Design, synthesis, chemical and biological evaluation of 2,5,5-trisubstituted-1,2-thiazepan-6-one 1,1-dioxides

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ABSTRACT

Keywords:
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Sulfonamides
Sultam–polymer conjugates

In this article, we designed and synthesized a series of novel 2,5,5-trisubstituted (including spirocyclic) 1,2-thiazepan-6-one 1,1-dioxides (put simply, γ,γ-disubstituted β-keto ε-sultams), prepared a number of derivatives and evaluated their cytotoxic activity against MDA-MB-231 breast cancer cell line. In particular, alkylation of *N*-monosubstituted methanesulfonamides with α,α-disubstituted β-halogenated esters (including cyclic representatives) afforded the corresponding *N*-mesylated β-amino acid esters. The latters were involved in CSIC (*Carbanion-mediated Sulfonamide Intramolecular Cyclization*) reaction to give the target γ,γ-disubstituted β-keto ε-sultams (including spirocyclic representatives) in synthetically useful yields. This class of compounds can be considered as valuable building blocks since they possess carbonyl functionality and an EWG-activated methylene group capable of further functionalization. For instance, the condensation with DMFDMA afforded the corresponding α-dimethylaminomethylidene derivatives – the direct precursors for the heterocyclization reactions. Their treatment with hydrazine hydrate or guanidine hydrochloride provided the corresponding pyrazolo- and pyrimidofused ε-sultams. Despite the prepared β-keto ε-sultams showing weak cytotoxicity against the MDA-MB-231 breast cancer cell line, their pyrazolofused derivatives appeared perspective pharmacological templates with stable cytotoxic effects. Moreover, β-keto ε-sultams and their heterofused derivatives form the water-soluble conjugates with branched polymers based on dextran-polyacrylamide (D-PAA) that can be used as the transport module for the targeted drug delivery in biological media.

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1. Introduction

Anticancer drugs have revolutionized cancer treatment by improving survival rates and reducing mortality. Being essential for controlling cancer growth and spread they play a critical role in improving the quality of life and longevity of cancer patients [1–6].

The discovery of novel compounds possessing anticancer activity is essential to developing effective cancer therapies since it helps to expand the understanding of disease mechanisms and the potential therapeutic targets. The overcoming drug resistance and targeting previously unaffected cancer types through matching the right immune-targeted drugs to the individualized patient are other urgent challenges in precision oncology [7].

As an extension of our continuing search for the materials possessing (modified natural compounds [8], pyrrole derivatives [9]) or amplifying (carbon nanotubes [10,11], copolymer nanosystems [12–14]) anticancer and antitumor activity we next focused on sulfonamides and especially their cyclic analogues, considered as a separate class, sultams (from *sul*fa lact*ams*) [15–19].

Sulfonamides piqued our interest since they have been indispensable for medicinal chemistry and medicine on the whole from the emergence of the *sulfa drugs* [20,21]. Since then, SO_2–N fragment have been embedded into over 120 approved and marketed drugs along with more than 500 investigational and experimental drugs [22]. It is especially worth noting that nowadays sulfonamide functionality is widely exploited in anticancer drug design [23–30]. This is also true for cyclic sulfonamides [31].

The biological activity of sulfonamides underlay several ways for anticancer therapy. The main of them is based on inhibition of the cell cycle [32,33] since sulfonamides turned out good antagonists of the key enzyme activity: kinases [34], carbonic anhydrase [31,35], cyclooxygenases [36], *etc.*

The flip side of chemotherapy is its main disadvantage – non-selectivity of the chemical drugs and damage to normal tissues which causes serious complications and side effects [37]. The classic chemotherapy with doxorubicin [38] or paclitaxel [39] which have been the basis for cancer treatment may serve as an example. However, this imperfection can be bypassed *via* targeted drug delivery which significantly increases the effectiveness of chemotherapy and reduces the number of adverse effects [40]. For instance, nanocarriers used as a transport module for active compounds promote targeted drug delivery. This, in turn, prevents exposure to normal tissue and protects drugs from degradation thereby increasing the half-life, payload, and solubility of cytotoxic agents [41]. Branched polymers based on dextran-polyacrylamide (D-PAA) showed effectiveness in loading and transport of anticancer compounds for chemotherapy and photodynamic therapy [13,42].

The present work is devoted to the synthesis of novel 7-membered cyclic sulfonamides – ε-sultams, their biological evaluation as anticancer agents, and creating the water-soluble conjugates with D-PAA for the targeted drug delivery.

