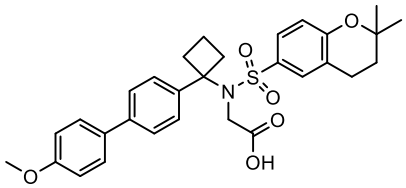
(s, 2H), 3.84 (s, 3H), 2.93 – 2.81 (m, 2H), 2.68 – 2.57 (m, 4H), 1.90 – 1.79 (m, 1H), 1.73 – 1.61 (m, 3H), 1.26 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.76, 157.76, 156.57, 140.76, 137.79, 130.97, 130.63, 129.84, 129.66, 129.44, 128.91, 127.14, 126.86, 121.14, 121.00, 117.50, 111.30, 75.68, 65.88, 55.57, 48.29, 35.14, 32.29, 26.89, 22.25, 14.98. HRMS $[C_{30}H_{33}NO_6S+Na]^+$: 558.19208 calculated, 558.19175 found.

_N_-((2,2-Dimethylchroman-6-yl)sulfonyl)-_N_-(1-(3'-methoxy-[1,1'-biphenyl]-4-yl)cyclobutyl)glycine (13)



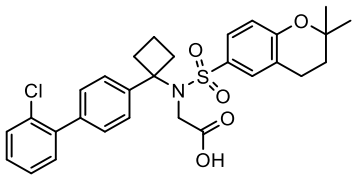
The title compound was synthesized according to general procedure **K** using _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**6**, 40 mg, 0.079 mmol, 1 eq), (3-methoxyphenyl)boronic acid (15.5 mg, 0.102 mmol, 1.3 eq), K_2CO_3 (54.4 mg, 0.393 mmol, 5 eq) and Pd(dppf)Cl_2·CH_2Cl_2 (3.2 mg, 3.9 µmol, 0.05 eq). Total time: 2 h at 85 °C. Preparative HPLC afforded the product as a white solid (5.0 mg, 9.3 µmol, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 4H), 7.37 (t, _J_ = 7.9 Hz, 1H), 7.20 – 7.14 (m, 2H), 7.13 – 7.11 (m, 1H), 6.95 (d, _J_ = 1.7 Hz, 1H), 6.91 (dd, _J_ = 8.5, 2.8 Hz, 1H), 6.61 (d, _J_ = 8.7 Hz, 1H), 4.05 (s, 2H), 3.88 (s, 3H), 2.85 (q, _J_ = 10.6 Hz, 2H), 2.63 (t, _J_ = 8.3 Hz, 2H), 2.50 (t, _J_ = 6.7 Hz, 2H), 1.85 (q, _J_ = 9.6 Hz, 1H), 1.70 – 1.58 (m, 3H), 1.23 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.94, 160.13, 157.84, 141.89, 141.47, 140.19, 130.30, 129.98, 129.54, 127.72, 127.08, 126.92, 121.22, 119.61, 117.42, 112.94, 112.91, 75.74, 65.74, 55.47, 48.40, 35.29, 32.18, 26.85, 22.27, 14.97. HRMS $[C_{30}H_{33}NO_6S+Na]^+$: 558.19208 calculated, 558.19171 found.

_N_-((2,2-Dimethylchroman-6-yl)sulfonyl)-_N_-(1-(4'-methoxy-[1,1'-biphenyl]-4-yl)cyclobutyl)glycine (14)



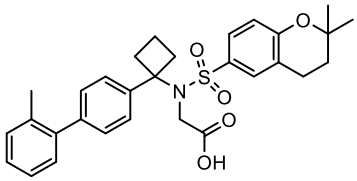
The title compound was synthesized according to general procedure **K** using _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**6**, 40 mg, 0.079 mmol, 1 eq), (4-methoxyphenyl)boronic acid (15.5 mg, 0.102 mmol, 1.3 eq), K_2CO_3 (54.4 mg, 0.393 mmol, 5 eq) and Pd(dppf)Cl_2·CH_2Cl_2 (3.2 mg, 3.9 µmol, 0.05 eq). Total time: 2 h at 85 °C. Preparative HPLC afforded the product as a white solid (8.0 mg, 0.015 mmol, 19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H), 7.45 (s, 4H), 7.22 (dd, _J_ = 8.7, 2.4 Hz, 1H), 7.01 – 6.95 (m, 3H), 6.63 (d, _J_ = 8.7 Hz, 1H), 4.05 (s, 2H), 3.86 (s, 3H), 2.90 – 2.79 (m, 2H), 2.65 – 2.56 (m, 2H), 2.51 (t, _J_ = 6.7 Hz, 2H), 1.89 – 1.79 (m, 1H), 1.70 – 1.57 (m, 3H), 1.23 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.65, 159.42, 157.74, 140.59, 139.88, 132.88, 130.66, 129.52, 128.11, 127.73, 127.05, 126.33, 121.20, 117.37, 114.39, 75.70, 65.69, 55.51, 48.27, 35.20, 32.19, 26.85, 22.26, 14.93. HRMS $[C_{30}H_{33}NO_6S+Na]^+$: 558.19208 calculated, 558.19175 found.

_N_-(1-(2'-Chloro-[1,1'-biphenyl]-4-yl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (15)



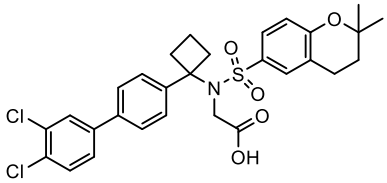
The title compound was synthesized according to general procedure **K** using _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**6**, 40 mg, 0.079 mmol, 1 eq), (2-chlorophenyl)boronic acid (18.5 mg, 0.118 mmol, 1.5 eq), K_2CO_3 (54.4 mg, 0.393 mmol, 5 eq) and Pd(dppf)Cl_2·CH_2Cl_2 (3.2 mg, 3.9 µmol, 0.05 eq). Total time: 2 h at 85 °C. Preparative HPLC afforded the product as a white solid (28 mg, 0.052 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 3H), 7.39 (d, _J_ = 8.4 Hz, 2H), 7.36 – 7.27 (m, 4H), 7.05 (dd, _J_ = 8.7, 2.1 Hz, 1H), 6.62 (d, _J_ = 8.7 Hz, 1H), 4.03 (s, 2H), 2.94 – 2.82 (m, 2H), 2.71 – 2.60 (m, 4H), 1.91 – 1.80 (m, 1H), 1.73 (t, _J_ = 6.7 Hz, 2H), 1.69 – 1.62 (m, 1H), 1.28 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.71, 157.87, 141.73, 139.87, 138.60, 132.50, 131.59, 130.62, 130.26, 129.76, 129.49, 128.79, 127.11, 127.07, 126.93, 121.12, 117.69, 75.77, 65.86, 48.24, 35.08, 32.30, 26.94, 22.38, 15.01. HRMS $[C_{29}H_{30}ClNO_5S+Na]^+$: 562.14254 calculated, 562.14210 found.

_N_-((2,2-Dimethylchroman-6-yl)sulfonyl)-_N_-(1-(2'-methyl-[1,1'-biphenyl]-4-yl)cyclobutyl)glycine (16)



The title compound was synthesized according to general procedure **K** using _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**6**, 40 mg, 0.079 mmol, 1 eq), _o_-tolylboronic acid (11 mg, 0.079 mmol, 1 eq), K_2CO_3 (54.4 mg, 0.393 mmol, 5 eq) and Pd(dppf)Cl_2·CH_2Cl_2 (3.2 mg, 3.9 µmol, 0.05 eq). Total time: 2 h at 85 °C. Preparative HPLC afforded the product as a white solid (24 mg, 0.046 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 2H), 7.33 (d, _J_ = 2.4 Hz, 1H), 7.30 – 7.20 (m, 6H), 7.11 (dd, _J_ = 8.7, 2.4 Hz, 1H), 6.62 (d, _J_ = 8.7 Hz, 1H), 4.03 (s, 2H), 2.95 – 2.82 (m, 2H), 2.71 – 2.56 (m, 4H), 2.31 (s, 3H), 1.89 – 1.79 (m, 1H), 1.74 (t, _J_ = 6.7 Hz, 2H), 1.70 – 1.59 (m, 1H), 1.29 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.93, 157.83, 141.26, 141.20, 140.79, 135.43, 130.90, 130.60, 129.98, 129.77, 129.20, 127.49, 127.10, 126.94, 125.96, 121.11, 117.57, 75.77, 65.87, 48.16, 34.99, 32.30, 26.94, 22.39, 20.75, 14.98. HRMS $[C_{30}H_{33}NO_5S+Na]^+$: 542.19716 calculated, 542.19694 found.

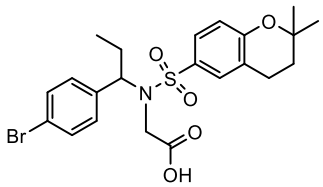
_N_-(1-(3',4'-Dichloro-[1,1'-biphenyl]-4-yl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (17)



The title compound was synthesized according to general procedure **K** using _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**6**, 40 mg, 0.079 mmol, 1 eq), (3,4-dichlorophenyl)boronic acid (22.5 mg, 0.118 mmol, 1.5 eq), K_2CO_3 (54.4 mg, 0.393 mmol, 5 eq) and Pd(dppf)Cl_2·CH_2Cl_2 (3.2 mg, 3.9 µmol, 0.05 eq). Total time: 2 h at 85 °C. Preparative HPLC afforded the product as a white solid (24 mg, 0.042 mmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, _J_ = 2.1 Hz, 1H), 7.55 – 7.47

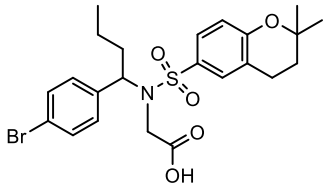
(m, 3H), 7.47 – 7.38 (m, 3H), 7.22 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.06 (d, *J* = 2.3 Hz, 1H), 6.63 (d, *J* = 8.7 Hz, 1H), 4.08 (s, 2H), 2.91 – 2.79 (m, 2H), 2.64 – 2.50 (m, 4H), 1.91 – 1.78 (m, 1H), 1.67 (t, *J* = 6.7 Hz, 2H), 1.65 – 1.57 (m, 1H), 1.27 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.95, 157.78, 142.43, 140.48, 137.80, 133.07, 131.78, 130.98, 130.93, 129.40, 128.88, 128.01, 127.00, 126.69, 126.33, 121.13, 117.46, 75.77, 65.60, 48.20, 35.04, 32.25, 26.87, 22.33, 14.85. HRMS $[C_{29}H_{29}Cl_2NO_5S+Na]^+$: 596.10357 calculated, 596.10313 found.

N-(1-(4-Bromophenyl)propyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (18)



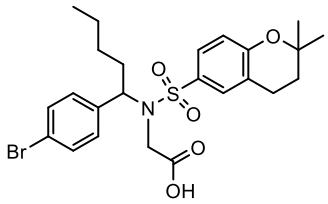
The title compound was synthesized according to general procedure **J** using methyl *N*-(1-(4-bromophenyl)propyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (**65a**, 10 mg, 0.020 mmol, 1 eq) and 2 M aq. NaOH (39 µL, 0.078 mmol, 4 eq). Total time: 2 h at rt. Preparative HPLC afforded the product as a white powder (5 mg, 0.01 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.45 (s, 1H), 7.39 – 7.33 (m, 2H), 6.97 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 1H), 4.72 (t, *J* = 7.7 Hz, 1H), 3.99 – 3.71 (m, 2H), 2.74 (t, *J* = 6.7 Hz, 2H), 1.90 (p, *J* = 7.5 Hz, 2H), 1.83 (t, *J* = 6.7 Hz, 2H), 1.36 (s, 6H), 0.80 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.34, 136.70, 131.76, 130.14, 130.00, 129.82, 127.40, 122.27, 121.64, 117.96, 75.97, 62.27, 45.39, 32.34, 26.93, 25.01, 22.40, 11.37. HRMS $[C_{22}H_{26}BrNO_5S+Na]^+$: 518.06073/520.05862 calculated, 518.06075/520.05854 found.

N-(1-(4-Bromophenyl)butyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (19)



The title compound was synthesized according to general procedure **J** using methyl *N*-(1-(4-bromophenyl)butyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (**65b**, 55.0 mg, 0.105 mmol, 1 eq) and 2 M aq. NaOH (0.21 mL, 0.42 mmol, 4 eq). Total time: 2 h at rt. Preparative HPLC afforded the product as a white powder (28 mg, 0.055 mmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.04 – 6.97 (m, 2H), 6.83 (d, *J* = 8.7 Hz, 1H), 4.81 (dd, *J* = 9.3, 6.0 Hz, 1H), 4.01 – 3.72 (m, 2H), 2.76 (t, *J* = 6.7 Hz, 2H), 1.92 – 1.80 (m, 3H), 1.77 – 1.67 (m, 1H), 1.36 (s, 6H), 1.29 – 1.12 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.98, 158.28, 136.76, 131.71, 130.26, 130.12, 129.92, 127.44, 122.27, 121.56, 117.90, 75.93, 60.00, 44.79, 33.58, 32.34, 26.91, 22.41, 19.74, 13.81. HRMS $[C_{23}H_{28}BrNO_5S+Na]^+$: 532.07638/534.07428 calculated, 532.07636/534.07413 found.

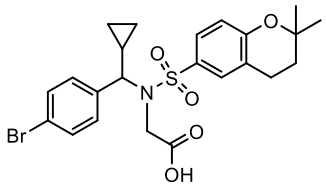
N-(1-(4-Bromophenyl)pentyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (20)



The title compound was synthesized according to general procedure **J** using methyl *N*-(1-(4-bromophenyl)pentyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (**65c**, 39 mg, 0.072 mmol, 1 eq) and 2 M aq. NaOH (139 µL, 0.278 mmol, 3.9 eq). Total time: 2 h at rt. Silica gel column chromatography (2-10% MeOH in DCM) afforded the product as a white powder (10.7 mg, 20.4 µmol, 29%). ^{1}H NMR (400 MHz,

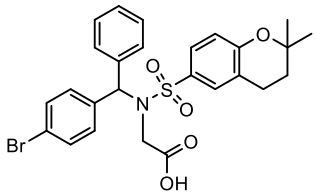
$CDCl_3$) δ 7.57 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.43 – 7.35 (m, 2H), 7.07 – 7.01 (m, 2H), 6.84 (d, *J* = 8.6 Hz, 1H), 4.83 (dd, *J* = 9.3, 6.1 Hz, 1H), 3.98 – 3.73 (m, 2H), 2.77 (t, *J* = 6.8 Hz, 2H), 1.91 – 1.69 (m, 4H), 1.36 (s, 6H), 1.30 – 1.06 (m, 4H), 0.80 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.88, 158.42, 136.79, 133.59, 131.83, 130.13, 129.94, 127.50, 122.38, 121.62, 118.00, 75.99, 60.46, 44.89, 32.35, 31.21, 28.76, 26.96, 26.93, 22.46, 14.02. HRMS $[C_{24}H_{30}BrNO_5S+Na]^+$: 546.09203/548.08993 calculated, 546.09222/548.09010 found.

_N_-((4-Bromophenyl)(cyclopropyl)methyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (21)



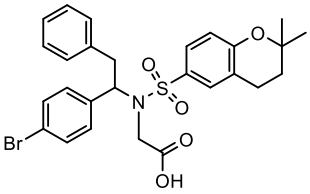
The title compound was synthesized according to general procedure **J** using methyl *N*-((4-bromophenyl)(cyclopropyl)methyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (**65d**, 38 mg, 0.073 mmol, 1 eq) and 2 M aq. NaOH (141 µL, 0.282 mmol, 3.9 eq). Total time: 2 h at rt. Silica gel column chromatography (2-10% MeOH in DCM) afforded the product as a white powder (8.2 mg, 0.016 mmol, 22%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.41 – 7.31 (m, 3H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 1H), 4.17 (d, *J* = 3.8 Hz, 1H), 4.16 – 3.86 (m, 2H), 2.77 – 2.65 (m, 2H), 1.83 (t, *J* = 6.7 Hz, 2H), 1.36 (s, 3H), 1.35 (s, 3H), 1.23 – 1.17 (m, 1H), 0.79 – 0.68 (m, 1H), 0.68 – 0.58 (m, 1H), 0.46 – 0.36 (m, 1H), 0.33 – 0.24 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.43, 138.03, 131.59, 129.94, 129.75, 127.37, 122.02, 121.60, 117.97, 114.17, 76.02, 66.17, 46.36, 32.32, 26.94, 22.41, 14.35, 6.37, 5.88. HRMS $[C_{23}H_{26}BrNO_5S+Na]^+$: 530.06073/532.05863 calculated, 530.06076/532.05860 found.

_N_-((4-Bromophenyl)(phenyl)methyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (22)



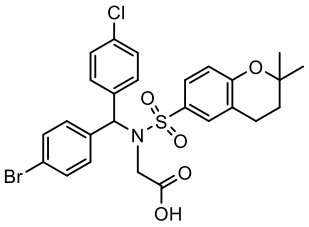
The title compound was synthesized according to general procedure **J** using methyl *N*-((4-bromophenyl)(phenyl)methyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)-glycinate (**65e**, 34 mg, 0.061 mmol, 1 eq) and 1 M aq. NaOH (237 µL, 0.237 mmol, 3.9 eq). Total time: 4 h at rt. Preparative HPLC afforded the product as a white powder (9.5 mg, 0.017 mmol, 29%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.39 – 7.32 (m, 3H), 7.26 – 7.19 (m, 3H), 7.05 – 6.99 (m, 2H), 6.98 – 6.92 (m, 2H), 6.77 (d, *J* = 8.7 Hz, 1H), 6.20 (s, 1H), 4.04 (s, 2H), 2.63 (t, *J* = 6.7 Hz, 2H), 1.80 (t, *J* = 6.7 Hz, 2H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.46, 158.33, 137.45, 137.31, 131.54, 130.67, 130.28, 129.51, 129.08, 128.66, 128.30, 127.53, 122.04, 121.41, 117.77, 75.93, 64.61, 46.74, 32.32, 26.94, 26.90, 22.33. HRMS $[C_{26}H_{26}BrNO_5S+Na]^+$: 566.06073/568.05864 calculated, 566.06065/568.05846 found.

_N_-(1-(4-Bromophenyl)-2-phenylethyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (23)



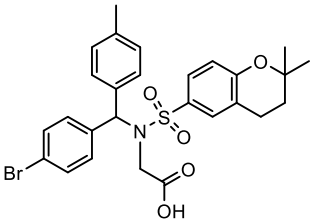
The title compound was synthesized according to general procedure **J** using methyl _N_-(1-(4-bromophenyl)-2-phenylethyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (**65f**, 83.2 mg, 0.145 mmol, 1 eq) and 2 M aq. NaOH (291 µL, 0.582 mmol, 4 eq). Total time: 4 h at rt. Silica gel column chromatography (30-70% dist. EtOAc in _n_-heptane with a drop of conc. HCl) afforded the product as a white powder (35 mg, 0.063 mmol, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, _J_ = 8.7, 2.4 Hz, 1H), 7.48 (d, _J_ = 2.3 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.20 – 7.09 (m, 3H), 7.07 – 6.99 (m, 4H), 6.80 (d, _J_ = 8.7 Hz, 1H), 5.14 (dd, _J_ = 9.8, 5.6 Hz, 1H), 4.15 – 3.74 (m, 2H), 3.28 – 3.15 (m, 2H), 2.73 (t, _J_ = 6.7 Hz, 2H), 1.81 (t, _J_ = 6.7 Hz, 2H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.01, 158.34, 137.24, 135.82, 131.67, 130.53, 130.01, 129.94, 129.13, 128.61, 127.41, 126.70, 122.45, 121.57, 118.00, 75.96, 61.79, 45.39, 37.97, 32.30, 27.00, 26.87, 22.41. HRMS $[C_{27}H_{28}BrNO_5S+Na]^+$: 580.07638/582.07430 calculated, 580.07598/582.07388 found.

_N_-((4-Bromophenyl)(4-chlorophenyl)methyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (24)



The title compound was synthesized according to general procedure **J** using methyl _N_-((4-bromophenyl)(4-chlorophenyl)methyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (**65g**, 63.2 mg, 0.107 mmol, 1 eq) and 2 M aq. NaOH (213 µL, 0.426 mmol, 4 eq). Total time: 4 h at rt. Silica gel column chromatography (30-70% dist. EtOAc in _n_-heptane with a drop of conc. HCl) afforded the product as a white powder (37 mg, 0.064 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, _J_ = 8.7, 2.4 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.23 – 7.16 (m, 2H), 7.02 – 6.96 (m, 2H), 6.96 – 6.90 (m, 2H), 6.77 (d, _J_ = 8.7 Hz, 1H), 6.14 (s, 1H), 4.03 (s, 2H), 2.63 (t, _J_ = 6.7 Hz, 2H), 1.80 (t, _J_ = 6.7 Hz, 2H), 1.35 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.36, 158.34, 136.75, 136.13, 134.15, 131.66, 130.67, 130.42, 130.15, 129.54, 128.72, 127.43, 122.30, 121.44, 117.81, 75.97, 64.01, 46.72, 32.28, 26.90, 26.87, 22.32. HRMS $[C_{26}H_{25}BrClNO_5S+Na]^+$: 600.02176/602.01948 calculated, 600.02139/602.01905 found.