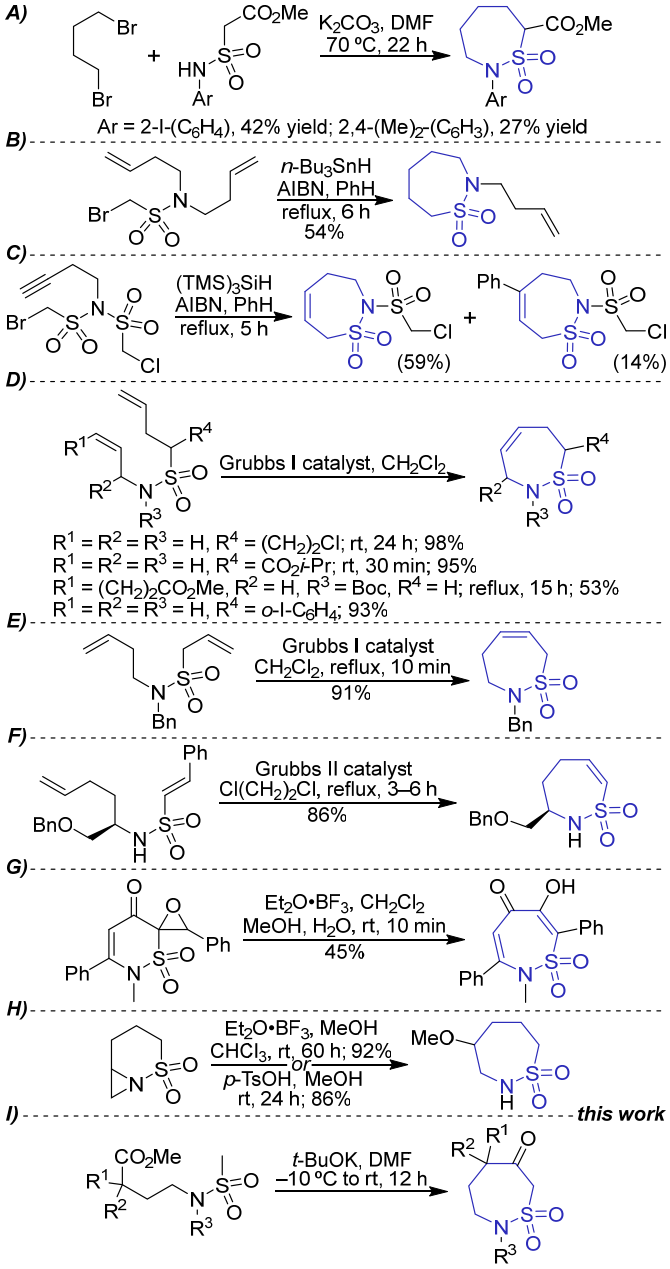
2. Results and discussion

2.1. Chemistry

Following the guidelines for lead-oriented synthesis [43] and considering the concept "*Escape from flatland*" [44,45] we focused on sp^3-enriched ε-sultams.

There are several approaches to the construction of unfused ε-sultam framework have been developed to date. Among them are intermolecular alkylation of methyl (*N*-arylsulfamoyl)acetates (Scheme 1, *A* [46,47]) and intramolecular radical cyclization of functionalized *N*-(butenyl)- and *N*-(butynyl)bromomethanesulfonamides (Scheme 1, *B* [48] and *C* [49]). The Ring-closing metathesis of acyclic sulfonamides decorated with unsaturated substituents is almost the main approach to access the structurally diverse ε-sultams (Scheme 1, *D* [50–54], *E* [55] and *F* [56]). Finally, worth noting the Lewis acid-catalyzed rearrangement reactions accompanied by the ring expansion. The substrates for these reactions are δ-sultams possessing annelated or spirosubstituted three-membered heterocycle (Scheme 1, *G* [57] and *H* [58,59]).

However, to the best of our knowledge, unfused δ-sultams have never been synthesized through the *sulfa*-Dieckmann reaction strategy (Scheme 1, *I*).



Scheme 1. Synthetic approaches toward unfused ε-sultams.

Recently we have reported the synthesis of *carbo*- and *hetero*fused 7-membered (*aza*)sultams [60–62] trough the CSIC (*Carbanion-mediated Sulfonate (Sulfonamide) Intermolecular Coupling (Intramolecular Cyclization)*) [63–68] reaction strategy. In present work we applied this strategy toward the synthesis of sp^3-enriched ε-sultams.

We envisaged the preparation of direct precursors for the *sulfa*-Dieckmann cyclization by the alkylation of *N*-monosubstituted methanesulfonamides with the corresponding β-

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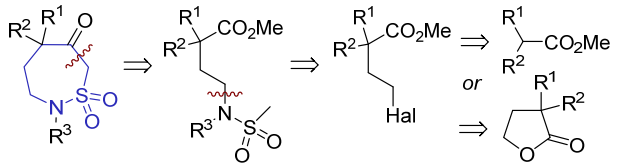
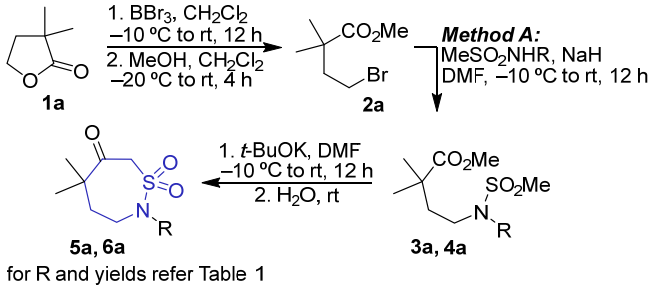
halogenated carboxylic esters, which in turn can be obtained from either α,α-disubstituted and cyclic carboxylic acids esters or α,α-disubstituted-γ-butyrolactones (Scheme 2).