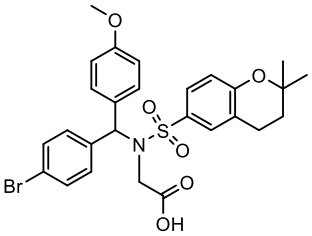
_N_-((4-Bromophenyl)(_p_-tolyl)methyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (25)



The title compound was synthesized according to general procedure **J** using methyl _N_-((4-bromophenyl)(_p_-tolyl)methyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (**65h**, 67.5 mg, 0.118 mmol, 1 eq) and 2 M aq. NaOH (236 µL, 0.472 mmol, 4 eq). Total time: overnight at rt. Silica gel column chromatography (30-70% dist. EtOAc in _n_-heptane with a drop of conc. HCl) afforded the product as a white powder (46 mg, 0.083 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, _J_ = 8.6, 2.4 Hz, 1H), 7.38 (d, _J_ = 2.3 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.03 (d, _J_ = 7.9 Hz, 2H), 6.99 – 6.94 (m, 2H), 6.92 – 6.86

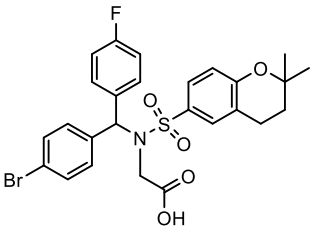
(m, 2H), 6.76 (d, *J* = 8.6 Hz, 1H), 6.14 (s, 1H), 4.02 (s, 2H), 2.63 (t, *J* = 6.7 Hz, 2H), 2.29 (s, 3H), 1.80 (t, *J* = 6.7 Hz, 2H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.62, 158.20, 138.14, 137.58, 134.35, 131.40, 130.54, 130.24, 129.62, 129.30, 129.05, 127.49, 121.83, 121.34, 117.68, 75.86, 64.36, 46.68, 32.30, 26.90, 26.83, 22.30, 21.16. HRMS $[C_{27}H_{28}BrNO_5S+Na]^+$: 580.07638/582.07430 calculated, 580.07598/582.07388 found.

_N_-((4-Bromophenyl)(4-methoxyphenyl)methyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (26)



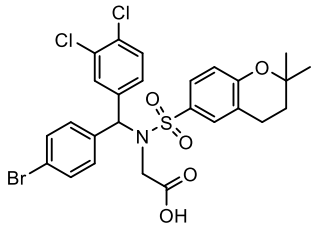
The title compound was synthesized according to general procedure **J** using methyl *N*-((4-bromophenyl)(4-methoxyphenyl)methyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)-glycinate (**65i**, 96.8 mg, 0.164 mmol, 1 eq) and 2 M aq. NaOH (329 µL, 0.658 mmol, 4 eq). Total time: 4 h at rt. The obtained residue was purified by silica gel column chromatography (30-70% dist. EtOAc in *n*-heptane with a drop of conc. HCl) afforded the product as a white powder (61.0 mg, 0.106 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.01 – 6.89 (m, 4H), 6.80 – 6.70 (m, 3H), 6.12 (s, 1H), 4.10 – 3.94 (m, 2H), 3.75 (s, 3H), 2.70 – 2.57 (m, 2H), 1.80 (t, *J* = 6.7 Hz, 2H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.55, 159.44, 158.18, 137.69, 131.40, 130.55, 130.36, 130.21, 129.67, 129.34, 127.43, 121.73, 121.34, 117.68, 113.91, 75.87, 64.14, 55.36, 46.64, 32.27, 26.89, 26.83, 22.28. HRMS $[C_{27}H_{28}BrNO_6S+Na]^+$: 596.07129/598.06923 calculated, 596.07091/598.06877 found.

_N_-((4-Bromophenyl)(4-fluorophenyl)methyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (27)



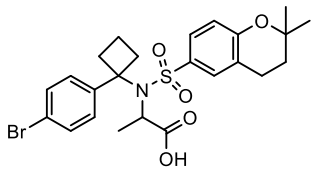
The title compound was synthesized according to general procedure **J** using methyl *N*-((4-bromophenyl)(4-fluorophenyl)methyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)-glycinate (**65j**, 36 mg, 0.062 mmol, 1 eq) and 2 M aq. NaOH (125 µL, 0.250 mmol, 4 eq). Total time: 4 h at rt. Silica gel column chromatography (30-70% dist. EtOAc in *n*-heptane with a drop of conc. HCl) afforded the product as a white powder (22 mg, 0.040 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.08 – 6.97 (m, 2H), 6.99 – 6.86 (m, 4H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.17 (s, 1H), 4.15 – 3.93 (m, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 1.80 (t, *J* = 6.7 Hz, 2H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.19, 162.49 (d, $J_{C\text{-}F}$ = 248.1 Hz), 158.35, 137.03, 133.36 (d, $J_{C\text{-}F}$ = 3.2 Hz), 131.64, 130.97 (d, $J_{C\text{-}F}$ = 8.2 Hz), 130.50, 130.18, 129.56, 127.45, 122.17, 121.44, 117.81, 115.53 (d, $J_{C\text{-}F}$ = 21.6 Hz), 75.97, 63.95, 46.61, 32.29, 26.91, 26.86, 22.32. HRMS $[C_{26}H_{25}BrFNO_5S+Na]^+$: 584.05131/586.04923 calculated, 584.05116/586.04896 found.

_N_-((4-Bromophenyl)(3,4-dichlorophenyl)methyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (28)



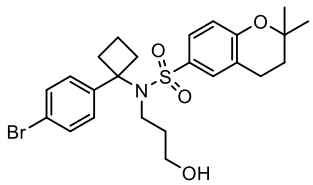
The title compound was synthesized according to general procedure **J** using methyl _N_-((4-bromophenyl)(3,4-dichlorophenyl)methyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (**65k**, 22 mg, 0.036 mmol, 1 eq) and 2 M aq. NaOH (71 µL, 0.14 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (30-70% dist. EtOAc in _n_-heptane with a drop of conc. HCl) afforded the product as a white powder (13.4 mg, 21.8 µmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, _J_ = 8.6 Hz, 1H), 7.39 (d, _J_ = 7.2 Hz, 3H), 7.31 (d, _J_ = 8.2 Hz, 1H), 7.09 (d, _J_ = 1.9 Hz, 1H), 6.97 – 6.89 (m, 3H), 6.79 (d, _J_ = 8.5 Hz, 1H), 6.12 (s, 1H), 4.04 (s, 2H), 2.66 (t, _J_ = 6.0 Hz, 2H), 1.81 (t, _J_ = 6.6 Hz, 2H), 1.35 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.14, 158.57, 137.97, 136.05, 132.82, 132.37, 131.92, 130.81, 130.50, 130.07, 129.31, 128.17, 127.48, 122.75, 121.61, 117.93, 76.08, 63.64, 46.66, 32.27, 26.95, 22.38. HRMS $[C_{26}H_{24}BrCl_2NO_5S+NH_4]^+$: 629.02739/631.02520 calculated, 629.02721/631.02471 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)alanine (29)



The title compound was synthesized according to general procedure **J** using methyl _N_-(1-(4-bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)alaninate (**66a**, 23 mg, 0.043 mmol, 1 eq) and 2 M aq. NaOH (86 µL, 0.17 mmol, 4 eq). Total time: overnight at rt. Preparative HPLC afforded the product (9.0 mg, 0.017 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, _J_ = 8.7, 2.5 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.37 – 7.30 (m, 2H), 7.17 (d, _J_ = 2.4 Hz, 1H), 6.76 (d, _J_ = 8.7 Hz, 1H), 4.24 (q, _J_ = 7.1 Hz, 1H), 3.04 – 2.90 (m, 2H), 2.69 (t, _J_ = 6.7 Hz, 2H), 2.48 – 2.38 (m, 2H), 1.83 (t, _J_ = 6.8 Hz, 2H), 1.80 – 1.71 (m, 1H), 1.54 (d, _J_ = 7.2 Hz, 3H), 1.53 – 1.41 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.27, 157.84, 142.22, 132.55, 131.25, 129.72, 129.67, 127.01, 121.56, 121.21, 117.65, 75.89, 65.83, 56.22, 35.33, 34.89, 32.41, 27.58, 26.96, 22.42, 18.02, 15.12. HRMS $[C_{24}H_{28}BrNO_5S+Na]^+$: 544.07638/546.07428 calculated, 544.07626/546.07410 found.

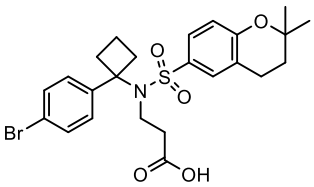
_N_-(1-(4-Bromophenyl)cyclobutyl)-_N_-(3-hydroxypropyl)-2,2-dimethylchromane-6-sulfonamide (30)



The title compound was synthesized according to general procedure **J** using 3-((_N_-(1-(4-bromophenyl)cyclobutyl)-2,2-dimethylchromane)-6-sulfonamido)propyl acetate (**66b**, 58.0 mg, 0.105 mmol, 1 eq) and 2 M aq. NaOH (0.2 mL, 0.4 mmol, 3.8 eq). Total time: 4 h at rt. Silica gel column chromatography (20-30 % EtOAc in _n_-pentane) afforded the product (48 mg, 0.094 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 4H), 7.33 (dd, _J_ = 8.7, 2.5 Hz, 1H), 6.99 (d, _J_ = 2.5 Hz, 1H), 6.73 (d, _J_ = 8.6 Hz, 1H), 3.61 (q, _J_ = 4.7 Hz, 2H), 3.37 (t, _J_ = 7.1 Hz, 2H), 2.75 – 2.63 (m, 4H), 2.57 – 2.46 (m, 2H), 2.08 (t, _J_ = 4.5 Hz, 1H), 1.81 (t, _J_ = 6.7 Hz, 2H), 1.77 – 1.69 (m, 3H), 1.60 – 1.50 (m, 1H), 1.34 (s, 6H). ^{13}C NMR (101 MHz,

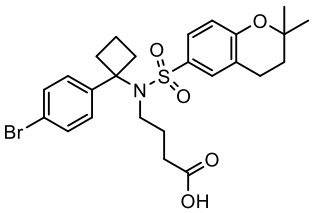
$CDCl_3$) δ 157.47, 142.95, 131.95, 131.31, 129.11, 128.90, 126.49, 121.33, 117.48, 75.75, 65.23, 59.66, 44.20, 35.14, 33.99, 32.41, 26.97, 22.41, 14.52. HRMS $[C_{24}H_{30}BrNO_4S+Na]^+$: 530.09711/532.09501 calculated, 530.09721/532.09496 found.

3-((*N*-(1-(4-Bromophenyl)cyclobutyl)-2,2-dimethylchromane)-6-sulfonamido)propanoic acid (31)



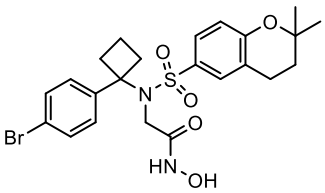
Jones reagent was added dropwise to a solution of *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-(3-hydroxypropyl)-2,2-dimethylchromane-6-sulfonamide (**30**, 10 mg, 0.020 mmol, 1 eq) in acetone (0.60 mL, 0.33 M) at 0 °C until the color remained orange. 2-propanol was added until the orange color disappeared and only green suspension remained. The mixture was filtered and the filtrate was diluted in water 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 (50% EtOAc in *n*-pentane) to afford the product (6.0 mg, 0.011 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.39 – 7.34 (m, 2H), 7.30 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 8.6 Hz, 1H), 3.51 – 3.42 (m, 2H), 2.78 – 2.70 (m, 2H), 2.69 – 2.60 (m, 4H), 2.59 – 2.52 (m, 2H), 1.81 (t, *J* = 6.7 Hz, 2H), 1.78 – 1.71 (m, 1H), 1.63 – 1.51 (m, 1H), 1.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.33, 157.66, 142.32, 131.50, 131.13, 129.03, 126.70, 121.58, 121.40, 117.50, 75.81, 65.46, 42.39, 36.02, 35.35, 32.40, 26.99, 22.40, 14.46. HRMS $[C_{24}H_{28}BrNO_5S+Na]^+$: 544.07638/546.07428 calculated, 544.07639/546.07415 found.

4-((*N*-(1-(4-Bromophenyl)cyclobutyl)-2,2-dimethylchromane)-6-sulfonamido)butanoic acid (32)



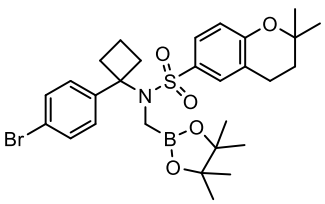
The title compound was synthesized according to general procedure **J** using methyl 4-((*N*-(1-(4-bromophenyl)cyclobutyl)-2,2-dimethylchromane)-6-sulfonamido)butanoate (**66c**, 22 mg, 0.040 mmol, 1 eq) and 2 M aq. NaOH (0.1 mL, 0.2 mmol, 5 eq). Total time: 4 h at rt. Silica gel column chromatography (20-40% EtOAc in *n*-pentane with a drop of conc. HCl) afforded the product (12 mg, 0.022 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 4H), 7.28 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 3.26 – 3.19 (m, 2H), 2.76 – 2.66 (m, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.58 – 2.49 (m, 2H), 2.35 (t, *J* = 6.9 Hz, 2H), 2.01 – 1.91 (m, 2H), 1.80 (t, *J* = 6.7 Hz, 2H), 1.77 – 1.73 (m, 1H), 1.62 – 1.52 (m, 1H), 1.33 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.52, 157.46, 142.66, 131.64, 131.31, 129.14, 129.00, 126.65, 121.33, 121.28, 117.36, 75.74, 65.38, 46.52, 35.49, 32.41, 31.12, 26.97, 26.26, 22.39, 14.67. HRMS $[C_{25}H_{30}BrNO_5S+Na]^+$: 558.09203/560.08994 calculated, 558.09202/560.08982 found.

2-((*N*-(1-(4-Bromophenyl)cyclobutyl)-2,2-dimethylchromane)-6-sulfonamido)-*N*-hydroxyacetamide (33)



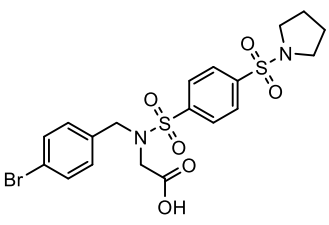
To a solution of *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycine (**6**, 40 mg, 0.079 mmol, 1 eq) in anhydrous DMF (1 mL, 0.08 M) was added EDCI (22.6 mg, 0.118 mmol, 1.5 eq), HOBt (15.9 mg, 0.118 mmol, 1.5 eq), DIPEA (41 µL, 0.236 mmol, 3 eq) and hydroxylammonium chloride (8.2 mg, 0.12 mmol, 1.5 eq). The reaction was stirred at rt for overnight. The mixture was diluted in water and extracted 3× with EtOAc. Combined organic layers were washed with sat. $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC to afford the product (11 mg, 0.021 mmol, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (bs, 1H), 7.42 – 7.36 (m, 2H), 7.31 – 7.25 (m, 2H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.66 – 6.55 (m, 2H), 3.91 (s, 2H), 2.82 – 2.67 (m, 2H), 2.65 – 2.51 (m, 4H), 1.88 – 1.80 (m, 1H), 1.77 (t, *J* = 6.7 Hz, 2H), 1.61 – 1.51 (m, 1H), 1.31 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.19, 158.25, 140.98, 131.53, 129.36, 129.05, 128.34, 127.18, 121.92, 121.60, 117.53, 76.01, 65.66, 48.68, 35.75, 32.27, 26.96, 22.28, 14.87. HRMS $[C_{23}H_{27}BrN_2O_5S+H]^+$: 523.08968/525.08758 calculated, 523.08964/525.08757 found.

***N*-(1-(4-Bromophenyl)cyclobutyl)-2,2-dimethyl-*N*-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)chromane-6-sulfonamide (34)**



The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-2,2-dimethylchromane-6-sulfonamide (**60c**, 92 mg, 0.20 mmol, 1 eq), 2-(bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (90 mg, 0.41 mmol, 2 eq) and BEMP (1 M in hexane, 0.41 mL, 0.41 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (5-10% EtOAc in *n*-pentane) afforded the product (105 mg, 0.178 mmol, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.39 – 7.34 (m, 4H), 7.16 (d, *J* = 2.4 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 2.78 – 2.71 (m, 2H), 2.66 (t, *J* = 6.6 Hz, 2H), 2.64 (s, 2H), 2.48 – 2.42 (m, 2H), 1.80 (t, *J* = 6.8 Hz, 2H), 1.73 – 1.67 (m, 1H), 1.54 – 1.47 (m, 1H), 1.33 (s, 6H), 1.26 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.25, 141.74, 131.83, 130.99, 129.33, 127.32, 121.14, 120.83, 117.10, 84.06, 75.53, 65.43, 34.60, 32.50, 31.93, 26.98, 24.95, 22.37, 14.38. HRMS $[C_{28}H_{37}BBrNO_5S+Na]^+$: 612.15661/614.15415 calculated, 612.15545/614.15335.

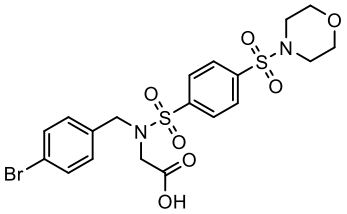
***N*-(4-Bromobenzyl)-*N*-((4-(pyrrolidin-1-ylsulfonyl)phenyl)sulfonyl)glycine (35)**



The title compound was synthesized according to general procedure **J** using methyl *N*-(4-bromobenzyl)-*N*-((4-(pyrrolidin-1-ylsulfonyl)phenyl)sulfonyl)glycinate (**68a**, 10 mg, 0.019 mmol, 1 eq) and 2 M aq. NaOH (38 µL, 0.076 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (2-4% MeOH in DCM) afforded the product (2.0 mg, 3.9 µmol, 21%). ^{1}H NMR (400 MHz, DMSO) δ 8.11 – 8.03 (m,

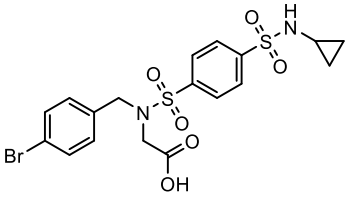
2H), 7.98 – 7.91 (m, 2H), 7.54 – 7.47 (m, 2H), 7.25 – 7.17 (m, 2H), 4.47 (s, 2H), 3.78 (s, 2H), 3.21 – 3.13 (m, 4H), 1.72 – 1.61 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 169.56, 143.79, 139.59, 135.55, 131.34, 130.40, 128.15, 127.97, 120.81, 50.37, 48.49, 47.95, 24.81. HRMS $[C_{19}H_{21}BrN_2O_6S_2+H]^+$: 517.00972/519.00754 calculated , 517.00956/519.00730 found.

***N*-(4-Bromobenzyl)-*N*-((4-(morpholinosulfonyl)phenyl)sulfonyl)glycine (36)**



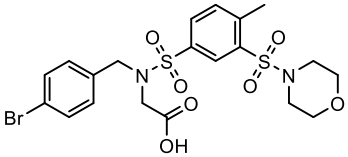
The title compound was synthesized according to general procedure **J** using methyl *N*-(4-bromobenzyl)-*N*-((4-(morpholinosulfonyl)-phenyl)sulfonyl)glycinate (**68b**, 10 mg, 0.018 mmol, 1 eq) and 2 M aq. NaOH (36 µL, 0.072 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (30-70% dist. EtOAc in *n*-heptane with a drop of conc. HCl) afforded the product (4.2 mg, 7.9 µmol, 43%). ^{1}H NMR (400 MHz, DMSO) δ 8.14 – 8.07 (m, 2H), 7.93 – 7.87 (m, 2H), 7.55 – 7.47 (m, 2H), 7.24 – 7.18 (m, 2H), 4.46 (s, 2H), 3.96 (s, 2H), 3.69 – 3.62 (m, 4H), 2.95 – 2.88 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 169.54, 143.81, 138.15, 135.21, 131.37, 130.45, 128.50, 128.19, 120.98, 65.31, 50.85, 48.04, 45.88. HRMS $[C_{19}H_{21}BrN_2O_7S_2+H]^+$: 533.00463/535.00247 calculated, 533.00438/535.00232 found.

***N*-(4-Bromobenzyl)-*N*-((4-(*N*-cyclopropylsulfamoyl)phenyl)sulfonyl)glycine (37)**



The title compound was synthesized according to general procedure **J** using methyl *N*-(4-bromobenzyl)-*N*-((4-(N-cyclopropylsulfamoyl)-phenyl)sulfonyl)glycinate (**68c**, 15 mg, 0.028 mmol, 1 eq) and 2 M aq. NaOH (56.0 µL, 0.112 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (30-70% dist. EtOAc in *n*-heptane with a drop of conc. HCl) afforded the product (8.0 mg, 0.016 mmol, 56%). ^{1}H NMR (400 MHz, DMSO) δ 8.18 (d, *J* = 2.7 Hz, 1H), 8.12 – 8.05 (m, 2H), 8.01 – 7.93 (m, 2H), 7.55 – 7.47 (m, 2H), 7.26 – 7.19 (m, 2H), 4.44 (s, 2H), 3.94 (s, 2H), 2.18 – 2.08 (m, 1H), 0.56 – 0.45 (m, 2H), 0.43 – 0.35 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 169.53, 143.95, 142.97, 135.25, 131.36, 130.46, 128.06, 127.69, 120.97, 50.83, 47.95, 24.10, 5.20. HRMS $[C_{18}H_{19}BrN_2O_6S_2+H]^+$: 502.99407/504.99189 calculated, 502.99354/504.99125 found.

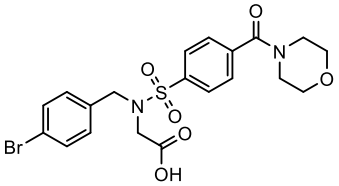
***N*-(4-bromobenzyl)-*N*-((4-methyl-3-(morpholinosulfonyl)phenyl)sulfonyl)glycine (38)**



The title compound was synthesized according to general procedure **J** using methyl *N*-(4-bromobenzyl)-*N*-((4-methyl-3-(morpholinosulfonyl)phenyl)sulfonyl)glycinate (**68d**, 9.2 mg, 0.016 mmol, 1 eq) and 2 M aq. NaOH (32 µL, 0.064 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (30-50 % dist. EtOAc in *n*-heptane with a drop of conc. HCl) afforded the product (8.6 mg, 0.016 mmol, 96%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 8.31 (d, *J* = 2.0 Hz, 1H), 7.97 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.56 – 7.53 (m, 1H), 7.48 – 7.41 (m, 2H), 7.21 – 7.13 (m, 2H), 4.45 (s, 2H), 3.92 (s, 2H), 3.75 – 3.68 (m, 4H), 3.22 – 3.15 (m, 4H), 2.70 (s, 3H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 170.52, 143.90, 139.00,

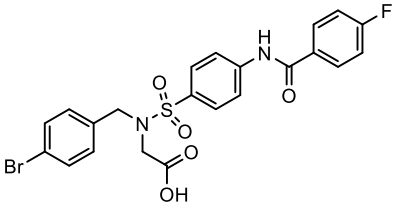
137.00, 134.52, 134.38, 132.45, 132.10, 130.83, 129.70, 122.76, 66.83, 51.18, 47.12, 45.89, 21.10. HRMS $[C_{20}H_{23}BrN_2O_7S_2+H]^+$: 547.02028/549.01813 calculated, 547.02015/549.01787 found.

_N_-(4-Bromobenzyl)-_N_-((4-(morpholine-4-carbonyl)phenyl)sulfonyl)glycine (39)



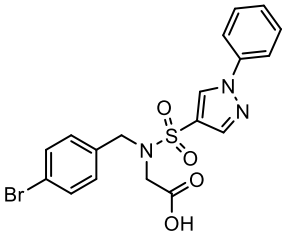
The title compound was synthesized according to general procedure **J** using methyl *N*-(4-bromobenzyl)-*N*-((4-(morpholine-4-carbonyl)phenyl)sulfonyl)glycinate (**68e**, 27 mg, 0.054 mmol, 1 eq) and 2 M aq. NaOH (113 µL, 0.216 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (30-70% dist. EtOAc in *n*-heptane) afforded the product (14 mg, 0.027 mmol, 51%). ^{1}H NMR (400 MHz, DMSO) δ 7.89 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 4.41 (s, 2H), 3.92 (s, 2H), 3.75 – 3.18 (m, 8H). ^{13}C NMR (101 MHz, DMSO) δ 169.67, 167.67, 140.21, 139.70, 135.36, 131.25, 130.46, 127.68, 127.30, 120.84, 65.99, 50.85, 48.46, 47.53, 41.96. HRMS $[C_{20}H_{21}BrN_2O_6S+H]^+$: 497.03765/499.03554 calculated, 497.03737/499.03520 found.

_N_-(4-Bromobenzyl)-_N_-((4-(4-fluorobenzamido)phenyl)sulfonyl)glycine (40)



The title compound was synthesized according to general procedure **J** using methyl *N*-(4-bromobenzyl)-*N*-((4-(4-fluorobenzamido)phenyl)sulfonyl)glycinate (**68f**, 101 mg, 0.188 mmol, 1 eq), 2 M aq. NaOH (564 µL, 0.564 mmol, 3 eq). Total time: 2 h at rt. Silica gel column chromatography (20-40% EtOAc in *n*-pentane with a drop of conc. HCl) afforded the product (23 mg, 0.044 mmol, 23%). ^{1}H NMR (400 MHz, DMSO) δ 10.65 (s, 1H), 8.11 – 8.02 (m, 2H), 8.02 – 7.95 (m, 2H), 7.88 – 7.80 (m, 2H), 7.56 – 7.49 (m, 2H), 7.49 – 7.35 (m, 2H), 7.28 – 7.20 (m, 2H), 4.38 (s, 2H), 3.84 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 169.75, 165.01, 164.34 (d, J_{C-F} = 251.1), 143.17, 135.68, 133.59, 131.30, 130.94 (d, J_{C-F} = 2.8 Hz), 130.68 (d, J_{C-F} = 9.2 Hz), 130.50, 128.23, 120.81, 119.83, 115.51 (d, J_{C-F} = 22.1 Hz), 50.81, 47.96. HRMS $[C_{22}H_{18}BrFN_2O_5S+H]^+$: 521.01766/523.01556 calculated, 521.01750/523.01528 found.

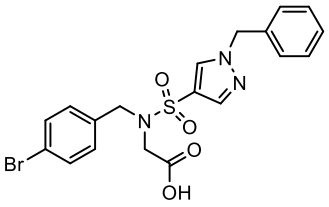
_N_-(4-Bromobenzyl)-_N_-((1-phenyl-1_H_-pyrazol-4-yl)sulfonyl)glycine (41)



The title compound was synthesized according to general procedure **J** using methyl *N*-(4-bromobenzyl)-*N*-((1-phenyl-1*H*-pyrazol-4-yl)sulfonyl)glycinate (**68g**, 74.5 mg, 0.160 mmol, 1 eq), 2 M aq. NaOH (481 µL, 0.481 mmol, 3 eq). Total time: 2 h at rt. Silica gel column chromatography (20-40% EtOAc in *n*-pentane with a drop of conc. HCl) afforded the product (58.3 mg, 0.129 mmol, 81%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 8.46 (d, *J* = 0.7 Hz, 1H), 7.99 (d, *J* = 0.7 Hz, 1H), 7.73 – 7.61 (m, 2H), 7.52 – 7.34 (m, 5H), 7.24 – 7.16 (m, 2H), 4.42 (s, 2H), 3.94 (s, 2H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 170.98, 140.42, 139.37, 134.53, 132.23, 130.68, 130.06, 130.01, 128.50, 123.94, 122.54, 120.27, 51.04,

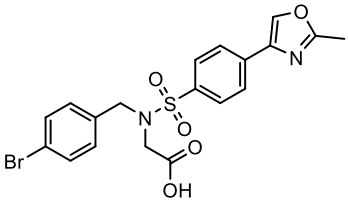
47.40. HRMS $[C_{18}H_{16}BrN_3O_4S+H]^+$: 450.01177/452.00965 calculated, 450.01152/452.00927 found.

N-((1-Benzyl-1*H*-pyrazol-4-yl)sulfonyl)-*N*-(4-bromobenzyl)glycine (42)



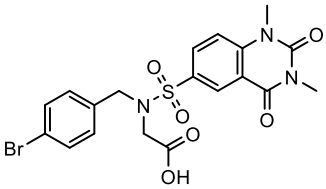
The title compound was synthesized according to general procedure **J** from methyl *N*-((1-benzyl-1*H*-pyrazol-4-yl)sulfonyl)-*N*-(4-bromobenzyl)glycinate (**68h**, 18 mg, 0.038 mmol, 1 eq) and 2 M aq. NaOH (56.5 µL, 0.113 mmol, 3 eq). Total time: 2 h at rt. Silica gel column chromatography (10-40% EtOAc in *n*-pentane with a drop of conc. HCl) afforded the product (13 mg, 0.028 mmol,74%). ^{1}H NMR (400 MHz, $CDCl_3$+MeOD) δ 7.95 – 7.82 (m, 2H), 7.50 – 7.11 (m, 9H), 5.32 (s, 2H), 4.38 (s, 2H), 3.90 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$+MeOD) δ 170.65, 139.21, 134.65, 134.10, 131.86, 131.80, 130.23, 129.09, 128.73, 128.03, 122.13, 122.00, 56.60, 50.51, 46.84. HRMS $[C_{19}H_{18}BrN_3O_4S+H]^+$: 464.02742/ 466.02530 calculated, 464.02752/466.02538 found.

N-(4-Bromobenzyl)-*N*-((4-(2-methyloxazol-4-yl)phenyl)sulfonyl)glycine (43)



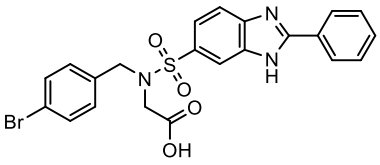
The title compound was synthesized according to general procedure **J** using methyl *N*-(4-bromobenzyl)-*N*-((4-(2-methyloxazol-4-yl)phenyl)sulfonyl)glycinate (**68i**, 19 mg, 0.039 mmol, 1 eq) and 2 M aq. NaOH (78.0 µL, 0.156 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (20-50% dist. EtOAc in *n*-heptane with a drop of conc. HCl) afforded the product (8.8 mg, 0.019 mmol, 48%). ^{1}H NMR (400 MHz, DMSO) δ 8.68 (s, 1H), 7.99 – 7.82 (m, 4H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 4.40 (s, 2H), 3.88 (s, 2H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.65, 161.99, 138.36, 138.08, 136.73, 135.49, 135.24, 131.27, 130.45, 127.74, 125.44, 120.82, 50.80, 47.84, 13.55. HRMS $[C_{19}H_{17}BrN_2O_5S+H]^+$: 465.01143/467.00932 calculated, 465.01124/467.00905 found.

N-(4-Bromobenzyl)-*N*-((1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)sulfonyl)glycine (44)



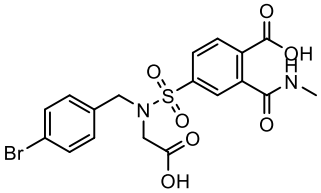
The title compound was synthesized according to general procedure **J** using methyl *N*-(4-bromobenzyl)-*N*-((1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)sulfonyl)-glycinate (**68j**, 31 mg, 0.061 mmol, 1 eq) and 2 M aq. NaOH (122 µL, 0.244 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (20-80% dist. EtOAc in *n*-heptane with a drop of conc. HCl) afforded the product (19 mg, 0.039 mmol, 63%). ^{1}H NMR (400 MHz, DMSO) δ 8.29 (d, *J* = 2.3 Hz, 1H), 8.16 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.24 – 7.16 (m, 2H), 4.40 (s, 2H), 3.95 (s, 2H), 3.56 (s, 3H), 3.32 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.79, 160.50, 150.45, 143.18, 135.25, 133.50, 133.23, 131.33, 130.48, 127.16, 120.88, 115.83, 114.60, 50.88, 48.19, 31.14, 28.39. HRMS $[C_{19}H_{18}BrN_3O_6S+H]^+$: 496.01725/498.01515 calculated, 496.01697/498.01467 found.

_N_-(4-Bromobenzyl)-_N_-((2-phenyl-1_H_-benzo[_d_]imidazol-6-yl)sulfonyl)glycine (45)



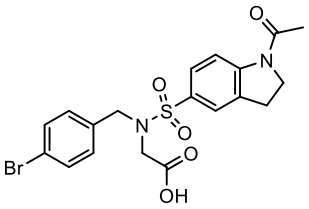
The title compound was synthesized according to general procedure **J** using methyl _N_-(4-bromobenzyl)-_N_-((2-phenyl-1_H_-benzo[_d_]imidazol-6-yl)sulfonyl)glycinate (**68k**, 17 mg, 0.034 mmol, 1 eq) and 2 M aq. NaOH (68.0 µL, 0.136 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (4-10% MeOH in DCM) afforded the product (12 mg, 0.024 mmol, 70%). ^{1}H NMR (400 MHz, MeOD) δ 8.18 – 8.08 (m, 3H), 7.83 – 7.70 (m, 2H), 7.63 – 7.52 (m, 3H), 7.43 – 7.35 (m, 2H), 7.19 – 7.11 (m, 2H), 4.52 (s, 2H), 3.87 (s, 2H). ^{13}C NMR (101 MHz, MeOD) δ 156.46, 136.64, 135.74, 132.63, 132.16, 131.59, 130.33, 130.31, 128.16, 123.12, 122.64, 116.91, 116.03, 52.00, 49.07. HRMS $[C_{22}H_{18}BrN_3O_4S+H]^+$: 500.02742/502.02531 calculated, 500.02718/502.02500 found.

4-(_N_-(4-Bromobenzyl)-_N_-(carboxymethyl)sulfamoyl)-2-(methylcarbamoyl)benzoic acid (46)



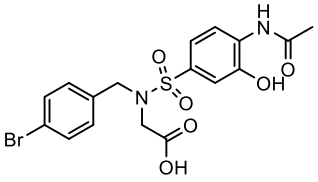
The title compound was synthesized according to general procedure **J** using methyl _N_-(4-bromobenzyl)-_N_-((2-methyl-1,3-dioxoisoindolin-5-yl)sulfonyl)glycinate (**68l**, 15 mg, 0.032 mmol, 1 eq) and 2 M aq. NaOH (64.0 µL, 0.128 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (50-80% dist. EtOAc in _n_-heptane with a drop of conc. HCl) afforded the product (4.0 mg, 8.2 µmol, 27%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 8.06 (d, _J_ = 8.2 Hz, 1H), 7.95 (d, _J_ = 8.1 Hz, 1H), 7.88 (s, 1H), 7.46 (d, _J_ = 8.0 Hz, 2H), 7.18 (d, _J_ = 8.0 Hz, 2H), 4.46 (s, 2H), 3.91 (s, 2H), 2.91 (s, 3H). HRMS $[C_{18}H_{17}BrN_2O_7S+H]^+$: 485.00126/486.99916 calculated, 485.00106/486.99887 found.

_N_-((1-Acetylindolin-5-yl)sulfonyl)-_N_-(4-bromobenzyl)glycine (47)



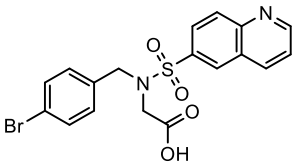
The title compound was synthesized according to general procedure **J** using methyl _N_-((1-acetylindolin-5-yl)sulfonyl)-_N_-(4-bromobenzyl)glycinate (**68m**, 35 mg, 0.072 mmol, 1 eq) and 2 M aq. NaOH (143 µL, 0.286 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (30-80% EtOAc in _n_-pentane with a drop of conc. HCl) afforded the product (22 mg, 0.047 mmol, 66%). ^{1}H NMR (400 MHz, DMSO) δ 8.13 (d, _J_ = 8.4 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.55 – 7.47 (m, 2H), 7.26 – 7.19 (m, 2H), 4.34 (s, 2H), 4.17 (t, _J_ = 8.7 Hz, 2H), 3.84 (s, 2H), 3.19 (t, _J_ = 8.6 Hz, 2H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 169.85, 169.60, 135.68, 133.08, 131.24, 131.12, 130.53, 127.40, 123.84, 120.77, 115.22, 50.95, 48.68, 48.10, 27.03, 24.13. HRMS $[C_{19}H_{19}BrN_2O_5S+H]^+$: 467.02708/469.02497 calculated, 467.02731/469.02518 found.

_N_-((4-Acetamido-3-hydroxyphenyl)sulfonyl)-_N_-(4-bromobenzyl)glycine (48)



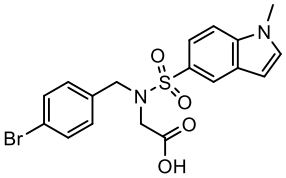
The title compound was synthesized according to general procedure **J** using methyl _N_-(4-bromobenzyl)-_N_-((2-methylbenzo[_d_]oxazol-6-yl)sulfonyl)glycinate (**68n**, 28 mg, 0.062 mmol, 1 eq) and 2 M aq. NaOH (124 µL, 0.247 mmol, 4 eq). Total time: 2 h at rt. Preparative HPLC afforded the product (18 mg, 0.039 mmol, 64%). ^{1}H NMR (400 MHz, MeOD) δ 8.14 – 8.10 (m, 1H), 7.43 – 7.38 (m, 2H), 7.34 – 7.29 (m, 2H), 7.14 – 7.09 (m, 2H), 4.41 (s, 2H), 3.82 (s, 2H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 171.45, 171.27, 147.57, 135.07, 135.02, 132.31, 131.45, 130.90, 122.54, 121.26, 119.75, 114.46, 51.40, 47.45, 24.19. HRMS $[C_{17}H_{17}BrN_2O_6S+H]^+$: 457.00635/459.00432 calculated, 457.00606/459.00392 found.

_N_-(4-Bromobenzyl)-_N_-(quinolin-6-ylsulfonyl)glycine (49)



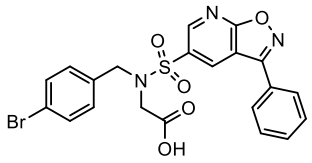
The title compound was synthesized according to general procedure **J** using methyl _N_-(4-bromobenzyl)-_N_-(quinolin-6-ylsulfonyl)glycinate (**68o**, 24 mg, 0.053 mmol, 1 eq) and 2 M aq. NaOH (106 µL, 0.212 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (3-10% MeOH in DCM) afforded the product (18 mg, 0.043 mmol, 80%). ^{1}H NMR (400 MHz, DMSO) δ 9.05 (dd, _J_ = 4.2, 1.7 Hz, 1H), 8.60 (d, _J_ = 2.0 Hz, 1H), 8.57 (dd, _J_ = 8.2, 2.1 Hz, 1H), 8.18 – 8.07 (m, 2H), 7.67 (dd, _J_ = 8.3, 4.2 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.26 – 7.19 (m, 2H), 4.50 (s, 2H), 3.80 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 170.21, 153.12, 148.65, 137.61, 137.57, 135.71, 131.29, 130.43, 130.11, 128.64, 126.95, 126.65, 122.74, 120.74, 50.39, 48.52. HRMS $[C_{18}H_{15}BrN_2O_4S+H]^+$: 435.00087/436.99874 calculated, 435.00082/436.99860 found.

_N_-(4-Bromobenzyl)-_N_-((1-methyl-1_H_-indol-5-yl)sulfonyl)glycine (50)



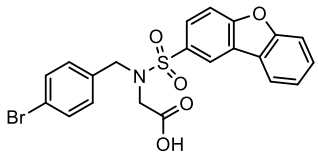
The title compound was synthesized according to general procedure **J** from methyl _N_-(4-bromobenzyl)-_N_-((1-methyl-1_H_-indol-5-yl)sulfonyl)glycinate (**68p**, 29 mg, 0.064 mmol, 1 eq) and 2 M aq. NaOH (96.0 µL, 0.192 mmol, 3 eq). Total time: 2 h at rt. Silica gel column chromatography (3-10% MeOH in DCM) afforded the product (28 mg, 0.064 mmol, 100%). ^{1}H NMR (400 MHz, MeOD) δ 8.15 (d, _J_ = 1.8 Hz, 1H), 7.65 (dd, _J_ = 8.7, 1.8 Hz, 1H), 7.46 (d, _J_ = 8.7 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.26 (d, _J_ = 3.1 Hz, 1H), 7.11 – 7.05 (m, 2H), 6.59 (d, _J_ = 3.1 Hz, 1H), 4.41 (s, 2H), 3.85 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 171.56, 139.29, 135.38, 132.27, 132.17, 130.98, 130.23, 128.61, 122.44, 122.25, 120.70, 110.43, 103.21, 51.57, 47.65, 33.26. HRMS $[C_{18}H_{17}BrN_2O_4S+H]^+$: 437.01652/439.01439 calculated, 437.01633/439.01414 found.

_N_-(4-Bromobenzyl)-_N_-((3-phenylisoxazolo[5,4-_b_]pyridin-5-yl)sulfonyl)glycine (51)



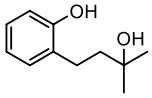
The title compound was synthesized according to general procedure **J** using methyl _N_-(4-bromobenzyl)-_N_-((3-phenylisoxazolo[5,4-_b_]pyridin-5-yl)sulfonyl)glycinate (**68q**, 29 mg, 0.056 mmol, 1 eq) and 2 M aq. NaOH (112 µL, 0.224 mmol, 4 eq). Total time: 2 h at rt. Silica gel column chromatography (20-50% EtOAc in _n_-pentane with a drop of conc. HCl) afforded the product (21 mg, 0.042 mmol, 74%). ^{1}H NMR (500 MHz, MeOD+$CDCl_3$) δ 9.10 (d, _J_ = 2.2 Hz, 1H), 8.84 (d, _J_ = 2.2 Hz, 1H), 7.98 – 7.91 (m, 2H), 7.63 – 7.55 (m, 3H), 7.46 – 7.39 (m, 2H), 7.22 – 7.15 (m, 2H), 4.45 (s, 2H), 4.02 (s, 2H). ^{13}C NMR (126 MHz, MeOD+$CDCl_3$) δ 171.27, 170.54, 158.57, 150.38, 134.34, 133.82, 133.78, 132.33, 131.82, 130.64, 129.89, 128.14, 127.55, 122.78, 112.43, 51.07, 47.23. HRMS [$C_{21}H_{16}BrN_3O_5S$+H]$^+$: 502.00668/504.00458 calculated, 502.00654/504.00443 found.

_N_-(4-bromobenzyl)-_N_-(dibenzo[_b_,_d_]furan-2-ylsulfonyl)glycine (52)



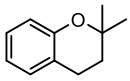
The title compound was synthesized according to general procedure **J** using methyl _N_-(4-bromobenzyl)-_N_-(dibenzo[_b_,_d_]furan-3-ylsulfonyl)glycinate (**68r**, 40 mg, 0.081 mmol, 1 eq), 1 M aq. NaOH (244 µL, 0.244 mmol, 3 eq). Total time: 2 h at rt. Silica gel column chromatography (20-40% EtOAc in _n_-heptane with a drop of conc. HCl) afforded the product (17 mg, 0.035 mmol, 44%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 8.49 (d, _J_ = 2.0 Hz, 1H), 8.02 (dt, _J_ = 7.8, 1.0 Hz, 1H), 7.97 (dd, _J_ = 8.7, 2.0 Hz, 1H), 7.68 (d, _J_ = 8.7 Hz, 1H), 7.64 – 7.57 (m, 1H), 7.57 – 7.49 (m, 1H), 7.45 – 7.36 (m, 3H), 7.18 – 7.11 (m, 2H), 4.49 (s, 2H), 3.94 (s, 2H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 171.00, 158.75, 157.56, 134.78, 132.28, 130.82, 129.03, 127.00, 125.35, 124.13, 123.60, 122.55, 121.71, 121.40, 112.70, 112.41, 51.35, 47.32. HRMS [$C_{21}H_{16}BrNO_5S$+H]$^+$: 474.00053/475.99842 calculated, 474.00033/475.99815 found.