Scheme 2. Retrosynthetic disconnection for the assembly of unfused ε-sultams.

We initially chose α,α-dimethyl-γ-butyrolactone **1a** as a model substrate, and investigated the viability of this strategy toward the synthesis of target ε-sultams.

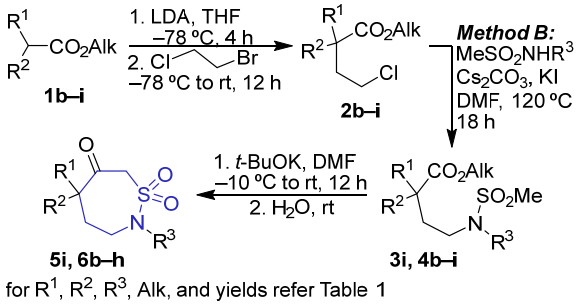
Following the literature method lactone **1a** was converted into the corresponding methyl 4-bromo-2,2-dimethylbutanoate (**2a**) which was used as an alkylating agent in the reaction with *N*-monosubstituted methane sulfonamides. The alkylation proceeded in DMF media at –20 °C using NaH as a base (*Method A*) and afforded the direct precursors **3a** and **4a** with good yields. Finally, the desired ε-sultams **5a** and **6a** were prepared by the treatment of above sulfonamides **3a**, **4a** with *t*-BuOK in DMF at –10 °C followed by appropriate workup procedure (Scheme 3 and Table 1, entries 1, 2).



Scheme 3. Synthesis of 5,5-dimethyl-3-substituted 1,2-thiazepan-6-one 1,1-dioxides.

However, the limited scope of accessible α,α-disubstituted and spirocyclic γ-butyrolactones prompted us to develop another more practical and robust method.

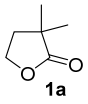
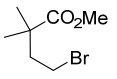
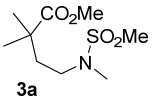
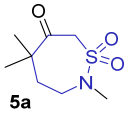
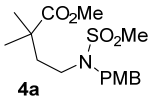
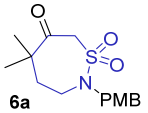
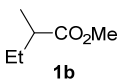
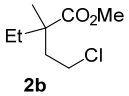
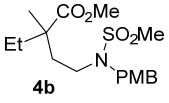
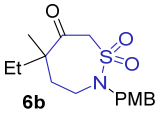
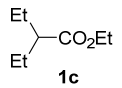
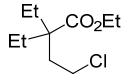
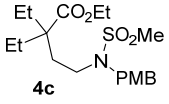
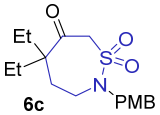
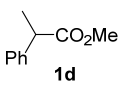
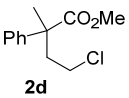
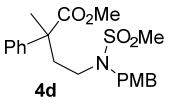
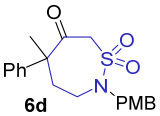
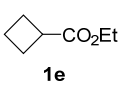
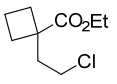
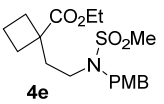
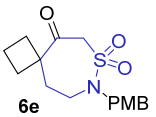
According to a novel strategy, a range of readily available α,α-disubstituted and *carbo*(*hetero*)cyclic esters **1b–i** were successfully alkylated with 1-bromo-2-chloro ethane under LDA-mediated conditions in THF at –78 °C to give the corresponding β-chloro esters **2b–i** with good to excellent yields (Scheme 3 and Table 1, entries 3–10). The subsequent reaction with *N*-monosubstituted methane sulfonamides was conducted in harsher conditions at elevated temperature (120 °C) and took more time (18 h) (*Method B*). The addition of KI as a catalyst (5 mol %) significantly improved the yield of sulfonamides **3i** and **4b–i**. The final step in this pathway – intramolecular *sulfa*-Dieckmann condensation was performed adopting the above reaction conditions so that the target 5,5-disubstituted and spirocyclic ε-sultams **5i** and **6b–h**. were isolated in synthetically useful yields (Scheme 4 and Table 1, entries 3–10). However, the most spatially crowded precursor **4i** failed to give the cyclized product, apparently because of steric hindrance (Table 1, entry 11).



Scheme 4. Synthesis of 3,5,5-trisubstituted and spirocyclic 1,2-thiazepan-6-one 1,1-dioxides.

Next, we demonstrated the synthetic utility of the obtained ε-sultams and involved them into further transformations and heterocyclizations.

Table 1. Starting, intermediate, and target compounds prepared *via* Schemes 3 and 4.