2-(3-Hydroxy-3-methylbutyl)phenol (53)



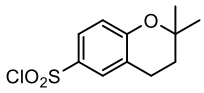
To a solution of dihydrocoumarin (1.2 g, 8.1 mmol, 1 eq) in anhydrous THF (12 mL, 0.7 M) at 0 °C was added CH_3MgBr (3 M in Et_2O, 9.0 mL, 27 mmol, 3.3 eq) dropwise. The reaction was slowly warmed to rt and stirred overnight. The mixture was treated with ice chips containing 5 mL of 1 M aq. H_2SO_4 and extracted 3× with Et_2O. Combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (10-30% EtOAc in _n_-pentane) to afford the product (1.22 g, 6.77 mmol, 84%). ^{1}H NMR (400 MHz, MeOD) δ 7.05 (dd, _J_ = 7.3, 1.4 Hz, 1H), 6.97 (td, _J_ = 8.0, 1.7 Hz, 1H), 6.76 – 6.69 (m, 2H), 2.70 – 2.62 (m, 2H), 1.77 – 1.70 (m, 2H), 1.25 (s, 6H). ^{13}C NMR (101 MHz, MeOD) δ 156.10, 130.78, 130.27, 127.72, 120.58, 115.85, 71.59, 44.92, 29.13, 26.20.

2,2-Dimethylchromane (54)



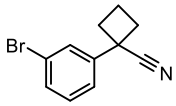
A solution of 2-(3-hydroxy-3-methylbutyl)phenol (**53**, 1.13 g, 6.27 mmol, 1 eq) in 15% aq. H_2SO_4 (10 mL) and toluene (3 mL) was refluxed for 2 h. After completion, the mixture was cooled to rt and extracted 3× with Et_2O. Combined organic layers were washed with water, 2 M aq. NaOH and brine, dried 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 as a white solid (0.73 g, 4.5 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 6.99 (m, 2H), 6.84 – 6.73 (m, 2H), 2.80 – 2.72 (m, 2H), 1.83 – 1.70 (m, 2H), 1.32 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.08, 129.55, 127.34, 120.99, 119.70, 117.33, 74.16, 32.89, 26.99, 22.55.

2,2-Dimethylchromane-6-sulfonyl chloride (55)



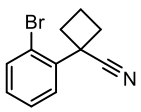
To a solution of 2,2-dimethylchromane (**54**, 560 mg, 3.45 mmol, 1 eq) in anhydrous DCM (15 mL) was added HSO_3Cl (230 µL, 3.45 mmol, 1 eq) dropwise at 0 °C. The reaction was stirred for 2 h and more HSO_3Cl (230 µL, 3.45 mmol, 1 eq) was added dropwise at 0°C. The mixture was slowly warm to rt and stirred overnight. The DCM layer was collected and concentrated to afford the product (570 mg, 2.19 mmol, 63%). ^{1}H NMR (400 MHz, DMSO) δ 7.34 (d, *J* = 2.1 Hz, 1H), 7.28 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 2.71 (t, *J* = 6.9 Hz, 2H), 1.74 (t, *J* = 6.8 Hz, 2H), 1.25 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 154.27, 138.52, 127.21, 124.92, 120.08, 116.05, 74.60, 32.08, 26.64, 21.91.

1-(3-Bromophenyl)cyclobutane-1-carbonitrile (56a)



The title compound was synthesized according to general procedure **A** using 2-(3-bromophenyl)acetonitrile (1.20 g, 6.12 mmol 1 eq), 1,3-dibromopropane (1.24 g, 6.12 mmol, 1 eq), TBABr (0.02 g, 0.06 mmol, 0.01 eq) and KOH (2.75 g, 49.0 mmol, 8 eq). Total time: 1.5 h at 100 °C to reflux. Silica gel column chromatography (4-5% Et_2O in *n*-pentane) afforded the product (880 mg, 3.73 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (t, *J* = 1.9 Hz, 1H), 7.45 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.35 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 2.87 – 2.76 (m, 2H), 2.66 – 2.54 (m, 2H), 2.51 – 2.36 (m, 1H), 2.14 – 2.01 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.01, 131.10, 130.58, 128.88, 124.40, 123.83, 123.09, 39.85, 34.62, 17.11.

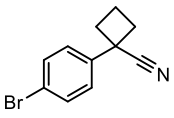
1-(2-Bromophenyl)cyclobutane-1-carbonitrile (56b)



To a suspension of KOH (600 mg, 10.7 mmol, 4.2 eq) in DMSO (4.5 mL, 0.57 M) was added a solution of 2-(2-bromophenyl)acetonitrile (500 mg, 2.55 mmol, 1 eq) and 1,3-dibromopropane (520 mg, 2.55 mmol, 1 eq) dropwise. The reaction was stirred at rt for 5 h. The mixture was diluted in water and extracted 3× with EtOAc. Combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (4-5% Et_2O in *n*-pentane) to afford the product (0.20 g, 0.85 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.37

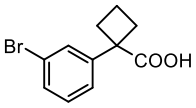
– 7.31 (m, 1H), 7.28 – 7.23 (m, 1H), 7.19 (ddd, *J* = 7.9, 7.3, 1.7 Hz, 1H), 3.03 – 2.93 (m, 2H), 2.70 – 2.60 (m, 2H), 2.55 – 2.41 (m, 1H), 2.00 – 1.89 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.59, 134.23, 129.78, 127.96, 127.71, 123.06, 122.69, 41.71, 34.22, 17.13.

1-(4-Bromophenyl)cyclobutane-1-carbonitrile (56c)



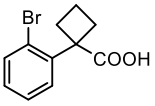
The title compound was synthesized according to general procedure **A** using 2-(4-bromophenyl)acetonitrile (1.0 g, 5.1 mmol, 1 eq), 1,3-dibromopropane (1.0 g, 5.1 mmol, 1 eq), TBABr (20 mg, 0.051 mmol, 0.1 eq) and KOH (2.30 g, 40.8 mmol, 8 eq). Total time: 1.5 h at 100 °C to reflux. Silica gel column (4-5% Et_2O in *n*-pentane) afforded the product (620 mg, 2.63 mmol, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.44 (m, 2H), 7.33 – 7.22 (m, 2H), 2.87 – 2.75 (m, 2H), 2.63 – 2.51 (m, 2H), 2.48 – 2.34 (m, 1H), 2.14 – 2.00 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.78, 131.99, 127.35, 123.82, 121.82, 39.70, 34.55, 17.00.

1-(3-Bromophenyl)cyclobutane-1-carboxylic acid (57a)



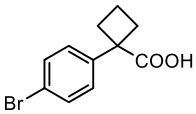
The title compound was synthesized according to general procedure **B** using 1-(3-bromophenyl)cyclobutane-1-carbonitrile (**56a**, 460 mg, 1.93 mmol, 1 eq) and KOH (650 mg, 11.6 mmol. 6 eq). Total time: overnight at reflux. Silica gel column chromatography (30% EtOAc in *n*-pentane with a drop of conc. HCl) afforded the product (450 mg, 1.75 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.92 (bs, 1H), 7.43 (t, *J* = 1.8 Hz, 1H), 7.37 (dt, *J* = 7.1, 1.8 Hz, 1H), 7.26 – 7.14 (m, 2H), 2.91 – 2.76 (m, 2H), 2.60 – 2.43 (m, 2H), 2.18 – 2.01 (m, 1H), 1.94 – 1.80 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.25, 145.46, 130.14, 130.00, 129.83, 125.28, 122.59, 52.08, 32.36, 16.76.

1-(2-Bromophenyl)cyclobutane-1-carboxylic acid (57b)



The title compound was synthesized according to general procedure **B** using 1-(2-bromophenyl)cyclobutane-1-carbonitrile (**56b,** 0.12 g, 0.52 mmol, 1 eq) and KOH (0.18 g, 3.1 mmol, 6 eq). Total time: 2 h at reflux. Silica gel column chromatography (30% EtOAc in *n*-pentane with a drop of conc. HCl) afforded the product (66 mg, 0.26 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.12 (ddd, *J* = 7.9, 6.5, 2.6 Hz, 1H), 2.97 – 2.87 (m, 2H), 2.64 – 2.53 (m, 2H), 2.37 – 2.23 (m, 1H), 1.91 – 1.79 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.16, 142.47, 133.63, 128.67, 128.63, 127.27, 123.30, 53.86, 32.18, 16.85.

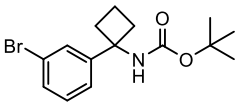
1-(4-Bromophenyl)cyclobutane-1-carboxylic acid (57c)



The title compound was synthesized according to general procedure **B** using 1-(4-bromophenyl)cyclobutane-1-carbonitrile (**56c**, 1.19 g, 5.04 mmol, 1 eq) and KOH (1.70 g, 30.2 mmol, 6 eq). Total time: 2 h at reflux. Silica gel column chromatography (20% EtOAc in *n*-pentane with 0.1% TFA) afforded the product (1.18 g, 4.63 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (bs, 1H), 7.48 – 7.41 (m, 2H), 7.20 – 7.14 (m, 2H), 2.88 – 2.78 (m, 2H), 2.53 – 2.41 (m, 2H), 2.14 – 2.01 (m, 1H), 1.92 – 1.80 (m,

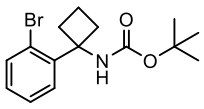
1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.35, 142.21, 131.54, 128.39, 121.04, 51.92, 32.33, 16.70.

tert-Butyl (1-(3-bromophenyl)cyclobutyl)carbamate (58a)



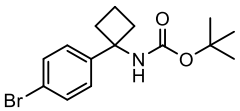
The title compound was synthesized according to general procedure **C** using 1-(3-bromophenyl)cyclobutane-1-carboxylic acid (**57a**, 200 mg, 0.784 mmol, 1 eq), diphenylphosphoryl azide (216 mg, 0.784 mmol, 1 eq) and Et_3N (120 µL, 0.862 mmol, 1.1 eq) in *t*-BuOH (10 mL, 0.08 M). Total time: 1 h at 30 °C and overnight at reflux. Silica gel column chromatography (5-7% EtOAc in *n*-pentane) afforded the product (178 mg, 0.546 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (t, *J* = 1.9 Hz, 1H), 7.43 – 7.29 (m, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 5.17 (bs, 1H), 2.60 – 2.28 (m, 4H), 2.17 – 2.03 (m, 1H), 1.94 – 1.80 (m, 1H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.24, 148.58, 129.86, 129.67, 128.85, 124.25, 122.44, 79.72, 58.84, 34.42, 28.42, 15.29. LC-MS $[C_{15}H_{20}BrNO_2+H]^+$: 326.08/328.07 calculated, 325.87/327.87 found.

tert-Butyl (1-(2-bromophenyl)cyclobutyl)carbamate (58b)



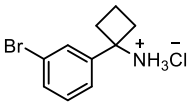
The title compound was synthesized according to general procedure **C** using 1-(2-bromophenyl)cyclobutane-1-carboxylic acid (**57b,** 55.0 mg, 0.216 mmol, 1 eq), diphenylphosphoryl azide (59.3 mg, 0.216 mmol, 1 eq) and Et_3N (33.0 µL, 0.237 mmol, 1.1 eq) in *t*-BuOH (2.75 mL, 0.08 M). Total time: 1 h at 30 °C and overnight at reflux. Silica gel column chromatography (5-7% EtOAc in *n*-pentane) afforded the product (29.4 mg, 0.112 mmol, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.47 (m, 2H), 7.35 – 7.24 (m, 1H), 7.08 (td, *J* = 7.6, 1.7 Hz, 1H), 5.56 (bs, 1H), 2.76 – 2.51 (m, 4H), 2.25 – 2.10 (m, 1H), 1.87 – 1.67 (m, 1H), 1.33 (s, 9H). LC-MS $[C_{15}H_{20}BrNO_2+H]^+$: 326.08/328.07 calculated, 325.80/327.80 found.

tert-Butyl (1-(4-bromophenyl)cyclobutyl)carbamate (58c)



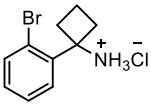
The title compound was synthesized according to general procedure **C** using 1-(4-bromophenyl)cyclobutane-1-carboxylic acid (**57c**, 1.2 g, 4.7 mmol, 1 eq), diphenylphosphoryl azide (1.0 mL, 4.7 mmol, 1 eq) and Et_3N (0.72 mL, 5.2 mmol, 1.1 eq) in *t*-BuOH (60 mL, 0.08 M) Total time: 1 h at 30 °C and overnight at reflux. Silica gel column chromatography (5-7% EtOAc in *n*-pentane) afforded the product (1.30 g, 3.98 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.14 (bs, 1H), 2.58 – 2.35 (m, 4H), 2.16 – 2.06 (m, 1H), 1.92 – 1.77 (m, 1H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.34, 145.32, 131.31, 127.45, 120.48, 79.56, 58.77, 34.29, 28.45, 15.30. LC-MS $[C_{15}H_{20}BrNO_2+H]^+$: 326.08/328.07 calculated, 325.60/327.87 found.

1-(3-Bromophenyl)cyclobutan-1-aminium chloride (59a)



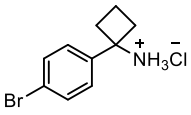
The title compound was synthesized according to general procedure **D** using *tert*-butyl (1-(3-bromophenyl)-cyclobutyl)carbamate (**58a**, 180 mg, 0.552 mmol, 1 eq) in 3 M aq. HCl in MeOH (5.5 mL, 0.1 M). Total time: 24 h at rt. The product was afforded after concentration (135 mg, 0.513 mmol, 93%). ^{1}H NMR (400 MHz, MeOD) δ 7.71 (t, *J* = 1.7 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 2.81 – 2.61 (m, 4H), 2.35 – 2.22 (m, 1H), 2.00 – 1.88 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 143.73, 133.02, 132.03, 130.46, 126.22, 123.93, 59.79, 33.19, 14.86. LC-MS $[C_{10}H_{12}BrN+H]^{+}$: 226.02/228.02 calculated, 226.00/228.00 found.

1-(2-Bromophenyl)cyclobutan-1-aminium chloride (59b)



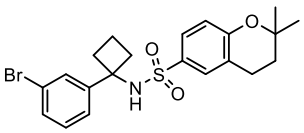
The title compound was synthesized according to general procedure **D** using *tert*-butyl (1-(2-bromophenyl)cyclobutyl)carbamate (**58b**, 29 mg, 0.089 mmol, 1 eq) in 3 M aq. HCl in MeOH (2.4 mL, 0.04 M). Total time: 24 h at rt. The product was afforded after concentration (26 mg, 0.098 mmol, quant.). ^{1}H NMR (400 MHz, MeOD) δ 7.70 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.35 (ddd, *J* = 8.0, 6.8, 2.3 Hz, 1H), 3.01 – 2.90 (m, 2H), 2.80 – 2.62 (m, 2H), 2.44 – 2.29 (m, 1H), 2.04 – 1.90 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 139.70, 135.66, 132.25, 130.47, 129.36, 122.71, 62.95, 34.14, 15.32. LC-MS $[C_{10}H_{12}BrN+H]^{+}$: 226.02/228.02 calculated, 226.00/227.93 found.

1-(4-Bromophenyl)cyclobutan-1-aminium chloride (59c)



The title compound was synthesized according to general procedure **D** using *tert*-butyl (1-(4-bromophenyl)cyclobutyl)carbamate (**58c**, 100 mg, 0.307 mmol) in 3 M aq. HCl in MeOH (1.2 mL, 0.26 M). Total time: 24 h at rt. The solvent was removed and the residue was washed with Et_2O to afford the product (80 mg, 0.31 mmol, 100%). ^{1}H NMR (400 MHz, MeOD) δ 7.68 – 7.60 (m, 2H), 7.52 – 7.44 (m, 2H), 2.81 – 2.59 (m, 4H), 2.35 – 2.20 (m, 1H), 2.01 – 1.87 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 140.50, 133.22, 129.38, 123.87, 59.84, 33.23, 14.81. LC-MS $[C_{10}H_{12}BrN+H]^{+}$: 226.02/228.02 calculated, 225.87/227.87 found.

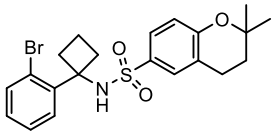
***N*-(1-(3-Bromophenyl)cyclobutyl)-2,2-dimethylchromane-6-sulfonamide (60a)**



The title compound was synthesized according to general procedure **G** using 1-(3-bromophenyl)-cyclobutan-1-aminium chloride (**59a**, 65 mg, 0.25 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonyl chloride (**55**, 129 mg, 0.495 mmol, 2 eq) and Et_3N (104 µL, 0.743 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (5-25% EtOAc in *n*-pentane) afforded the product (53.7 mg, 0.119 mmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 3H), 7.18 – 7.12 (m, 1H), 6.98 (t, *J* = 7.8 Hz, 1H), 6.92 (dd, *J* = 2.3, 1.1 Hz, 1H), 6.61 (d, *J* = 8.7 Hz, 1H), 5.45 (s, 1H), 2.62 – 2.46 (m, 6H), 2.13 – 2.02 (m, 1H), 1.80 – 1.67 (m, 3H), 1.33 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.38, 144.62, 131.66, 130.47, 129.81, 129.37, 129.01, 126.29, 125.65,

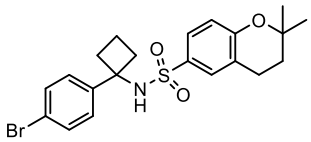
122.17, 120.65, 117.43, 75.58, 61.15, 35.72, 32.39, 27.06, 22.25, 15.36. LC-MS $[C_{21}H_{24}BrNO_3S+H]^+$: 450.07/452.07 calculated, 450.07 /452.00 found.

_N_-(1-(2-Bromophenyl)cyclobutyl)-2,2-dimethylchromane-6-sulfonamide (60b)



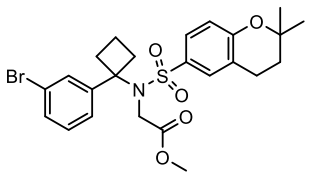
The title compound was synthesized according to general procedure **G** using 1-(2-bromophenyl)cyclobutan-1-aminium chloride (**59b**, 26 mg, 0.099 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonyl chloride (**55**, 51.6 mg, 0.198 mmol, 2 eq) and Et_3N (41.0 µL, 0.297 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (5-25% EtOAc in *n*-pentane) afforded the product (21 mg, 0.046 mmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.18 (td, *J* = 7.5, 1.3 Hz, 1H), 7.11 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.06 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.93 (dt, *J* = 2.1, 0.9 Hz, 1H), 6.89 (ddd, *J* = 7.9, 7.3, 1.7 Hz, 1H), 6.46 (d, *J* = 8.6 Hz, 1H), 5.63 (s, 1H), 2.85 – 2.72 (m, 2H), 2.67 – 2.56 (m, 2H), 2.53 (t, *J* = 6.8 Hz, 2H), 2.41 – 2.26 (m, 1H), 1.82 – 1.75 (m, 1H), 1.72 (t, *J* = 6.8 Hz, 2H), 1.30 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.08, 140.13, 133.47, 131.02, 130.02, 128.65, 128.59, 126.70, 126.36, 122.23, 120.28, 117.02, 75.38, 63.63, 35.12, 32.40, 26.89, 22.20, 15.97. LC-MS $[C_{21}H_{24}BrNO_3S+H]^+$: 450.07/452.07 calculated, 450.07/452.07 found.

_N_-(1-(4-Bromophenyl)cyclobutyl)-2,2-dimethylchromane-6-sulfonamide (60c)



The title compound was synthesized according to general procedure **G** using 1-(4-bromophenyl)cyclobutan-1-aminium chloride (**59c**, 300 mg, 1.15 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonyl chloride (**55**, 300 mg, 1.15 mmol, 1 eq) and Et_3N (1.0 mL, 5.7 mmol, 5 eq). Total time: overnight at rt. Silica gel column chromatography (5-20% EtOAc in *n*-pentane) afforded the product (457 mg, 1.02 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.23 – 7.18 (m, 2H), 7.08 – 7.03 (m, 2H), 6.86 (d, *J* = 2.7 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 5.74 (s, 1H), 2.62 – 2.46 (m, 6H), 2.10 – 2.01 (m, 1H), 1.80 (t, 2H), 1.74 – 1.66 (m, 1H), 1.33 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.29, 141.35, 131.97, 130.78, 129.00, 126.25, 120.91, 120.63, 117.51, 75.63, 61.09, 35.73, 32.41, 26.94, 22.22, 15.32. LC-MS $[C_{21}H_{24}BrNO_3S+H]^+$: 450.07/452.07 calculated, 449.60/451.60 found.