Entry	Starting compound	Alkylating agent	Yield (%)	Direct precursor	Yield (%)[a]	Target ε-sultam	Yield (%)
1	 **1a**	 **2a**	87	 **3a**	67 (*A*)	 **5a**	65
2	the same	the same	the same	 **4a**	83 (*A*)	 **6a**	83
3	 **1b**	 **2b**	86	 **4b**	65 (*B*)	 **6b**	70
4	 **1c**	 **2c**	89	 **4c**	48 (*B*)	 **6c**	59
5	 **1d**	 **2d**	93	 **4d**	43 (*B*)	 **6d**	50
6	 **1e**	 **2e**	45	 **4e**	45 (*B*)	 **6e**	67

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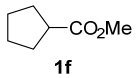
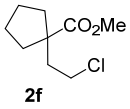
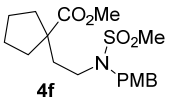
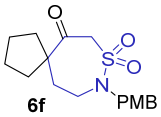
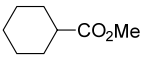
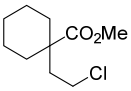
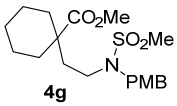
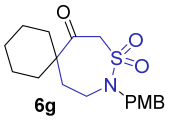
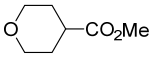
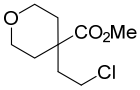
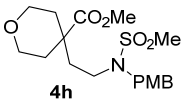
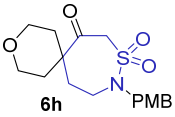
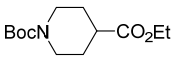
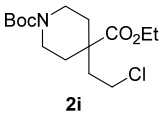
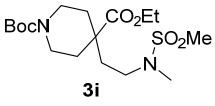
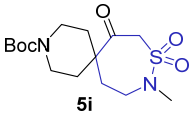
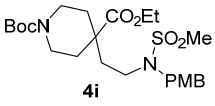
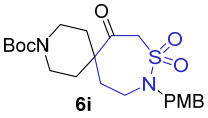
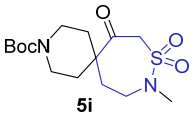
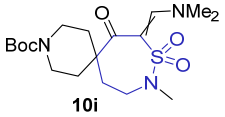
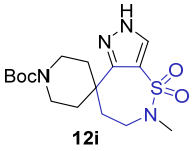
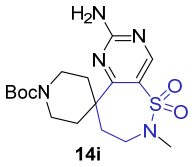
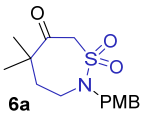
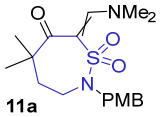
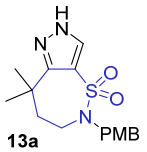
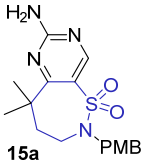
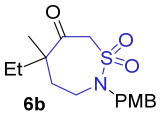
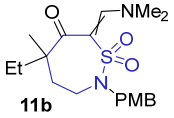
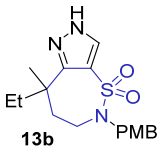
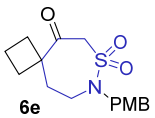
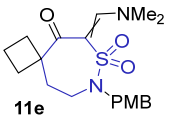
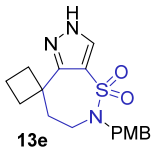
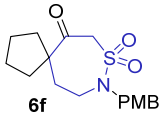
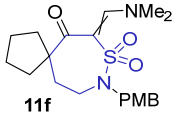
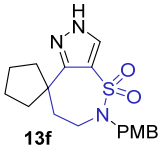
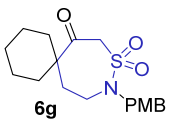
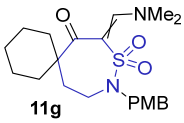
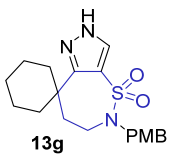
7	 **1f**	 **2f**	81	 **4f**	70 (*B*)	 **6f**	87
8	 **1g**	 **2g**	85	 **4g**	56 (*B*)	 **6g**	72
9	 **1h**	 **2h**	87	 **4h**	50 (*B*)	 **6h**	75
10	 **1i**	 **2i**	90	 **3i**	71 (*B*)	 **5i**	61
11	the same	the same	the same	 **4i**	48 (*B*)	 **6i**	not formed

[a]The applied *Method* is in parentheses.

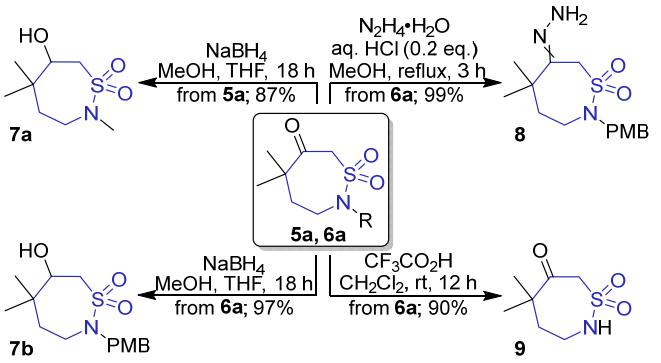
Table 2. Starting, intermediate, and target compounds prepared *via* Schemes 6.

Entry	Starting ε-sultam	Direct precursor	Yield (%)	Target pyrazole	Yield (%)[a]	Target pyrimidine	Yield (%)
1	 **5i**	 **10i**	84	 **12i**	79	 **14i**	88
2	 **6a**	 **11a**	92	 **13a**	87	 **15a**	93
3	 **6b**	 **11b**	82	 **13b**	91	–	–
4	 **6e**	 **11e**	75	 **13e**	84	–	–
5	 **6f**	 **11f**	83	 **13f**	94	–	–
6	 **6g**	 **11g**	88	 **13g**	92	–	–

The carbonyl functionality of model ε-sultams **5a** and **6a** was readily reduced with $NaBH_4$ in MeOH–THF media to give the corresponding alcohols **7a** (87%) and **7b** (97%). This functionality was also capable of forming hydrazones when refluxing with N_2H_4•H_2O and catalytic amounts of HCl in MeOH media. In this way, the corresponding hydrazine **8** was isolated in almost quantitative yield (Scheme 5).

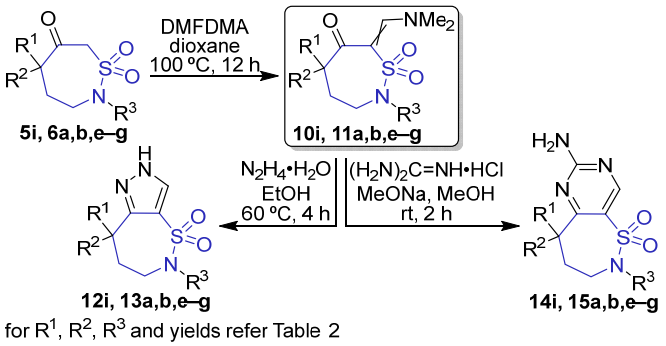
Next, we found the optimal reaction conditions for the acid-mediated cleavage of the *p*-methoxybenzyl (PMB) protecting group from the endocyclic nitrogen atom of the appropriately

substituted ε-sultams. Thus, the treatment of **6a** with CF_3CO_2H in CH_2Cl_2 media at rt afforded the *NH*-unsubstituted sultam **9** in 90% yield (Scheme 5).



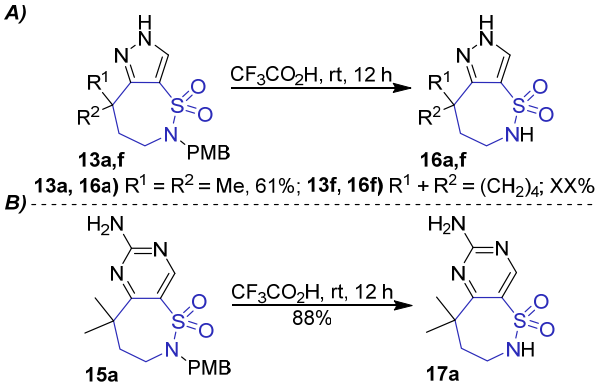
Scheme 5. Reactions of ε-sultams **5a** and **6a**

Then we turned our attention to the heterocyclization reactions. The convenient common precursors – the corresponding ketoenamines **10**, **11** were prepared from β-keto ε-sultams **5**, **6** and DMFDMA in 1,4-dioxane media with good yield. It should be noted, that *N*,*N*-dimethylaminomethylidene group is considered as the hidden aldehyde functionality and being adjacent to the ketone functionality acts as a stable 1,3-dicarbonyl equivalent [69–72]. With these key precursors in hands, we performed cyclization with *N*,*N*-binucleophiles. Thus, the reaction with N_2H_4•H_2O gave the fused pyrazoles **12**, **13**, while treatment with guanidine hydrochloride afforded amino pyrimidines **14**, **15** (Scheme 6 and Table 2).



Scheme 6. Sample text and their heterocyclizations

Finally, we subjected heterofused sultams **13** and **15** to the PMB deprotection procedure adopting the developed method (see Scheme 5). This provided access to the heterofused ε-sultams **16** and **17** possessing endocyclic NH group (Scheme 7).



Scheme 7. Cleavage of PMB-protecting group from **13a,f** and **15a**

2.2. Cytotoxicity of ε-sultams and their derivatives to breast cancer cells

Cytotoxic profile of the studied ε-sultams and their derivatives were tested against MDA-MB-231 breast cancer cell lines.

Compounds **5a**, **6a**, and **7b** showed weak cytotoxicity with maximum cell death of 30% (**5a**, **7b**) or its complete absence (**6a**) (Figure 1a). Compounds **6c**, **6b**, **6g 8**, **11a**, **15a**, and **17a** were more cytotoxic (Figure 1b–d). The number of cancer cells was decreased by 40–50% after incubation in 0.25 mM medium for 48 h. Despite these compounds exhibiting weak activity, they provide a basis for understanding the relationships of structure and biological activity [73,74]. Spirocyclic ε-sultam **6e** and heterofused derivative **13a** had stable cytotoxicity to cancer cells, reducing their number by more than 90% compared to the control (Figure 1c,d). IC_{50} for **13a** was 0.07 mM, **6e** was 0.13 mM. With that compounds **5i**, **6h**, **9**, **10i**, **12i**, **14i** did not possess cytotoxicity against MDA-MB-231 (Figure 1e,f).

A slight sensitivity of cancer cells toward compounds **13b** (maximum effect 85% at 0.25 mM) and **13f** (65% at the same concentration) was revealed (Figure 1g). Cell death was 98% at 0.25 mM for **13e**. IC_{50} for **13g** was 0.06 mM. The data obtained allowed us to deduce annulation of the pyrazole ring to the ε-sultam framework has a positive effect on cytotoxicity against MDA-MB-231.