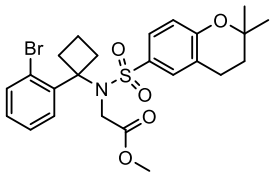
Methyl _N_-(1-(3-bromophenyl)cyclobutyl)-_N_-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (61a)



The title compound was synthesized according to general procedure **I** using *N*-(1-(3-bromophenyl)cyclobutyl)-2,2-dimethylchromane-6-sulfonamide (**60a**, 53.7 mg, 0.119 mmol, 1 eq), methyl 2-bromoacetate (23.0 µL, 0.238 mmol, 2 eq) and BEMP (1 M in hexane, 238 µL, 0.238 mmol, 2 eq). Total time: overnight at 80 °C. The product was afforded without purification (68 mg, 0.13 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, *J* = 1.9 Hz, 1H), 7.40 (ddd, *J* = 7.9, 2.0, 1.0 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.03 (dd, *J* = 2.3, 1.1 Hz, 1H), 6.69 (d, *J* = 8.7 Hz, 1H), 4.07 (s, 2H), 3.74 (s, 3H), 2.89 – 2.77 (m,

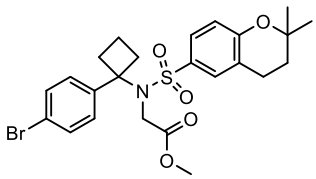
2H), 2.65 (t, *J* = 6.7 Hz, 2H), 2.51 – 2.43 (m, 2H), 1.89 – 1.74 (m, 3H), 1.64 – 1.52 (m, 1H), 1.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.83, 157.67, 145.19, 131.65, 130.72, 130.33, 129.67, 129.26, 126.81, 125.87, 122.40, 121.01, 117.40, 75.68, 65.30, 52.53, 48.00, 34.83, 32.38, 27.03, 22.36, 14.66. LC-MS $[C_{24}H_{28}BrNO_5S+Na]^+$: 544.08/546.07 calculated, 544.40/546.33 found.

Methyl *N*-(1-(2-bromophenyl)cyclobutyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (61b)



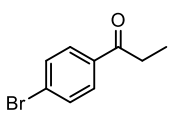
The title compound was synthesized according to general procedure **I** using *N*-(1-(2-bromophenyl)cyclobutyl)-2,2-dimethylchromane-6-sulfonamide (**60b**, 21 mg, 0.046 mmol, 1 eq), methyl 2-bromoacetate (8.7 µL, 0.092 mmol, 2 eq) and BEMP (1 M in hexane, 92 µL, 92 µmol, 2 eq). Total time: overnight at 80 °C. The product was afforded without purification (22 mg, 0.042 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.20 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.06 (td, *J* = 7.6, 1.6 Hz, 1H), 6.92 – 6.85 (m, 1H), 6.55 (dd, *J* = 2.3, 1.2 Hz, 1H), 6.49 (d, *J* = 8.7 Hz, 1H), 4.40 (s, 2H), 3.88 (s, 3H), 3.10 – 2.98 (m, 2H), 2.84 – 2.71 (m, 2H), 2.49 (t, *J* = 6.7 Hz, 2H), 1.85 – 1.75 (m, 1H), 1.72 (t, *J* = 6.8 Hz, 2H), 1.54 – 1.44 (m, 1H), 1.30 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.01, 157.17, 139.34, 134.42, 131.42, 130.94, 128.78, 128.44, 126.86, 126.20, 124.78, 120.28, 116.93, 75.79, 66.65, 52.55, 50.97, 35.36, 32.41, 26.82, 22.28, 15.06. LC-MS $[C_{24}H_{28}BrNO_5S+Na]^+$: 544.08/546.07 calculated, 544.33/546.33 found.

Methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (61c)



The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-2,2-dimethylchromane-6-sulfonamide (**60c**, 371 mg, 0.824 mmol, 1 eq), methyl 2-bromoacetate (161 µL, 1.65 mmol, 2 eq) and BEMP (1 M in hexane, 1.24 mL, 1.24 mmol, 1.5 eq). Total time: overnight at 80 °C. Silica gel column chromatography (10-20% EtOAc in *n*-pentane) afforded the product (416 mg, 0.796 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 6.97 (dd, *J* = 2.3, 1.1 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 4.05 (s, 2H), 3.73 (s, 3H), 2.86 – 2.74 (m, 2H), 2.64 (t, *J* = 6.7 Hz, 2H), 2.52 – 2.42 (m, 2H), 1.86 – 1.72 (m, 3H), 1.61 – 1.48 (m, 1H), 1.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.86, 157.60, 141.78, 131.74, 131.18, 129.30, 129.24, 126.80, 121.41, 121.05, 117.40, 75.72, 65.28, 52.50, 47.86, 34.85, 32.40, 26.95, 22.34, 14.67. LC-MS $[C_{24}H_{28}BrNO_5S+Na]^+$: 544.08/546.07 calculated, 544.07/546.07 found.

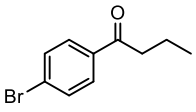
1-(4-Bromophenyl)propan-1-one (62a)



To a solution of 4-bromobenzonitrile (300 mg, 1.65 mmol, 1 eq) in anhydrous THF (5 mL, 0.3 M) under N_2 was added ethylmagnesium bromide (1 M in THF, 5 mL, 5 mmol, 3 eq) dropwise and the reaction was refluxed for 2 h. After

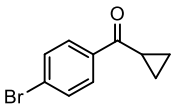
completion, the mixture was cooled down to rt and quenched with cold 2 M aq. HCl. The mixture was extracted 3× with EtOAc and combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (1% EtOAc in *n*-pentane) to afford the product (320 mg, 1.50 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.63 – 7.54 (m, 2H), 2.96 (q, *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.69, 135.62, 131.88, 129.56, 128.01, 31.81, 8.16.

1-(4-Bromophenyl)butan-1-one (62b)



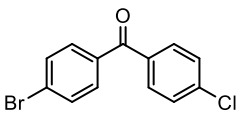
To a solution of 4-bromobenzonitrile (300 mg, 1.65 mmol, 1 eq) in anhydrous THF (5 mL, 0.3 M) under N_2 was added propylmagnesium bromide (2 M in THF, 2.5 mL, 5.0 mmol, 3 eq) dropwise and the reaction was refluxed for 2 h. After completion, the mixture was cooled down to rt and quenched with cold 2 M aq. HCl. The mixture was extracted 3× with EtOAc and 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 (1% EtOAc in *n*-pentane) to afford the product (323 mg, 1.42 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.76 (m, 2H), 7.63 – 7.54 (m, 2H), 2.90 (t, *J* = 7.3 Hz, 2H), 1.75 (h, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.23, 135.77, 131.84, 129.59, 127.99, 40.87, 17.66, 13.87.

(4-Bromophenyl)(cyclopropyl)methanone (62d)



To a solution of the 1,4-dibromobenzene (500 mg, 2.12 mmol, 1 eq) in anhydrous THF (5 mL, 2.4 M) at -78 °C was added *n*-BuLi (2.5 M in hexane, 890 µL, 2.23 mmol, 1.05 eq) dropwise and the mixture was stirred for 30 min. A solution of *N*-methoxy-*N*-methylcyclopropanecarboxamide (287 mg, 2.23 mmol, 1.05 eq) in anhydrous THF (2 mL) was added. The mixture was warmed to rt and stirred for 2 h. The reaction was quenched by H_2O (10 mL) and sat. NH_4Cl (10 mL). The aqueous layer was extracted 3× with EtOAc and combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (1% EtOAc in *n*-pentane) to afford the product (63 mg, 0.28 mmol, 13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.85 (m, 2H), 7.63 – 7.58 (m, 2H), 2.61 (tt, *J* = 7.8, 4.5 Hz, 1H), 1.27 – 1.22 (m, 2H), 1.10 – 1.03 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.67, 136.74, 131.87, 129.65, 127.93, 17.22, 12.04.

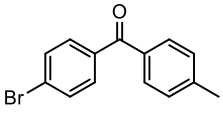
(4-Bromophenyl)(4-chlorophenyl)methanone (62g)



The title compound was synthesized according to general procedure **E** using 1-bromo-4-chlorobenzene (383 mg, 2.00 mmol, 1 eq), *n*-BuLi (2.5 M in hexane, 0.88 mL, 2.2 mmol, 1.1 eq), 4-bromobenzaldehyde (389 mg, 2.10 mmol, 1.05 eq), I_2 (812 mg, 3.20 mmol, 1.6 eq) and K_2CO_3 (829 mg, 6.00 mmol, 3 eq). Total time: 30 min at -78 °C, 1 h at rt and 3 h at reflux. Silica gel column chromatography (1-3% Et_2O in *n*-pentane) afforded the product (0.23 g, 0.77 mmol, 39%). ^{1}H NMR (850 MHz,

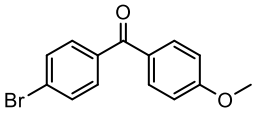
$CDCl_3$) δ 7.74 – 7.70 (m, 2H), 7.66 – 7.60 (m, 4H), 7.48 – 7.45 (m, 2H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 194.44, 139.26, 135.99, 135.48, 131.83, 131.51, 131.43, 128.86, 127.86. LC-MS $[C_{13}H_8BrClO+H]^+$: 294.95/296.95 calculated, 295.00/297.08 found.

(4-Bromophenyl)(*p*-tolyl)methanone (62h)



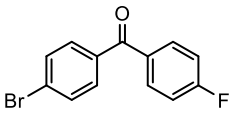
The title compound was synthesized according to general procedure **E** using 1-bromo-4-methylbenzene (342 mg, 2.00 mmol, 1 eq), *n*-BuLi (2.5 M in hexane, 0.88 mL, 2.2 mmol, 1.1 eq), 4-bromobenzaldehyde (389 mg, 2.10 mmol, 1.05 eq), I_2 (812 mg, 3.20 mmol, 1.6 eq) and K_2CO_3 (829 mg, 6.00 mmol, 3 eq). Total time: 30 min at -78 °C, 1 h at rt and 3 h at reflux. Silica gel column chromatography (0.5-1% Et_2O in *n*-pentane) afforded the product (0.24 g, 0.87 mmol, 43%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 3H), 7.66 – 7.61 (m, 3H), 7.31 – 7.27 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.47, 143.69, 136.75, 134.55, 131.64, 131.57, 130.29, 129.21, 127.29, 21.79. LC-MS $[C_{14}H_{11}BrO+H]^+$: 275.01/277.00 calculated, 275.08/277.08 found.

(4-Bromophenyl)(4-methoxyphenyl)methanone (62i)



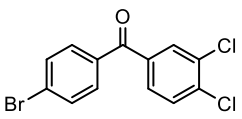
The title compound was synthesized according to general procedure **E** using 1-bromo-4-methoxybenzene (374 mg, 2.00 mmol, 1 eq), *n*-BuLi (2.5 M in hexane, 0.88 mL, 2.2 mmol, 1.1 eq), 4-bromobenzaldehyde (389 mg, 2.10 mmol, 1.05 eq), I_2 (812 mg, 3.20 mmol, 1.6 eq) and K_2CO_3 (829 mg, 6.00 mmol, 3 eq). Total time: 30 min at -78 °C, 1 h at rt and 3 h at reflux. Silica gel column chromatography (0-20% Et_2O in *n*-pentane) afforded the product (317 mg, 1.09 mmol, 54%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 2H), 7.66 – 7.58 (m, 4H), 6.99 – 6.94 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.50, 163.51, 137.09, 132.57, 131.60, 131.39, 129.81, 126.93, 113.79, 55.64. LC-MS $[C_{14}H_{11}BrO_2+H]^+$: 291.00/293.00 calculated, 291.08/293.08 found.

(4-Bromophenyl)(4-fluorophenyl)methanone (62j)



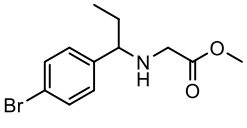
The title compound was synthesized according to general procedure **E** using 1,4-dibromobenzene (472 mg, 2.00 mmol, 1 eq), *n*-BuLi (2.5 M in hexane, 0.88 mL, 2.2 mmol, 1.1 eq), 4-fluorobenzaldehyde (261 mg, 2.10 mmol, 1.05 eq), I_2 (812 mg, 3.20 mmol, 1.6 eq) and K_2CO_3 (829 mg, 6.00 mmol, 3 eq). Total time: 30 min at -78 °C, 1 h at rt and 3 h at reflux. The crude was used without purification. LC-MS $[C_{13}H_8BrFO+H]^+$: 278.98/280.98 calculated, 279.00/281.08 found.

(4-Bromophenyl)(3,4-dichlorophenyl)methanone (62k)



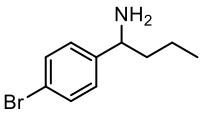
The title compound was synthesized according to general procedure **E** using 1,4-dibromobenzene (472 mg, 2.00 mmol, 1 eq), *n*-BuLi (2.5 M in hexane, 0.88 mL, 2.2 mmol, 1.1 eq), 3,4-dichlorobenzaldehyde (368 mg, 2.10 mmol, 1.05 eq), I_2 (812 mg, 3.20 mmol, 1.6 eq) and K_2CO_3 (829 mg, 6.00 mmol, 3 eq). Total time: 30 min at -78 °C, 1 h at rt and 3 h at reflux. The crude was used without purification.

Methyl (1-(4-bromophenyl)propyl)glycinate (63a)



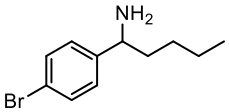
To a mixture of 1-(4-bromophenyl)propan-1-one (**62a**, 100 mg, 0.469 mmol, 1 eq) and 2-methoxy-2-oxoethan-1-aminium chloride (236 mg, 1.88 mmol, 4 eq) in anhydrous MeOH with 3 Å molecular sieves was added Et_3N (262 µL, 1.88 mmol, 4 eq) and AcOH (134 µL, 2.35 mmol, 5 eq). After 1 h, $NaBH_3CN$ (88.0 mg, 1.41 mmol, 3 eq) was added and the mixture was stirred at rt for overnight and refluxed for 24 h. The mixture was diluted in sat. $NaHCO_3$ and EtOAc and filtered through Celite. The filtrate was separated through funnel. The aqueous layer was extracted 2× with EtOAc and combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (20-30% EtOAc in *n*-pentane) to afford the product (100 mg, 0.349 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 2H), 7.21 – 7.13 (m, 2H), 3.69 (s, 3H), 3.49 (dd, *J* = 7.7, 5.9 Hz, 1H), 3.27 (d, *J* = 17.5 Hz, 1H), 3.16 (d, *J* = 17.5 Hz, 1H), 1.95 (s, 1H), 1.81 – 1.69 (m, 1H), 1.68 – 1.55 (m, 1H), 0.81 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 173.11, 142.26, 131.57, 129.36, 120.95, 63.93, 51.85, 48.59, 31.06, 10.62. LC-MS $[C_{12}H_{16}BrNO_2+H]^+$: 286.04/288.04 calculated, 286.00/288.00 found.

1-(4-Bromophenyl)butan-1-amine (63b)



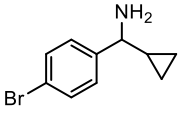
The title compound was synthesized according to general procedure **F** using 1-(4-bromophenyl)butan-1-one (**62b**, 0.10 g, 0.44 mmol, 1 eq), ammonium acetate (0.34 mg, 4.4 mmol, 10 eq) and $NaBH_3CN$ (41.5 mg, 0.661 mmol, 1.5 eq). Total time: over-weekend at reflux. The product was afforded without purification (35 mg, 0.15 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.33 (m, 2H), 7.23 – 7.10 (m, 2H), 3.90 – 3.77 (m, 1H), 1.74 – 1.47 (m, 4H), 1.41 – 1.10 (m, 2H), 0.95 – 0.78 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.72, 131.54, 128.26, 120.55, 55.56, 41.85, 19.71, 14.09. LC-MS $[C_{10}H_{14}BrN+H]^+$: 228.04/230.04 calculated, 227.93/229.87 found.

1-(4-Bromophenyl)pentan-1-amine (63c)



The title compound was synthesized according to general procedure **F** using 1-(4-bromophenyl)pentan-1-one (commercial **62c**, 0.20 g, 0.83 mmol, 1 eq), ammonium acetate (1.28 g, 16.6 mmol, 20 eq) and $NaBH_3CN$ (89.0 mg, 1.41 mmol, 1.7 eq). Total time: overnight at reflux. The product was afforded without purification (30.2 mg, 0.125 mmol, 15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 2H), 7.25 – 7.16 (m, 2H), 3.92 – 3.80 (m, 1H), 1.83 – 1.52 (m, 4H), 1.38 – 1.05 (m, 4H), 0.94 – 0.81 (m, 3H). LC-MS $[C_{11}H_{16}BrN+H]^+$: 242.05/244.05 calculated, 242.00/243.87 found.

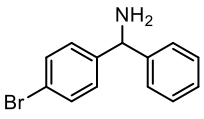
(4-Bromophenyl)(cyclopropyl)methanamine (63d)



To a solution of (4-bromophenyl)(cyclopropyl)methanone (**62d**, 59 mg, 0.26 mmol, 1 eq) in pyridine (1 mL, 0.26 M) was added *O*-methylhydroxylammonium chloride (32.8 mg, 0.393 mmol, 1.5 eq) at rt. The

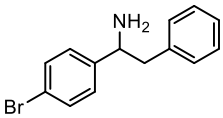
mixture was stirred at rt for over-weekend. Pyridine was removed under vacuum and the residue was extracted with Et_2O, filtered and concentrated. The remaining was dissolved in anhydrous THF (2 mL, 0.13 M) and borane tetrahydrofuran complex (1 M, 1.3 mL, 1.3 mmol, 5 eq) was added dropwise under N_2. The mixture was refluxed for 5 h and then cooled to rt. H_2O (1 mL) and aq. NaOH (20% w/v, 2 mL) were slowly added to the mixture under ice bath and it was stirred at 0 °C for 10 min. The mixture was then heated to 85 °C for overnight. The reaction mixture was diluted in water and extracted 3× with EtOAc. Combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The product was afforded without purification (45 mg, 0.20 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 2H), 7.33 – 7.27 (m, 2H), 3.16 (d, *J* = 8.6 Hz, 1H), 1.32 – 1.19 (m, 2H), 1.10 – 1.01 (m, 1H), 0.66 – 0.41 (m, 2H), 0.40 – 0.20 (m, 2H). LC-MS $[C_{10}H_{12}BrN+H]^+$: 226.02/228.02 calculated, 225.80/227.80 found.

(4-Bromophenyl)(phenyl)methanamine (63e)



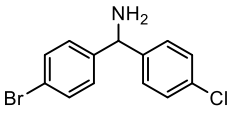
To a solution of 4-bromophenyl(phenyl)-methanone (commercial **62e**, 400 mg, 1.53 mmol, 1 eq) in EtOH (10 mL, 0.15 M) was added hydroxyl ammonium chloride (319 mg, 4.60 mmol, 3 eq). The mixture was refluxed for overnight. After completion the solvent was evaporated, and the residue was dissolved in DCM. The organic layer was washed with water and sat. $NaHCO_3$, dried with Na_2SO_4 and concentrated. The remaining was dissolved in anhydrous THF (5 mL, 0.3 M) and $LiAlH_4$ (1 M in THF, 1.5 mL, 1.5 mmol, 1 eq) was added slowly at reflux. The reaction mixture was allowed to stir overnight. After completion, the reaction was slowly quenched with aq. NaOH over 1 h. The mixture was extracted 3× with DCM and combined organic layers were concentrated. Silica gel column chromatography (3-5% EtOAc in *n*-pentane) afforded the product (44 mg, 0.17 mmol, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.39 – 7.18 (m, 7H), 5.15 (s, 1H), 1.77 (s, 2H). LC-MS $[C_{13}H_{12}BrN+H]^+$: 262.02/264.02 calculated, 262.13/264.00 found.

1-(4-Bromophenyl)-2-phenylethan-1-amine (63f)



The title compound was synthesized according to general procedure **F** using 1-(4-bromophenyl)-2-phenylethan-1-one (commercial **62f**, 0.15 g, 0.55 mmol, 1 eq), ammonium acetate (0.84 g, 11 mmol, 20 eq) and $NaBH_3CN$ (93 mg, 1.5 mmol, 2.7 eq). Total time: overnight at reflux. The product was afforded without purification (0.16 g, 0.56 mmol, quant.). LC-MS $[C_{14}H_{14}BrN+H]^+$: 276.04/278.04 calculated, 275.92/277.92 found.

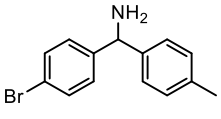
(4-Bromophenyl)(4-chlorophenyl)methanamine (63g)



The title compound was synthesized according to general procedure **F** using (4-bromophenyl)(4-chlorophenyl)methanone (**62g**, 115 mg, 0.390 mmol, 1 eq), ammonium acetate (600 mg, 7.78 mmol, 20 eq) and $NaBH_3CN$ (66.0 mg, 1.05 mmol, 2.7 eq). Total time: overnight at reflux. The product was

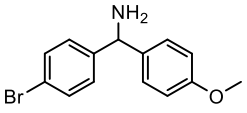
afforded without purification (116 mg, 0.390 mmol, quant.). LC-MS $[C_{13}H_{11}BrClN–NH_2]^+$: 278.96/280.96 calculated, 279.08/281.08 found.

(4-Bromophenyl)(*p*-tolyl)methanamine (63h)



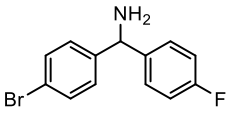
The title compound was synthesized according to general procedure **F** using (4-bromophenyl)(*p*-tolyl)methanone (**62h**, 115 mg, 0.420 mmol, 1 eq), ammonium acetate (644 mg, 8.36 mmol, 20 eq) and $NaBH_3CN$ (71.0 mg, 1.13 mmol, 2.7 eq). Total time: overnight at reflux. The product was afforded without purification (112 mg, 0.406 mmol, 97%). LC-MS $[C_{14}H_{14}BrN–NH_2]^+$: 259.01/261.01 calculated, 259.08/261.08 found.