Next, compounds **6b**, **6e 7b**, and **13a** possessing different levels of anticancer activity were selected for loading into the copolymer D-PAA and subsequent biological evaluation of obtained conjugates. Considering that nanocarriers can potentially increase cytotoxic effects in case of low bioavailability and insufficient penetration of active compounds into cells [75,76] we expected to improve the cytotoxic profile of the studied compounds. However, to our regret, no increase in the cytotoxicity was found for the conjugates with D-PAA (Figure 1h). Their cytotoxicity was close to those for active compounds at the same concentration without copolymer.

It should be taken into account that the cytotoxicity of polymer–small molecule conjugates is determined by several factors. Among them is the release of the active compounds into an aqueous solution. Since the studied ε-sultams and their heterofused derivatives are insoluble in water, it was assumed that they form stable conjugates resistant to dissociation. As a consequence, it prevents interaction with cellular targets. On the other hand, low affinity (as indicated by a high IC_{50}) for these targets can also be a reason for the weak activity of the conjugates [77–79].

Thus, among the studied ε-sultams and their derivatives, compounds **13a** and **13g** are the most perspective and have stable cytotoxic effects against breast cancer cell line MDA-MB-231.

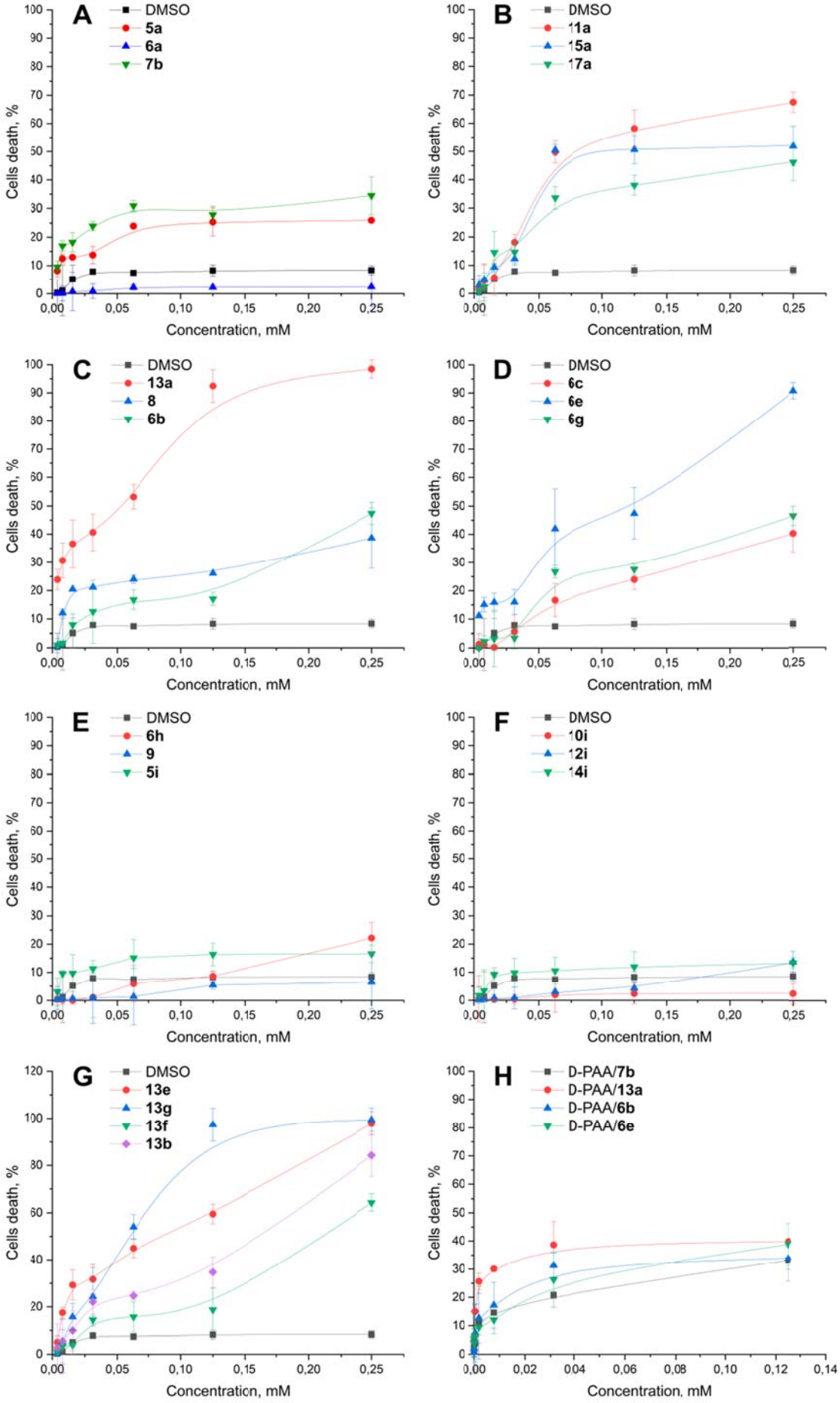


Figure 1. Cytotoxicity of studied compounds against breast cancer cell line MDA-MB-231 (M±SD)

2.3. Interaction between D-PAA and sulfonamides

DLS-derived distributions represented in the figure are plotted in R_H* coordinates. We consider R_H* as a quantity estimated

from diffusion coefficients by applying the Einstein-Stokes equation only to provide an intuitive scale for sample intercomparison. However, we note that RH* is not equivalent to the hydrodynamic radius R_H of non-electrolyte colloid particles.