(4-Bromophenyl)(4-methoxyphenyl)methanamine (63i)



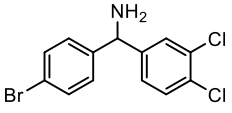
The title compound was synthesized according to general procedure **F** using (4-bromophenyl)(4-methoxyphenyl)methanone (**62i**, 115 mg, 0.400 mmol, 1 eq), ammonium acetate (609 mg, 7.90 mmol, 20 eq) and $NaBH_3CN$ (67.0 mg, 1.07 mmol, 2.7 eq). Total time: overnight at reflux. The product was afforded without purification (113.8 mg, 0.39 mmol, 99%). LC-MS $[C_{14}H_{14}BrNO–NH_2]^+$: 275.01/277.00 calculated, 275.08/277.08 found.

(4-Bromophenyl)(4-fluorophenyl)methanamine (63j)



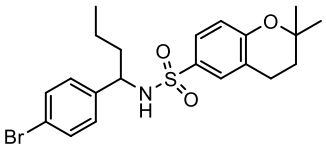
The title compound was synthesized according to general procedure **F** using (4-bromophenyl)(4-fluorophenyl)methanone (**62j**, 200 mg, 0.720 mmol, 1 eq), ammonium acetate (1.10 g, 14.3 mmol, 20 eq) and $NaBH_3CN$ (122 mg, 1.94 mmol, 2.7 eq). Total time: overnight at reflux. The product was afforded without purification (173 mg, 0.618 mmol, 86%). LC-MS $[C_{13}H_{11}BrF–NH_2]^+$: 262.99/264.98 calculated, 263.06/265.00 found.

(4-Bromophenyl)(3,4-dichlorophenyl)methanamine (63k)



The title compound was synthesized according to general procedure **F** using (4-bromophenyl)(3,4-dichlorophenyl)methanone (**62k**, 80 mg, 0.24 mmol, 1 eq), ammonium acetate (374 mg, 4.85 mmol, 20 eq) and $NaBH_3CN$ (41 mg, 0.66 mmol, 2.7 eq). Total time: overnight at reflux. The product was afforded without purification (75 mg, 0.23 mmol, 93%). LC-MS $[C_{13}H_{10}BrCl_2N–NH_2]^+$: 312.92/314.92 calculated, 312.93/314.93 found.

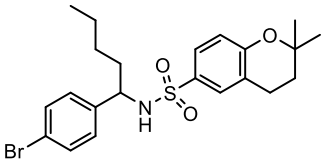
***N*-(1-(4-Bromophenyl)butyl)-2,2-dimethylchromane-6-sulfonamide (64b)**



The title compound was synthesized according to general procedure **G** using 1-(4-bromophenyl)butan-1-amine (**63b**, 34 mg, 0.15 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonyl chloride (**55**, 46.6 mg,

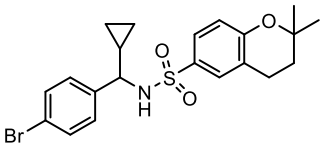
0.179 mmol, 1.2 eq) and Et_3N (62 µL, 0.45 mmol, 3 eq). Total time: overnight at rt. The product was afforded without purification (67 mg, 0.15 mmol, 99%).

N-(1-(4-Bromophenyl)pentyl)-2,2-dimethylchromane-6-sulfonamide (64c)



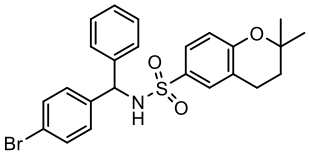
The title compound was synthesized according to general procedure **G** using 1-(4-bromophenyl)-pentan-1-amine (**63c**, 30.0 mg, 0.124 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonylchloride (**55**, 48.5 mg, 0.186 mmol, 1.5 eq) and Et_3N (52 µL, 0.37 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (5-25% EtOAc in *n*-pentane) afforded the product (32 mg, 0.068 mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.13 (dt, *J* = 2.4, 1.1 Hz, 1H), 6.92 – 6.85 (m, 2H), 6.69 (d, *J* = 8.6 Hz, 1H), 4.83 (d, *J* = 7.0 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 1H), 2.67 – 2.52 (m, 2H), 1.79 (td, *J* = 6.8, 2.3 Hz, 2H), 1.74 – 1.67 (m, 1H), 1.64 – 1.55 (m, 1H), 1.34 (s, 3H), 1.32 (s, 3H), 1.27 – 1.20 (m, 4H), 0.81 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.71, 140.35, 131.38, 130.82, 129.29, 128.54, 124.98, 121.14, 121.11, 117.68, 75.74, 57.80, 37.49, 32.34, 28.03, 27.02, 26.85, 22.31, 13.97. LC-MS $[C_{22}H_{28}BrNO_3S+H]^+$: 466.10/468.10 calculated, 465.87/467.80 found.

N-((4-Bromophenyl)(cyclopropyl)methyl)-2,2-dimethylchromane-6-sulfonamide (64d)



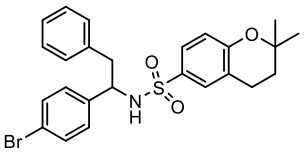
The title compound was synthesized according to general procedure **G** using (4-bromophenyl)(cyclopropyl)-methanamine (**63d**, 45 mg, 0.20 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonylchloride (**55**, 104 mg, 0.398 mmol, 2 eq) and Et_3N (83 µL, 0.60 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (5-25% EtOAc in *n*-pentane) afforded the product (30 mg, 0.066 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.32 – 7.24 (m, 2H), 7.13 (dt, *J* = 2.3, 1.1 Hz, 1H), 7.01 – 6.93 (m, 2H), 6.71 (d, *J* = 8.6 Hz, 1H), 4.97 (d, *J* = 5.0 Hz, 1H), 3.64 (dd, *J* = 8.7, 5.0 Hz, 1H), 2.70 – 2.51 (m, 2H), 1.86 – 1.73 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 1.05 (qt, *J* = 8.1, 4.9 Hz, 1H), 0.62 – 0.43 (m, 2H), 0.34 – 0.24 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.77, 139.54, 131.29, 130.75, 129.44, 128.90, 126.71, 121.33, 121.06, 117.74, 75.77, 62.28, 32.35, 27.03, 26.84, 22.30, 18.37, 4.61, 3.90. LC-MS $[C_{21}H_{24}BrNO_3S+H]^+$: 450.07/452.07 calculated, 449.87/451.73 found.

N-((4-Bromophenyl)(phenyl)methyl)-2,2-dimethylchromane-6-sulfonamide (64e)



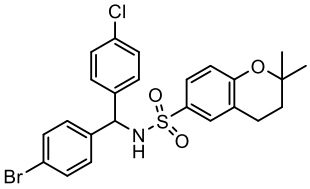
The title compound was synthesized according to general procedure **G** using (4-bromophenyl)-(phenyl)methanamine (**63e**, 44 mg, 0.17 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonylchloride (**55**, 52.5 mg, 0.201 mmol, 1.2 eq) and Et_3N (70 µL, 0.50 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (5-13% EtOAc in *n*-pentane) afforded the product (41 mg, 0.085 mmol, 51%). LC-MS $[C_{24}H_{24}BrNO_3S+H]^+$: 486.07/488.07 calculated, 485.67/487.80 found.

_N_-(1-(4-Bromophenyl)-2-phenylethyl)-2,2-dimethylchromane-6-sulfonamide (64f)



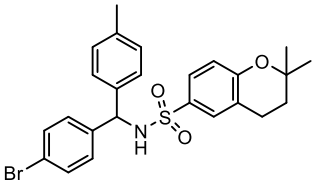
The title compound was synthesized according to general procedure **G** using (4-bromophenyl)-2-phenylethan-1-amine (**63f**, 75 mg, 0.27 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonylchloride (**55**, 142 mg, 0.398 mmol, 2 eq) and Et_3N (114 µL, 0.815 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (5-20% EtOAc in *n*-pentane) afforded the product (74.1 mg, 0.148 mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 3H), 7.23 – 7.18 (m, 3H), 7.07 (dt, *J* = 2.3, 1.1 Hz, 1H), 6.97 – 6.88 (m, 4H), 6.66 (d, *J* = 8.6 Hz, 1H), 4.81 (d, *J* = 5.6 Hz, 1H), 4.50 (q, *J* = 6.8 Hz, 1H), 3.00 – 2.87 (m, 2H), 2.67 – 2.50 (m, 2H), 1.83 – 1.76 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.81, 139.62, 135.94, 131.35, 130.19, 129.41, 129.30, 128.81, 128.77, 127.21, 126.72, 121.37, 121.13, 117.71, 75.76, 58.64, 44.14, 32.34, 27.12, 26.79, 22.31. LC-MS $[C_{25}H_{26}BrNO_3S+H]^+$: 500.09/502.09 calculated, 499.58/501.50 found.

_N_-((4-Bromophenyl)(4-chlorophenyl)methyl)-2,2-dimethylchromane-6-sulfonamide (64g)



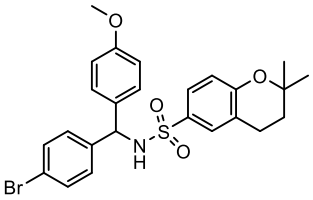
The title compound was synthesized according to general procedure **G** using (4-bromophenyl)(4-chlorophenyl)methanamine (**63g**, 58 mg, 0.20 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonylchloride (**55**, 102 mg, 0.391 mmol, 2 eq) and Et_3N (82 µL, 0.59 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (5-15% EtOAc in *n*-pentane) afforded the product (53.7 mg, 0.103 mmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.19 (dt, *J* = 2.3, 1.1 Hz, 1H), 7.18 – 7.14 (m, 2H), 7.05 – 7.00 (m, 2H), 6.99 – 6.94 (m, 2H), 6.70 (d, *J* = 8.7 Hz, 1H), 5.63 (d, *J* = 7.7 Hz, 1H), 5.48 (d, *J* = 7.7 Hz, 1H), 2.56 (t, *J* = 6.7 Hz, 2H), 1.78 (t, *J* = 6.7 Hz, 2H), 1.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.97, 139.26, 138.68, 133.74, 131.75, 130.21, 129.39, 129.17, 128.85, 128.80, 126.77, 121.87, 121.33, 117.79, 75.85, 60.31, 32.26, 26.91, 26.89, 22.27.

_N_-((4-Bromophenyl)(*p*-tolyl)methyl)-2,2-dimethylchromane-6-sulfonamide (64h)



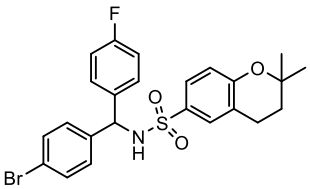
The title compound was synthesized according to general procedure **G** using (4-bromophenyl)(*p*-tolyl)methanamine (**63h**, 112 mg, 0.406 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonylchloride (**55**, 106 mg, 0.406 mmol, 1 eq) and Et_3N (170 µL, 1.22 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (5-15% EtOAc in *n*-pentane) afforded the product (79.7 mg, 0.159 mmol, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.23 (d, *J* = 2.5 Hz, 1H), 7.04 – 6.98 (m, 4H), 6.97 – 6.91 (m, 2H), 6.69 (d, *J* = 8.6 Hz, 1H), 5.52 (d, *J* = 7.5 Hz, 1H), 5.47 (d, *J* = 7.4 Hz, 1H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 1.77 (t, *J* = 6.8 Hz, 2H), 1.33 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.77, 139.93, 137.60, 137.33, 131.47, 130.47, 129.44, 129.39, 129.23, 127.29, 126.77, 121.40, 121.18, 117.67, 75.69, 60.67, 32.30, 26.90, 26.84, 22.24, 21.14. LC-MS $[C_{25}H_{26}BrNO_3S+NH_4]^+$: 517.12/519.11 calculated, 516.50/518.50 found.

_N_-((4-Bromophenyl)(4-methoxyphenyl)methyl)-2,2-dimethylchromane-6-sulfonamide (64i)



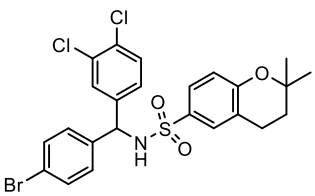
The title compound was synthesized according to general procedure **G** using (4-bromophenyl)(4-methoxyphenyl)methanamine (**63i**, 114 mg, 0.389 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonylchloride (**55**, 132 mg, 0.506 mmol, 1.3 eq) and Et_3N (163 µL, 1.17 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (5-20% EtOAc in *n*-pentane) afforded the product (82.5 mg, 0.160 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.21 (dt, *J* = 2.3, 1.1 Hz, 1H), 7.03 – 6.99 (m, 2H), 6.99 – 6.94 (m, 2H), 6.73 – 6.67 (m, 3H), 5.52 (d, *J* = 7.5 Hz, 1H), 5.46 (d, *J* = 7.5 Hz, 1H), 3.73 (s, 3H), 2.57 (t, *J* = 6.8 Hz, 2H), 1.77 (t, *J* = 6.8 Hz, 2H), 1.33 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.12, 157.77, 139.97, 132.35, 131.47, 130.47, 129.46, 129.20, 128.66, 126.74, 121.39, 121.19, 117.66, 113.53, 75.70, 60.38, 55.31, 32.26, 26.91, 26.84, 22.24. LC-MS $[C_{25}H_{26}BrNO_4S+NH_4]^+$: 533.11/535.11 calculated, 532.50/534.58 found.

_N_-((4-Bromophenyl)(4-fluorophenyl)methyl)-2,2-dimethylchromane-6-sulfonamide (64j)



The title compound was synthesized according to general procedure **G** using (4-bromophenyl)(4-fluorophenyl)methanamine (**63j**, 80 mg, 0.29 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonylchloride (**55**, 74.5 mg, 0.286 mmol, 1 eq) and Et_3N (119 µL, 0.857 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (5-20% EtOAc in *n*-pentane) afforded the product (34 mg, 0.067 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.20 (dt, *J* = 2.3, 1.1 Hz, 1H), 7.09 – 7.02 (m, 2H), 7.01 – 6.95 (m, 2H), 6.93 – 6.84 (m, 2H), 6.71 (d, *J* = 8.6 Hz, 1H), 5.50 (s, 2H), 2.58 (t, *J* = 6.7 Hz, 2H), 1.78 (t, *J* = 6.8 Hz, 2H), 1.34 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.23 (d, $J_{C\text{-}F}$ = 247.2 Hz), 157.95, 139.47, 136.03 (d, $J_{C\text{-}F}$ = 3.4 Hz), 131.71, 130.29, 129.34 (d, $J_{C\text{-}F}$ = 16.0 Hz), 129.18, 126.77, 121.78, 121.29, 117.78, 115.58 (d, $J_{C\text{-}F}$ = 21.7 Hz), 75.83, 61.23, 32.26, 26.94, 26.84, 21.86.

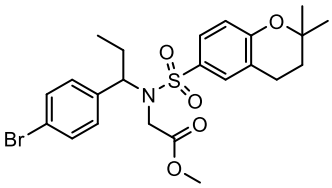
_N_-((4-Bromophenyl)(3,4-dichlorophenyl)methyl)-2,2-dimethylchromane-6-sulfonamide (64k)



The title compound was synthesized according to general procedure **G** using (4-bromophenyl)(3,4-dichlorophenyl)methanamine (**63k**, 74.7 mg, 0.226 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonylchloride (**55**, 64.7 mg, 0.248 mmol, 1.1 eq) and Et_3N (94 µL, 0.68 mmol, 3 eq). Total time: overnight at rt. Silica gel column chromatography (5-20% EtOAc in *n*-pentane) afforded the product (28 mg, 50 µmol, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.26 (d, *J* = 1.8 Hz, 1H), 7.23 (dt, *J* = 2.1, 0.9 Hz, 1H), 7.19 – 7.15 (m, 1H), 6.99 – 6.92 (m, 3H), 6.73 (d, *J* = 8.6 Hz, 1H), 5.47 (d, *J* = 7.4 Hz, 1H), 5.41 (d, *J* = 7.4 Hz, 1H), 2.60 (t, *J* = 6.9, 2H), 1.80 (t, *J*

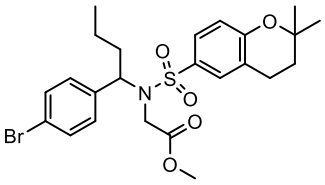
= 6.7 Hz, 2H), 1.34 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.19, 140.29, 138.67, 132.85, 132.00, 130.64, 129.97, 129.48, 129.35, 129.14, 128.36, 126.85, 126.83, 122.28, 121.47, 117.91, 75.95, 59.97, 32.25, 26.97, 26.95, 22.33.

Methyl *N*-(1-(4-bromophenyl)propyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (65a)



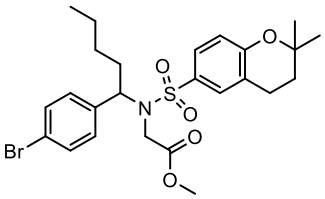
The title compound was synthesized according to general procedure **G** using methyl (1-(4-bromophenyl)propyl)glycinate (**63a**, 20 mg, 0.070 mmol, 1 eq), 2,2-dimethylchromane-6-sulfonylchloride (**55**, 30 mg, 0.12 mmol, 1.65 eq) and Et_3N (19 µL, 0.14 mmol, 2 eq). Total time: over-weekend at rt. Silica gel column chromatography (5-10% EtOAc in *n*-pentane) afforded the product (10 mg, 0.020 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.58 – 7.55 (m, 1H), 7.41 – 7.34 (m, 2H), 7.03 – 6.97 (m, 2H), 6.84 (d, *J* = 8.6 Hz, 1H), 4.69 (dd, *J* = 9.0, 6.4 Hz, 1H), 3.98 – 3.74 (m, 2H), 3.57 (s, 3H), 2.79 (t, *J* = 6.7 Hz, 2H), 1.94 – 1.78 (m, 4H), 1.37 (s, 6H), 0.80 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.47, 158.12, 136.67, 131.63, 130.86, 130.26, 129.98, 127.13, 122.15, 121.38, 117.86, 75.85, 61.84, 52.24, 44.84, 32.41, 26.96, 26.92, 24.60, 22.47, 11.36. LC-MS $[C_{23}H_{28}BrNO_5S+H]^+$: 510.09/512.09 calculated, 510.00/511.93 found.

Methyl *N*-(1-(4-bromophenyl)butyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (65b)



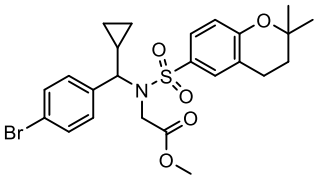
The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)butyl)-2,2-dimethylchromane-6-sulfonamide (**64b**, 67 mg, 0.15 mmol, 1 eq), methyl 2-bromoacetate (28 µL, 0.30 mmol, 2 eq) and BEMP (1 M in hexane, 296 µL, 0.296 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (5-10% EtOAc in *n*-pentane) afforded the product (55.0 mg, 0.105 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.59 – 7.56 (m, 1H), 7.40 – 7.34 (m, 2H), 7.05 – 6.99 (m, 2H), 6.84 (d, *J* = 8.6 Hz, 1H), 4.78 (dd, *J* = 9.3, 6.0 Hz, 1H), 3.98 – 3.75 (m, 2H), 3.57 (s, 3H), 2.79 (t, *J* = 6.8 Hz, 2H), 1.91 – 1.79 (m, 3H), 1.73 – 1.67 (m, 1H), 1.37 (s, 3H), 1.36 (s, 3H), 1.24 – 1.12 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.40, 158.09, 136.84, 131.56, 130.74, 130.18, 129.96, 127.51, 122.08, 121.34, 117.81, 75.80, 59.75, 52.18, 44.74, 33.35, 32.36, 26.90, 26.84, 22.42, 19.71, 13.80. LC-MS $[C_{24}H_{30}BrNO_5S+H]^+$: 524.11/526.11 calculated, 523.80/525.93 found.

Methyl *N*-(1-(4-bromophenyl)pentyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (65c)



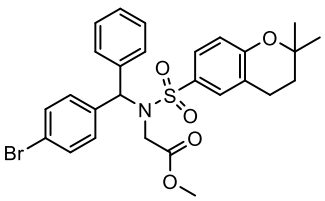
The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)pentyl)-2,2-dimethylchromane-6-sulfonamide (**64c**, 32 mg, 0.069 mmol, 1 eq), methyl 2-bromoacetate (13 µL, 0.14 mmol, 2 eq) and BEMP (1 M in hexane, 137 µL, 0.137 mmol, 2 eq). Total time: overnight at 80 °C. The product was afforded without purification (39 mg, 0.072 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.59 (d, *J* = 2.4 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.07 – 7.00 (m, 2H), 6.85 (d, *J* = 8.6 Hz, 1H), 4.75 (dd, *J* = 9.3, 6.1 Hz, 1H), 3.99 – 3.74 (m, 2H), 3.56 (s, 3H), 2.79 (t, *J* = 6.8 Hz, 2H), 1.84 (t, *J* = 6.8 Hz, 3H), 1.77 – 1.68 (m, 1H), 1.37 (s, 3H), 1.36 (s, 3H), 1.30 – 1.05 (m, 4H), 0.79 (t, *J* = 7.2 Hz, 3H). LC-MS $[C_{25}H_{32}BrNO_5S+Na]^+$: 560.11/562.11 calculated, 560.27/562.20 found.