Polyelectrolyte effects are clearly visible in Figure 2a, where we observe a complex three-mode distribution instead of a single-peak distribution from an uncharged polymer solution, namely, counter-ion mode, fast polyelectrolyte diffusion mode, and slow polyelectrolyte diffusion mode, as explained in detail elsewhere [80].

R_H* distributions from D-PAA/sulfonamide conjugates show a significant shift of the slow polyelectrolyte diffusion mode to lower R_H* and higher diffusion coefficient values, along with the complete (Figure 2e–f) or partial (Figure 2b–d) disappearance of the fast diffusion mode. These shifts (Figure 2b–f) indirectly indicate a particular quenching of the polyelectrolyte effect in D-PAAan/sulfonamide conjugates. Polyelectrolyte effect quenching increases in the following series: **7b** < **6b** < **6e** < **6h** < **13a**.

Additionally, the zeta potentials of D-PAA and D-PAA/sulfonamide conjugates (Table 3) reveal that sulfonamides decrease the charge of D-PAA. However, bare sulfonamides have no surface charge.

Table 3. Surface potentials of D-PAA and D-PAA/sultam conjugates

Entry	Sample	Zeta-potential, mV
1	D-PAA	–70.1
2	D-PAA/**7b**	–30.8
3	D-PAA/**6b**	–53.0
4	D-PAA/**6e**	–56.6
5	D-PAA/**6h**	–28.4
6	D-PAA/**13a**	–54.1

Quenching of a polyelectrolyte effect was not in accordance to zeta potential decreasing after different sulfonamide addition probably due to variance in sulfonamides solubility in water.