Methyl *N*-((4-bromophenyl)(cyclopropyl)methyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (65d)



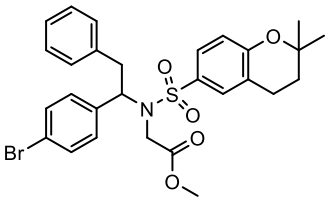
The title compound was synthesized according to general procedure **I** using *N*-((4-bromophenyl)-(cyclopropyl)methyl)-2,2-dimethylchromane-6-sulfonamide (**64d**, 30 mg, 0.067 mmol, 1 eq), methyl 2-bromoacetate (12.6 µL, 0.133 mmol, 2 eq) and BEMP (1 M in hexane, 133 µL, 0.133 mmol, 2 eq). Total time: overnight at 80 °C. The product was afforded without purification (38 mg, 0.073 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.50 (m, 1H), 7.47 (s, 1H), 7.39 – 7.30 (m, 2H), 7.23 – 7.16 (m, 2H), 6.81 (d, *J* = 8.6 Hz, 1H), 4.25 – 3.87 (m, 3H), 3.62 (s, 3H), 2.79 – 2.62 (m, 2H), 1.83 (t, *J* = 6.7 Hz, 2H), 1.35 (s, 6H), 0.94 – 0.77 (m, 1H), 0.68 (tt, *J* = 9.8, 4.6 Hz, 1H), 0.54 (tt, *J* = 8.5, 4.9 Hz, 1H), 0.30 – 0.13 (m, 2H). LC-MS $[C_{24}H_{28}BrNO_5S+Na]^+$): 544.08/546.07 calculated, 544.27/546.20 found.

Methyl *N*-((4-bromophenyl)(phenyl)methyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (65e)



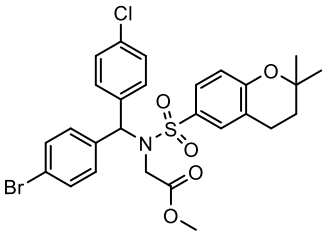
The title compound was synthesized according to general procedure **I** using *N*-((4-bromophenyl)-(phenyl)methyl)-2,2-dimethylchromane-6-sulfonamide (**64e**, 41 mg, 0.084 mmol, 1 eq), methyl 2-bromoacetate (16 µL, 0.17 mmol, 2 eq) and BEMP (1 M in hexane, 169 µL, 0.169 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (3-10% EtOAc in *n*-pentane) afforded the product (34 mg, 0.062 mmol, 73%). LC-MS $[C_{27}H_{28}BrNO_5S+Na]^+$: 580.08/582.07 calculated, 580.20/582.13 found.

Methyl *N*-(1-(4-bromophenyl)-2-phenylethyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (65f)



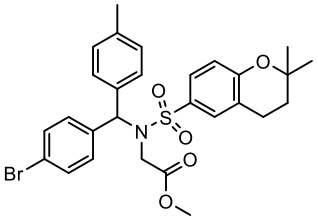
The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)-2-phenylethyl)-2,2-dimethylchromane-6-sulfonamide (**64f**, 74.1 mg, 0.148 mmol, 1 eq), methyl 2-bromoacetate (28 µL, 0.30 mmol, 2 eq) and BEMP (1 M in hexane, 296 µL, 0.296 mmol, 2 eq). Total time: overnight at 80 °C. The product was afforded without purification (83.2 mg, 0.145 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.35 – 7.30 (m, 2H), 7.19 – 7.10 (m, 3H), 7.09 – 7.04 (m, 2H), 7.03 – 6.98 (m, 2H), 6.81 (d, *J* = 8.7 Hz, 1H), 5.09 (dd, *J* = 9.4, 5.9 Hz, 1H), 4.10 – 3.80 (m, 2H), 3.59 (s, 3H), 3.24 – 3.18 (m, 2H), 2.75 (t, *J* = 6.7 Hz, 2H), 1.82 (t, *J* = 6.8 Hz, 2H), 1.35 (d, *J* = 2.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.35, 158.10, 137.40, 135.88, 131.46, 130.59, 130.50, 129.92, 129.06, 128.50, 127.43, 126.56, 122.22, 121.33, 117.87, 75.79, 61.68, 52.24, 45.44, 37.79, 32.30, 26.98, 26.82, 22.38. LC-MS $[C_{28}H_{30}BrNO_5S+Na]^+$: 594.09/596.09 calculated, 594.00/596.00 found.

Methyl *N*-((4-bromophenyl)(4-chlorophenyl)methyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (65g)



The title compound was synthesized according to general procedure **I** using *N*-((4-bromophenyl)(4-chlorophenyl)methyl)-2,2-dimethylchromane-6-sulfonamide (**64g**, 53.7 mg, 0.103 mmol, 1 eq), methyl 2-bromoacetate (20 µL, 0.21 mmol, 2 eq) and BEMP (1 M in hexane, 206 µL, 0.206 mmol, 2 eq). Total time: overnight at 80 °C. The product was afforded without purification (63.2 mg, 0.107 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.40 (dt, *J* = 2.3, 1.1 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.23 – 7.17 (m, 2H), 7.04 – 6.98 (m, 2H), 6.97 – 6.92 (m, 2H), 6.79 (d, *J* = 8.7 Hz, 1H), 6.10 (s, 1H), 4.02 (s, 2H), 3.50 (s, 3H), 2.67 (t, *J* = 6.7 Hz, 2H), 1.81 (t, *J* = 6.7 Hz, 2H), 1.35 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.66, 158.21, 136.88, 136.26, 134.02, 131.55, 130.71, 130.44, 130.19, 129.87, 128.59, 127.51, 122.16, 121.29, 117.77, 75.86, 63.92, 52.17, 46.78, 32.29, 26.87, 26.86, 22.33.

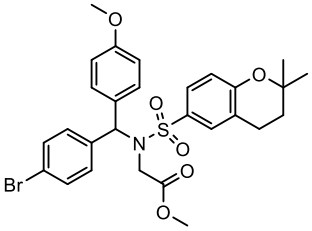
Methyl *N*-((4-bromophenyl)(*p*-tolyl)methyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (65h)



The title compound was synthesized according to general procedure **I** using *N*-((4-bromophenyl)(*p*-tolyl)methyl)-2,2-dimethylchromane-6-sulfonamide (**64h**, 79.7 mg, 0.159 mmol, 1 eq), methyl 2-bromoacetate (30 µL, 0.32 mmol, 2 eq) and BEMP (1 M in hexane, 319 µL, 0.319 mmol, 2 eq). Total time: overnight at 80 °C. Silica gel column chromatography (5-15% EtOAc in *n*-pentane) afforded the product (67.5 mg, 0.118 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.45 (dt, *J* = 2.4, 1.1 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.07 – 6.95 (m, 4H), 6.92 – 6.86 (m, 2H), 6.78 (d, *J* = 8.6

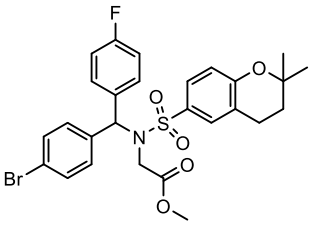
Hz, 1H), 6.11 (s, 1H), 4.02 (s, 2H), 3.47 (s, 3H), 2.67 (t, *J* = 6.6 Hz, 2H), 2.29 (s, 3H), 1.80 (t, *J* = 6.8 Hz, 2H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.84, 158.07, 137.91, 137.72, 134.54, 131.29, 130.61, 130.26, 130.03, 129.15, 129.09, 127.58, 121.69, 121.18, 117.67, 75.75, 64.22, 52.04, 46.69, 32.32, 26.88, 26.82, 22.32, 21.15. LC-MS $[C_{28}H_{30}BrNO_5S+NH_4]^+$: 589.14/591.13 calculated, 588.75/590.75 found.

Methyl *N*-((4-bromophenyl)(4-methoxyphenyl)methyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (65i)



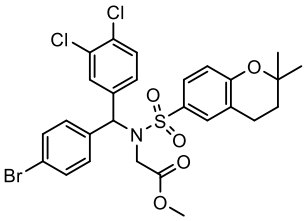
The title compound was synthesized according to general procedure **I** using *N*-((4-bromophenyl)(4-methoxyphenyl)methyl)-2,2-dimethylchromane-6-sulfonamide (**64i**, 82.5 mg, 0.160 mmol, 1 eq), methyl 2-bromoacetate (30 µL, 0.32 mmol, 2 eq) and BEMP (1 M in hexane, 319 µL, 0.319 mmol, 2 eq). Total time: overnight at 80 °C. The product was afforded without purification (96.8 mg, 0.164 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.43 (dt, *J* = 2.3, 1.1 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.03 – 6.97 (m, 2H), 6.96 – 6.91 (m, 2H), 6.80 – 6.70 (m, 3H), 6.10 (s, 1H), 4.01 (d, *J* = 5.3 Hz, 2H), 3.76 (s, 3H), 3.49 (s, 3H), 2.67 (td, *J* = 6.8, 1.8 Hz, 2H), 1.80 (t, *J* = 6.8 Hz, 2H), 1.35 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.83, 159.31, 158.03, 137.81, 131.27, 130.52, 130.41, 130.20, 130.02, 129.47, 127.49, 121.59, 121.16, 117.63, 113.72, 75.74, 63.98, 55.30, 52.04, 46.64, 32.26, 26.84, 26.80, 22.28. LC-MS $[C_{28}H_{30}BrNO_6S+NH_4]^+$: 605.13/607.13 calculated, 604.75/606.75 found.

Methyl *N*-((4-bromophenyl)(4-fluorophenyl)methyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (65j)



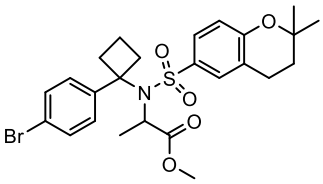
The title compound was synthesized according to general procedure **I** using *N*-((4-bromophenyl)(4-fluorophenyl)methyl)-2,2-dimethylchromane-6-sulfonamide (**64j**, 34 mg, 0.067 mmol, 1 eq), methyl 2-bromoacetate (13.0 µL, 0.135 mmol, 2 eq) and BEMP (1 M in hexane, 319 µL, 0.319 mmol, 2 eq). Total time: overnight at 80 °C. The product was afforded without purification (36 mg, 0.062 mmol, 93%). LC-MS $[C_{27}H_{27}BrFNO_5S+NH_4]^+$: 593.11/595.11 calculated, 592.83/594.75 found.

Methyl *N*-((4-bromophenyl)(3,4-dichlorophenyl)methyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)glycinate (65k)



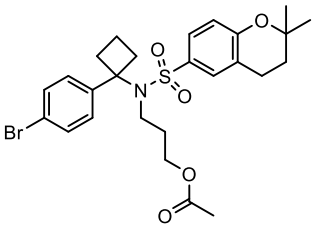
The title compound was synthesized according to general procedure **I** using *N*-((4-bromophenyl)(3,4-dichlorophenyl)methyl)-2,2-dimethylchromane-6-sulfonamide (**64k**, 27.5 mg, 0.050 mmol, 1 eq), methyl 2-bromoacetate (9.4 µL, 0.099 mmol, 2 eq) and BEMP (1 M in hexane, 99 µL, 0.099 mmol, 2 eq). Total time: overnight at 80 °C. The product was afforded without purification (22 mg, 0.036 mmol, 72%). LC-MS $[C_{27}H_{26}BrCl_2NO_5S+NH_4]^+$: 643.04/645.04 calculated, 642.75/644.75 found.

Methyl *N*-(1-(4-bromophenyl)cyclobutyl)-*N*-((2,2-dimethylchroman-6-yl)sulfonyl)alaninate (66a)



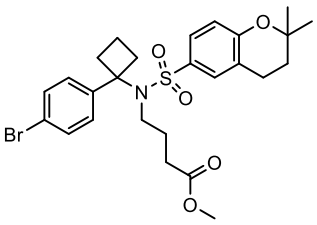
The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-2,2-dimethylchromane-6-sulfonamide (**60c**, 200 mg, 0.444 mmol, 1 eq), methyl 2-bromopropanoate (59 µL, 0.53 mmol, 1.2 eq) and BEMP (1 M in hexane, 0.488 mL, 0.488 mmol, 1.1 eq). Total time: 3 days at 80 °C. Silica gel column chromatography (5-20% EtOAc in *n*-pentane) afforded the product (23 mg, 0.043 mmol, 10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.41 – 7.32 (m, 4H), 7.25 (d, *J* = 2.4 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 1H), 3.71 (s, 3H), 3.03 – 2.85 (m, 2H), 2.71 (t, *J* = 6.7 Hz, 2H), 2.47 – 2.40 (m, 1H), 2.38 – 2.29 (m, 1H), 1.84 (t, *J* = 6.7 Hz, 2H), 1.78 – 1.68 (m, 1H), 1.55 (d, *J* = 7.3 Hz, 3H), 1.52 – 1.46 (m, 1H), 1.36 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.62, 157.55, 142.42, 133.45, 131.07, 129.70, 129.59, 126.91, 121.39, 121.00, 117.56, 75.75, 65.67, 56.38, 52.55, 34.98, 34.72, 32.44, 27.01, 26.92, 22.43, 18.46, 14.91. LC-MS $[C_{25}H_{30}BrNO_5S+Na]^+$: 558.09/560.09 calculated, 558.00/560.00 found.

3-((*N*-(1-(4-Bromophenyl)cyclobutyl)-2,2-dimethylchromane)-6-sulfonamido)propyl acetate (66b)



The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-2,2-dimethylchromane-6-sulfonamide (**60c**, 60.0 mg, 0.133 mmol, 1 eq), 3-bromopropyl acetate (50 mg, 0.28 mmol, 2.1 eq) and BEMP (1 M in hexane, 280 µL, 0.280 mmol, 2.1 eq). Total time: 3 days at 80 °C. Silica gel column chromatography (5-20% EtOAc in *n*-pentane) afforded the product (58 mg, 0.095 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 4H), 7.28 (d, *J* = 5.6 Hz, 1H), 6.88 (s, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.27 – 3.19 (m, 2H), 2.76 – 2.60 (m, 4H), 2.57 – 2.49 (m, 2H), 2.05 (s, 3H), 2.02 – 1.94 (m, 2H), 1.85 – 1.70 (m, 3H), 1.65 – 1.51 (m, 1H), 1.33 (s, 6H). LC-MS $[C_{26}H_{32}BrNO_5S+NH_4]^+$: 567.15/569.15 calculated, 566.83/568.83 found.

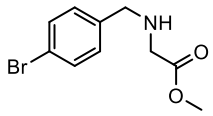
Methyl 4-((*N*-(1-(4-bromophenyl)cyclobutyl)-2,2-dimethylchromane)-6-sulfonamido)butanoate (66c)



The title compound was synthesized according to general procedure **I** using *N*-(1-(4-bromophenyl)cyclobutyl)-2,2-dimethylchromane-6-sulfonamide (**60c**, 20 mg, 0.044 mmol, 1 eq), methyl 4-bromobutanoate (10 µL, 0.079 mmol, 1.8 eq) and BEMP (1 M in hexane, 89 µL, 0.089 mmol, 2 eq). Total time: 3 days at 80 °C. Silica gel column chromatography (10-20% EtOAc in *n*-pentane) afforded the product (22 mg, 0.040 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 4H), 7.27 (dd, *J* = 8.7, 2.4 Hz 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 3.67 (s, 3H), 3.24 – 3.18 (m, 2H), 2.77 – 2.67 (m, 2H), 2.64 (t, *J* = 6.7 Hz, 2H), 2.59 – 2.50 (m, 2H), 2.30 (t, *J* = 7.0 Hz, 2H), 2.00 – 1.91 (m,

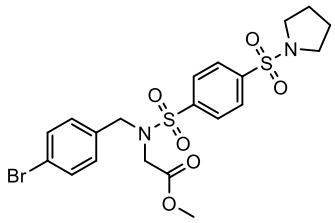
2H), 1.82 – 1.72 (m, 3H), 1.61 – 1.52 (m, 1H), 1.33 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.55, 157.38, 142.72, 131.70, 131.25, 129.13, 128.97, 126.62, 121.25, 121.21, 117.30, 75.68, 65.34, 51.77, 46.64, 35.48, 32.40, 31.24, 26.95, 26.58, 22.36, 14.66.

Methyl (4-bromobenzyl)glycinate (67)



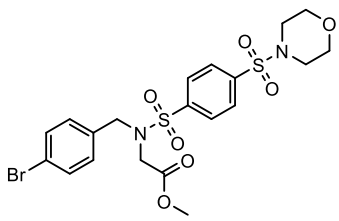
To a stirred solution of 4-bromobenzaldehyde (1.0 g, 5.4 mmol, 1 eq) in anhydrous MeOH (50 mL, 0.1 M) with 3 Å molecular sieves was added glycine methyl ester hydrochloride (0.81 g, 6.5 mmol, 1.2 eq), Et_3N (0.90 mL, 6.5 mmol, 1.2 eq) and AcOH (1.24 mL, 21.6 mmol, 4 eq) at rt. The mixture was stirred at rt for 1 h. $NaBH_3CN$ (0.41 g, 6.5 mmol, 1.2 eq) was added and the reaction was stirred at rt for another 2 h. The reaction mixture was filtered through Celite and the filtrate was concentrated. The residue was diluted in EtOAc, washed with sat. $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (20-30% EtOAc in *n*-pentane) to afford the product (1.06 g, 4.11 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.23 – 7.18 (m, 2H), 3.75 (s, 2H), 3.72 (s, 3H), 3.39 (s, 2H), 1.95 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.78, 138.53, 131.50, 129.94, 120.94, 52.51, 51.81, 49.78. LC-MS $[C_{10}H_{12}BrNO_2+H]^+$: 258.01/260.01 calculated, 258.00/259.92 found.

Methyl *N*-(4-bromobenzyl)-*N*-((4-(pyrrolidin-1-ylsulfonyl)phenyl)sulfonyl)glycinate (68a)



The title compound was synthesized according to general procedure **H** using methyl(4-bromobenzyl)glycinate (**67**, 25 mg, 0.097 mmol, 1.2 eq), 4-(pyrrolidin-1-ylsulfonyl)benzenesulfonyl chloride (25 mg, 0.081 mmol, 1 eq), Et_3N (45 µL, 0.32 mmol, 4 eq) and a drop of pyridine. Total time: overnight at rt. The product was afforded without purification (10 mg, 0.019 mmol, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.92 (m, 4H), 7.51 – 7.44 (m, 2H), 7.19 – 7.12 (m, 2H), 4.47 (s, 2H), 3.96 (s, 2H), 3.56 (s, 3H), 3.34 – 3.23 (m, 4H), 1.86 – 1.75 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.71, 143.67, 141.30, 133.53, 132.21, 130.40, 128.20, 128.12, 122.69, 52.33, 51.01, 48.19, 46.63, 25.47. LC-MS $[C_{20}H_{23}BrN_2O_6S_2+H]^+$: 531.03/533.02 calculated , 531.08/533.00 found.

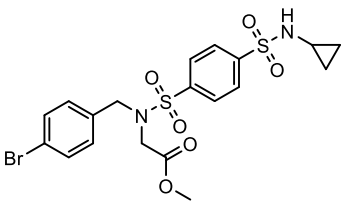
Methyl *N*-(4-bromobenzyl)-*N*-((4-(morpholinosulfonyl)phenyl)sulfonyl)glycinate (68b)



The title compound was synthesized according to general procedure **H** using methyl(4-bromobenzyl)glycinate (**67**, 24 mg, 0.092 mmol, 1.2 eq), 4-(morpholinosulfonyl)benzenesulfonyl chloride (25 mg, 0.077 mmol, 1 eq), Et_3N (43 µL, 0.31 mmol, 4 eq) and a drop of pyridine. Total time: overnight at rt. Silica gel column chromatography (20-50% EtOAc in *n*-pentane) afforded the product (10 mg, 0.018 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.02 (m, 2H), 7.94 – 7.86 (m, 2H), 7.51 – 7.47 (m, 2H), 7.19 – 7.13 (m, 2H), 4.47 (s, 2H), 3.97 (s, 2H), 3.80 – 3.74 (m, 4H), 3.57 (s, 3H), 3.08 – 3.01

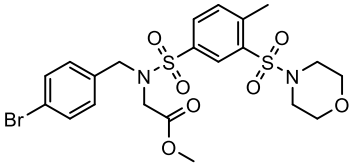
(m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.71, 144.30, 139.52, 133.46, 132.23, 130.40, 128.50, 128.30, 122.73, 66.16, 52.41, 51.02, 46.65, 46.10.

Methyl *N*-(4-bromobenzyl)-*N*-((4-(*N*-cyclopropylsulfamoyl)phenyl)sulfonyl)glycinate (68c)



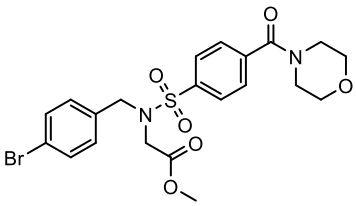
The title compound was synthesized according to general procedure **H** using methyl(4-bromobenzyl)glycinate (**67**, 26.2 mg, 0.101 mmol, 1.2 eq), 4-(*N*-cyclopropylsulfamoyl)benzenesulfonyl chloride (25 mg, 0.085 mmol, 1eq), Et_3N (47 µL, 0.34 mmol, 4 eq) and a drop of pyridine. Total time: overnight at rt. Silica gel column chromatography (20-50% EtOAc in *n*-pentane) afforded the product (15 mg, 0.028 mmol, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.99 (m, 4H), 7.51 – 7.44 (m, 2H), 7.21 – 7.13 (m, 2H), 5.09 (s, 1H), 4.47 (s, 2H), 3.97 (s, 2H), 3.56 (s, 3H), 2.33 – 2.27 (m, 1H), 0.70 – 0.58 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.74, 143.92, 143.87, 133.50, 132.21, 130.41, 128.24, 122.69, 52.36, 51.01, 46.66, 24.43, 6.42.

Methyl *N*-(4-bromobenzyl)-*N*-((4-methyl-3-(morpholinosulfonyl)phenyl)sulfonyl)glycinate (68d)



The title compound was synthesized according to general procedure **H** using methyl(4-bromobenzyl)glycinate (**67**, 22.8 mg, 0.088 mmol, 1.2 eq), 4-methyl-3-(morpholinesulfonyl)benzenesulfonyl chloride (25 mg, 0.074 mmol, 1 eq), Et_3N (41 µL, 0.30 mmol, 4 eq) and a drop of pyridine. Total time: overnight at rt. Silica gel column chromatography (20-50% EtOAc in *n*-pentane) afforded the product (9.2 mg, 0.016 mmol, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 2.0 Hz, 1H), 7.96 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.20 – 7.14 (m, 2H), 4.44 (s, 2H), 3.97 (s, 2H), 3.80 – 3.70 (m, 4H), 3.58 (s, 3H), 3.27 – 3.19 (m, 4H), 2.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.92, 143.43, 138.40, 136.86, 133.75, 133.63, 132.18, 131.53, 130.41, 129.50, 122.63, 66.45, 52.39, 50.87, 46.65, 45.48, 21.14.

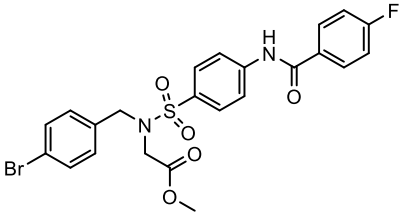
Methyl *N*-(4-bromobenzyl)-*N*-((4-(morpholine-4-carbonyl)phenyl)sulfonyl)glycinate (68e)



The title compound was synthesized according to general procedure **H** using methyl(4-bromobenzyl)glycinate (**67**, 26.7 mg, 0.104 mmol, 1.2 eq), 4-(morpholine-4-carbonyl)benzenesulfonyl chloride (25 mg, 0.086 mmol, 1 eq), Et_3N (48 µL, 0.34 mmol, 4 eq) and a drop of pyridine. Total time: overnight at rt. The product was afforded without purification (27 mg, 0.054 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 2H), 7.59 – 7.53 (m, 2H), 7.48 – 7.43 (m, 2H), 7.19 – 7.12 (m, 2H), 4.44 (s, 2H), 3.93 (s, 2H), 3.88 – 3.59 (m, 6H), 3.56 (s, 3H), 3.44 – 3.35 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.89, 168.71, 141.00, 139.80, 133.74, 132.09, 130.41,

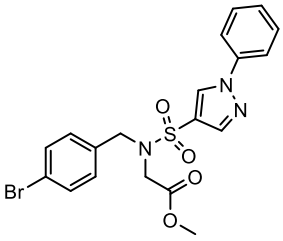
127.91, 127.82, 122.52, 66.90, 52.27, 51.00, 48.19, 46.74, 42.68. LC-MS $[C_{21}H_{23}BrN_2O_6S+H]^+$: 511.05/513.05 calculated, 511.08 / 513.00 found.

Methyl *N*-(4-bromobenzyl)-*N*-((4-(4-fluorobenzamido)phenyl)sulfonyl)glycinate (68f)



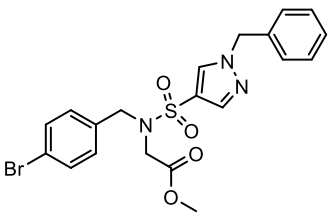
The title compound was synthesized according to general procedure **H** using methyl (4-bromobenzyl)glycinate (**67**, 40 mg, 0.16 mmol, 1 eq), 4-(4-fluorobenzamido)benzenesulfonyl chloride (97 mg, 0.31 mmol, 2 eq), Et_3N (86 µL, 0.62 mmol, 4 eq) and a drop of pyridine. Total time: 4 h at rt. Silica gel column chromatography (20-50% EtOAc in *n*-pentane) afforded the product (101 mg, 0.188 mmol, quant.). ^{1}H NMR (400 MHz, MeOD) δ 8.01 – 7.91 (m, 4H), 7.85 – 7.79 (m, 2H), 7.44 – 7.39 (m, 2H), 7.21 – 7.10 (m, 4H), 4.41 (s, 2H), 3.90 (s, 2H), 3.54 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 169.96, 167.13, 165.76 (d, $J_{C\text{-}F}$ = 252.6 Hz), 143.84, 134.83, 134.50, 132.37, 131.27 (d, $J_{C\text{-}F}$ = 3.1 Hz), 130.90, 130.81 (d, $J_{C\text{-}F}$ = 9.0 Hz), 128.99, 122.66, 120.92, 116.09 (d, $J_{C\text{-}F}$ = 21.9 Hz), 52.51, 51.66, 47.64. LC-MS $[C_{23}H_{20}BrFN_2O_5S+H]^+$: 535.03/537.03 calculated, 535.08/536.83 found.

Methyl *N*-(4-bromobenzyl)-*N*-((1-phenyl-1*H*-pyrazol-4-yl)sulfonyl)glycinate (68g)



The title compound was synthesized according to general procedure **H** using methyl (4-bromobenzyl)glycinate (**67**, 40 mg, 0.16 mmol, 1 eq), 1-phenyl-1*H*-pyrazole-4-sulfonyl chloride (75 mg, 0.31 mmol, 2 eq), Et_3N (86 µL, 0.62 mmol, 4 eq) and a drop of pyridine. Total time: 4 h at rt. Silica gel column chromatography (20-50% EtOAc in *n*-pentane) afforded the product (74.5 mg, 0.160 mmol, quant.). ^{1}H NMR (400 MHz, MeOD) δ 8.48 (d, *J* = 0.7 Hz, 1H), 7.98 (d, *J* = 0.7 Hz, 1H), 7.74 – 7.65 (m, 2H), 7.53 – 7.35 (m, 5H), 7.23 – 7.14 (m, 2H), 4.40 (s, 2H), 3.96 (s, 2H), 3.61 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 169.91, 140.34, 139.38, 134.41, 132.30, 130.73, 130.15, 130.02, 128.60, 123.71, 122.66, 120.27, 52.55, 51.39, 47.72. LC-MS $[C_{19}H_{18}BrN_3O_4S+H]^+$: 464.03/466.03 calculated, 464.17/466.08 found.

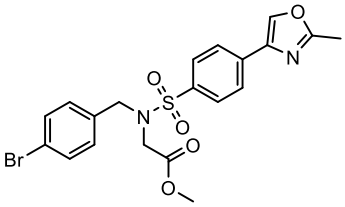
Methyl *N*-((1-benzyl-1*H*-pyrazol-4-yl)sulfonyl)-*N*-(4-bromobenzyl)glycinate (68h)



The title compound was synthesized according to general procedure **H** using methyl (4-bromobenzyl)glycinate (**67**, 25 mg, 0.097 mmol, 1 eq), 1-benzyl-1*H*-pyrazole-4-sulfonyl chloride (25 mg, 0.097 mmol, 1 eq), Et_3N (54 µL, 0.39 mmol, 4 eq) and a drop of pyridine. Total time: 2 h at rt. Silica gel column chromatography (5-40% EtOAc in *n*-pentane) afforded the product (38 mg, 0.079 mmol, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 0.7 Hz, 1H), 7.81 (d, *J* = 0.7 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.41 – 7.34 (m, 3H), 7.29 – 7.25 (m, 2H), 7.17 – 7.13 (m, 2H), 5.32 (s, 2H), 4.37 (s, 2H), 3.91 (s, 2H), 3.57 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.23, 139.26, 134.80, 134.11, 132.01, 131.51,

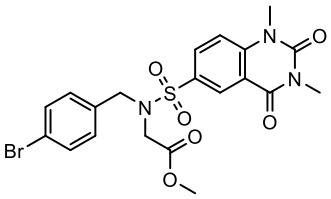
130.33, 129.22, 128.86, 128.25, 122.33, 122.03, 56.89, 52.17, 50.73, 46.95. LC-MS $[C_{20}H_{20}BrN_3O_4S+H]^+$: 478.04/480.04 calculated, 478.25/480.00 found.

Methyl *N*-(4-bromobenzyl)-*N*-((4-(2-methyloxazol-4-yl)phenyl)sulfonyl)glycinate (68i)



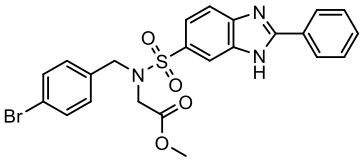
The title compound was synthesized according to general procedure **H** using methyl(4-bromobenzyl)glycinate (**67**, 30 mg, 0.12 mmol, 1.2 eq), 4-(2-methyloxazol-4-yl)benzenesulfonyl chloride (25 mg, 0.085 mmol, 1 eq), Et_3N (47 µL, 0.34 mmol, 4 eq) and a drop of pyridine. Total time: overnight at rt. Silica gel column chromatography (20-50% EtOAc in *n*-pentane) afforded the product (19 mg, 0.039 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.92 – 7.83 (m, 4H), 7.49 – 7.41 (m, 2H), 7.18 – 7.11 (m, 2H), 4.47 (s, 2H), 3.93 (s, 2H), 3.54 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.05, 162.52, 139.39, 138.57, 135.83, 134.98, 134.08, 132.05, 130.42, 128.07, 125.83, 122.40, 52.23, 50.94, 46.74, 14.11. LC-MS $[C_{20}H_{19}BrN_2O_5S+H]^+$: 479.03/481.03 calculated, 479.00/480.93 found.

Methyl *N*-(4-bromobenzyl)-*N*-((1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)sulfonyl)glycinate (68j)



The title compound was synthesized according to general procedure **H** using methyl(4-bromobenzyl)glycinate (**67**, 26.8 mg, 0.104 mmol, 1.2 eq), 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonyl chloride (25 mg, 0.087 mmol, 1 eq), Et_3N (49 µL, 0.35 mmol, 4 eq) and a drop of pyridine. Total time: overnight at rt. Silica gel column chromatography (20-50% EtOAc in *n*-pentane) afforded the product (31 mg, 0.061 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.3 Hz, 1H), 8.10 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.20 – 7.12 (m, 2H), 4.43 (s, 2H), 3.99 (s, 2H), 3.67 (s, 3H), 3.60 (s, 3H), 3.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.12, 160.83, 150.95, 143.30, 134.55, 133.71, 133.68, 132.10, 130.39, 129.08, 122.50, 115.46, 114.35, 52.39, 50.86, 46.81, 31.34, 28.91. LC-MS $[C_{20}H_{20}BrN_3O_6S+H]^+$: 510.03/512.03 calculated, 509.67/511.80 found.

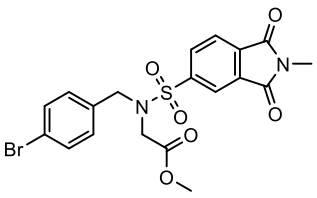
Methyl *N*-(4-bromobenzyl)-*N*-((2-phenyl-1*H*-benzo[*d*]imidazol-6-yl)sulfonyl)glycinate (68k)



The title compound was synthesized according to general procedure **H** using methyl(4-bromobenzyl)glycinate (**67**, 26 mg, 0.085 mmol, 1.2 eq), 2-phenyl-1*H*-benzo[*d*]imidazole-6-sulfonyl chloride (25 mg, 0.085 mmol, 1 eq), Et_3N (47.4 µL, 0.340 mmol, 4 eq) and a drop of pyridine. Total time: overnight at rt. Silica gel column chromatography (20-50% EtOAc in *n*-pentane) afforded the product (17 mg, 0.034 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (s, 1H), 8.16 – 8.08 (m, 3H), 7.77 – 7.70 (m, 1H),

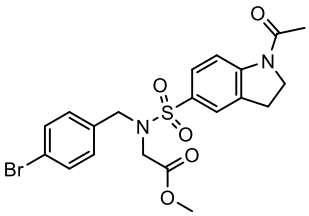
7.50 – 7.43 (m, 4H), 7.41 – 7.36 (m, 2H), 7.11 – 7.04 (m, 2H), 4.41 (s, 2H), 3.91 (s, 2H), 3.48 (s, 3H). LC-MS $[C_{23}H_{20}BrN_3O_4S+H]^+$: 514.04/516.04 calculated, 514.13/516.07 found.

Methyl *N*-(4-bromobenzyl)-*N*-((2-methyl-1,3-dioxoisoindolin-5-yl)sulfonyl)glycinate (68l)



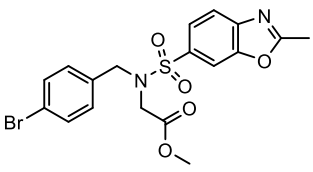
The title compound was synthesized according to general procedure **H** using methyl(4-bromobenzyl)glycinate (**67**, 29.8 mg, 0.116 mmol, 1.2 eq) and 2-methyl-1,3-dioxoisoindoline-5-sulfonyl chloride (25 mg, 0.096 mmol, 1 eq), Et_3N (54 µL, 0.38 mmol, 4 eq) and a drop of pyridine. Total time: overnight at rt. Silica gel column chromatography (20-50% EtOAc in *n*-pentane) afforded the product (15 mg, 0.032 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 1.6, 0.7 Hz, 1H), 8.21 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.99 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.21 – 7.13 (m, 2H), 4.47 (s, 2H), 4.00 (s, 2H), 3.58 (s, 3H), 3.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.79, 167.01, 166.92, 145.76, 135.37, 133.31, 133.04, 132.97, 132.24, 130.41, 123.92, 122.75, 122.35, 52.47, 51.01, 46.73, 24.53.

Methyl *N*-((1-acetylindolin-5-yl)sulfonyl)-*N*-(4-bromobenzyl)glycinate (68m)



The title compound was synthesized according to general procedure **H** using methyl (4-bromobenzyl)glycinate (**67**, 100 mg, 387 mmol, 1 eq), 1-acetylindoline-5-sulfonyl chloride (151 mg, 0.775 mmol, 1.5 eq), Et_3N (215 µL, 1.55 mmol, 4 eq) and a drop of pyridine. Total time: 4 h at rt. Silica gel column chromatography (20-70% EtOAc in *n*-pentane) afforded the product (34 mg, 0.072 mmol, 19%). ^{1}H NMR (400 MHz, MeOD+$CDCl_3$) δ 8.24 (d, *J* = 8.6 Hz, 1H), 7.67 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.61 (d, *J* = 1.9 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.16 – 7.06 (m, 2H), 4.38 (s, 2H), 4.18 (t, *J* = 8.6 Hz, 2H), 3.89 (s, 2H), 3.56 (s, 3H), 3.27 (t, *J* = 8.6 Hz, 2H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, MeOD+$CDCl_3$) δ 170.96, 169.79, 147.09, 134.52, 134.29, 133.25, 132.24, 130.73, 128.29, 124.33, 122.54, 117.04, 52.46, 51.48, 49.69, 47.48, 27.92, 24.29. LC-MS $[C_{20}H_{21}BrN_2O_5S+H]^+$: 481.04/483.04 calculated, 481.00/482.92 found.

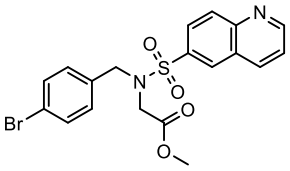
Methyl *N*-(4-bromobenzyl)-*N*-((2-methylbenzo[*d*]oxazol-6-yl)sulfonyl)glycinate (68n)



The title compound was synthesized according to general procedure **H** using methyl (4-bromobenzyl)glycinate (**67**, 25 mg, 0.097 mmol, 1 eq), 2-methylbenzo[*d*]oxazole-6-sulfonyl chloride (22 mg, 0.097 mmol, 1 eq), Et_3N (54 µL, 0.39 mmol, 4 eq) and a drop of pyridine. Total time: 2 h at rt. Silica gel column chromatography (20-50% EtOAc in *n*-pentane) afforded the product (28 mg, 0.062 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.85 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.77 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.17 – 7.11 (m, 2H), 4.46 (s, 2H), 3.96 (s, 2H), 3.54 (s, 3H), 2.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.05, 167.52, 150.43, 145.38, 136.04, 133.93, 132.05, 130.40, 123.88, 122.42,

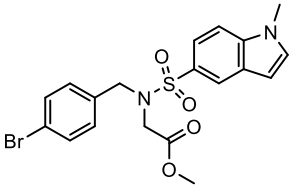
119.92, 110.50, 52.23, 50.98, 46.77, 14.91. LC-MS $[C_{18}H_{17}BrN_2O_5S+H]^+$: 453.01/455.01 calculated, 452.93/454.93 found.

Methyl *N*-(4-bromobenzyl)-*N*-(quinolin-6-ylsulfonyl)glycinate (68o)



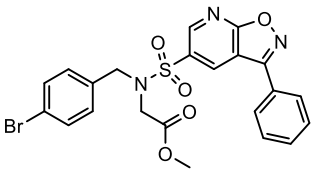
The title compound was synthesized according to general procedure **H** using methyl(4-bromobenzyl)glycinate (**67**, 40.8 mg, 0.158 mmol, 1.2 eq), quinoline-6-sulfonyl chloride (30 mg, 0.13 mmol, 1 eq), Et_3N (74 µL, 0.53 mmol, 4 eq) and a drop of pyridine. Total time: overnight at rt. Silica gel column chromatography (20-100% EtOAc in *n*-pentane) afforded the product (24 mg, 0.053 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.43 (d, *J* = 2.1 Hz, 1H), 8.29 (ddd, *J* = 8.3, 1.8, 0.7 Hz, 1H), 8.26 (dt, *J* = 9.0, 0.7 Hz, 1H), 8.09 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.56 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.20 – 7.12 (m, 2H), 4.52 (s, 2H), 4.01 (s, 2H), 3.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.01, 153.25, 149.54, 137.56, 137.35, 133.84, 132.09, 131.13, 130.43, 128.92, 127.31, 126.54, 122.74, 122.51, 52.27, 51.08, 46.83. LC-MS $[C_{19}H_{17}BrN_2O_4S+H]^+$: 449.02/451.01 calculated, 449.33/451.17 found.

Methyl *N*-(4-bromobenzyl)-*N*-((1-methyl-1*H*-indol-5-yl)sulfonyl)glycinate (68p)



The title compound was synthesized according to general procedure **H** using methyl (4-bromobenzyl)glycinate (**67**, 23 mg, 0.089 mmol, 1 eq), 1-methyl-1*H*-indole-5-sulfonyl chloride (20 mg, 0.087 mmol, 1 eq), Et_3N (49 µL, 0.35 mmol, 4 eq) and a drop of pyridine. Total time: 2 h at rt. Silica gel column chromatography (5-40% EtOAc in *n*-pentane) afforded the product (29 mg, 0.064 mmol, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 1.8 Hz, 1H), 7.69 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.44 – 7.38 (m, 3H), 7.19 (d, *J* = 3.2 Hz, 1H), 7.15 – 7.11 (m, 2H), 6.61 (dd, *J* = 3.2, 0.9 Hz, 1H), 4.44 (s, 2H), 3.91 (s, 2H), 3.85 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.38, 138.53, 134.62, 131.88, 131.30, 130.46, 129.97, 127.92, 122.11, 122.00, 120.43, 109.74, 102.90, 52.10, 51.07, 46.99, 33.30. LC-MS $[C_{19}H_{19}BrN_2O_4S+H]^+$: 451.03/453.03 calculated, 451.00/452.92 found.

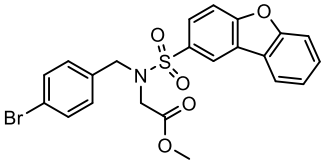
Methyl *N*-(4-bromobenzyl)-*N*-((3-phenylisoxazolo[5,4-*b*]pyridin-5-yl)sulfonyl)glycinate (68q)



The title compound was synthesized according to general procedure **H** using methyl (4-bromobenzyl)glycinate (**67**, 26.3 mg, 0.102 mmol, 1 eq), 3-phenylisoxazolo[5,4-*b*]pyridine-5-sulfonyl chloride (30 mg, 0.10 mmol, 1 eq), Et_3N (57 µL, 0.41 mmol, 4 eq) and a drop of pyridine. Total time: 2 h at rt. Silica gel column chromatography (2-20% EtOAc in *n*-pentane) afforded the product (29 mg, 0.056 mmol, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (d, *J* = 2.2 Hz, 1H), 8.83 (d, *J* = 2.2 Hz, 1H), 8.00 – 7.96 (m, 2H), 7.64 – 7.60 (m, 3H), 7.49 – 7.45 (m, 2H), 7.21 – 7.17 (m, 2H), 4.45 (s, 2H), 4.07 (s, 2H), 3.60 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.29, 169.15, 158.09, 150.17, 133.74, 133.19, 133.10, 132.26, 131.57, 130.38, 129.68,

127.94, 127.51, 122.82, 112.15, 52.55, 50.92, 46.90. LC-MS $[C_{22}H_{18}BrN_3O_5S+H]^+$: 516.02/518.02 calculated, 516.00/518.00 found.

Methyl *N*-(4-bromobenzyl)-*N*-(dibenzo[*b*,*d*]furan-2-ylsulfonyl)glycinate (68r)



The title compound was synthesized according to general procedure **H** using methyl (4-bromobenzyl)glycinate (**67**, 34.8 mg, 0.135 mmol, 1.2 eq), dibenzo[*b*,*d*]furan-2-sulfonyl chloride (30.0 mg, 0.112 mmol, 1 eq), Et_3N (62.4 µL, 0.450 mmol, 4 eq) and a drop of pyridine. Total time: 4 h at rt. Silica gel column chromatography (0-40% EtOAc in *n*-pentane) afforded the product (40 mg, 0.081 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 2.0, 0.5 Hz, 1H), 8.04 – 7.95 (m, 2H), 7.70 (dd, *J* = 8.6, 0.6 Hz, 1H), 7.64 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.56 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.50 – 7.40 (m, 3H), 7.20 – 7.13 (m, 2H), 4.50 (s, 2H), 3.98 (s, 2H), 3.51 (s, 3H). LC-MS $[C_{22}H_{18}BrNO_5S+H]^+$: 488.02/490.01 calculated, 487.83/489.83 found.

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