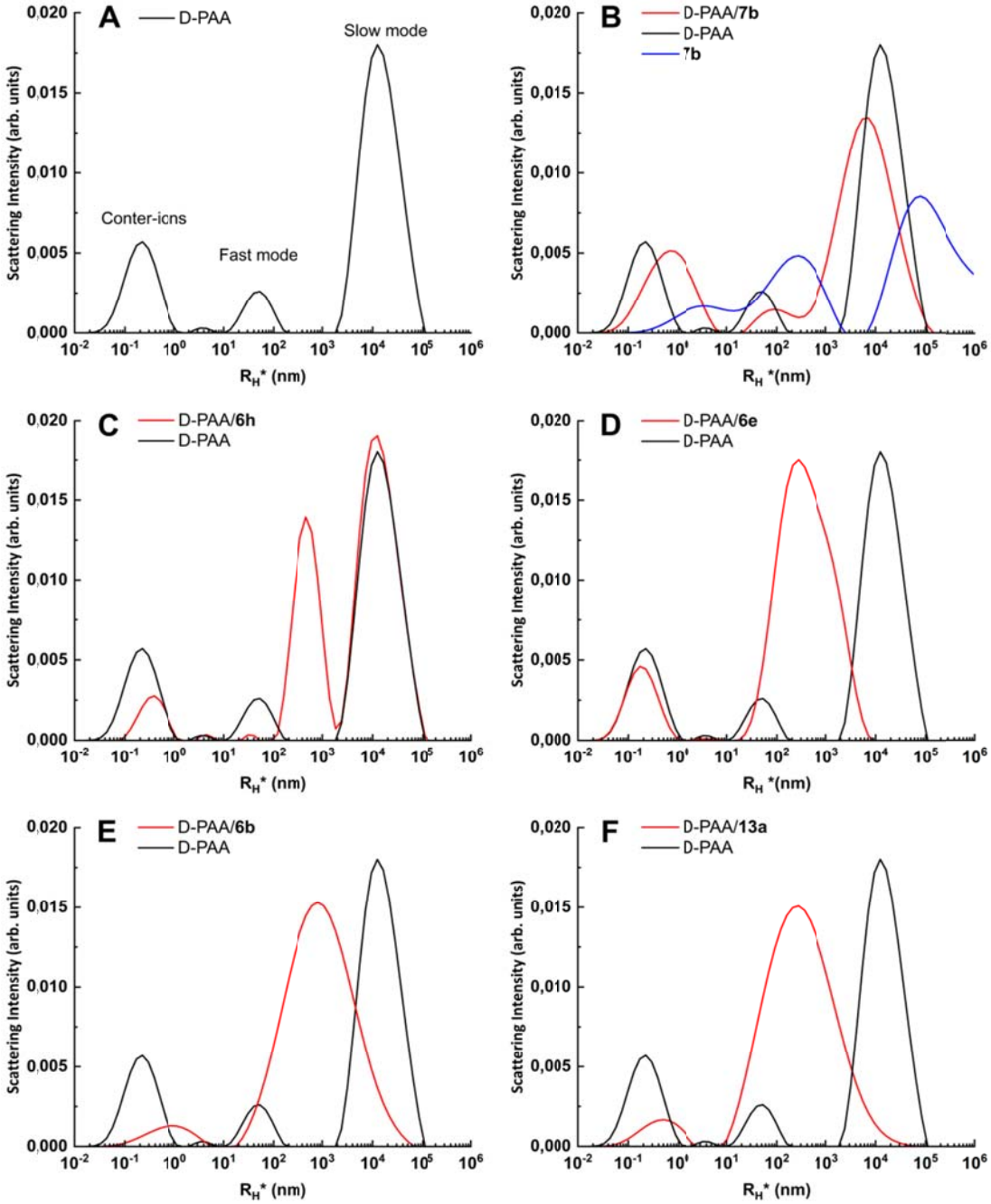


Figure 2. Aqueous R_H* distributions from D-PAA and D-PAA/sultam conjugates. A) D-PAA polyelectrolyte modes; B) D-PAA/**7b**, D-PAA, and **7b**; C) D-PAA/**6h** and D-PAA; D) D-PAA/**6e** and D-PAA; E) D-PAA/**6b** and D-PAA; F) D-PAA/**13a** and D-PAA. Bare sulphonamide scattering is shown where applicable

3. Conclusion

To sum up, we prepared a series of 2,5,5-trisubstituted and spirocyclic 1,2-thiazepan-6-one 1,1-dioxides, in other words, β-keto ε-sultams. This class of compounds possesses synthetically useful handles, namely carbonyl functionality and EWG-activated methylene group whose reactivity suggests the promising potential in organic and medicinal chemistry, that was supported by a number of derivatives prepared. Among them are alcohols **7**, hydrazone **8**, α-dimethylaminomethylidene derivatives **10**, **11** as well as pyrazolo- (**12**, **13**) and pyrimidofused ε-sultams (**14**, **15**). Moreover, cleavage of the PMB-protecting group allowed for the preparation of β-keto ε-sultam **9** and heterofused derivatives **16**, **17** bearing endocyclic NH group in the sultam core. Finally, the above compounds were tested against MDA-MB-231 breast cancer cell lines. It turned out, that pyrazolofused ε-sultams **13a** and **13g** are the most perspective templates since show stable cytotoxic effects against breast cancer cell lines (IC_{50} 0.07 and 0.06 mM, respectively). The use of water-soluble conjugates with D-PAA may facilitate targeted drug delivery in biological media. Further studies will be devoted to the clarification of the mechanisms of action, identifying the cellular targets, and formulation of the structure–activity relationship (SAR) with an aim of developing more potent sultam-derived anticancer agents as an underexplored pharmaceutically relevant chemical space.

4. Experimental

The solvents were purified according to the standard procedures [81]. All the starting materials were obtained from Enamine Ltd. and UORSY. Silica gel flash chromatography was performed using puriFlash® XS 520 Plus purification system. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. ^{1}H and ^{13}C{^{1}H} spectra were recorded on a Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR and 151 MHz for ^{13}C NMR), a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H and 126 MHz for ^{13}C), or a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H and 101 MHz for ^{13}C). Chemical shifts are reported in ppm downfield from TMS as an internal standard. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI). Elemental analyses were performed on a CHNOS elementary Vario MICRO Cube analyzer.

Methyl 4-bromo-2,2-dimethylbutanoate (2a). BBr_3 (48.3 g, 190 mmol) was added dropwise to the precooled (–10 °C) solution of 3,3-dimethyldihydrofuran-2(3*H*)-one (**1a**, 25 g, 170 mmol) in CH_2Cl_2 (400 mL). After the addition was complete the reaction mixture was stirred at 0 °C for 2 h and then was allowed to reach rt and left overnight. Then it was cooled to –20 °C followed by a dropwise addition of MeOH (100 mL). After the addition was complete the cooling bath was removed and the reaction mixture was allowed to equilibrate to rt. Then it was poured into an ice–water mixture (600 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was washed with saturated aqueous K_2CO_3 (1 × 150 mL) and brine (2 × 150 mL), dried (Na_2SO_4), and evaporated at reduced pressure. Thus obtained crude product was distilled in a vacuum to give the title product **2a**. Yield 30.7 g (148 mmol, 87%); colorless liquid; bp 47 °C (1 mmHg). Physical properties and spectra data were found to be identical to the ones described previously [82,83].

General procedure for the synthesis of β-chloro esters 2b–i. *n*-BuLi (66 mL, 165 mmol, 1.1 equiv, 2.5 M in hexane) was added dropwise to the precooled (–78 °C) solution of *i*-Pr_2NH (25.2 mL, 180 mmol, 1.2 equiv) in THF (500 mL) maintaining the above temperature. After the addition was complete the mixture was warmed to –10 °C in 10 min and then stirred at this temperature for 1 h. After the scheduled time the mixture was cooled to –78 °C again and the solution **1b–i** (150 mmol, 1.0 equiv) in THF (50 mL) was added dropwise over 30 min. The reaction mixture was stirred at −78 °C for 1 h then allowed to reach rt and left to stir overnight. Then it was poured into saturated aqueous NH_4Cl (500 mL) and extracted with EtOAc (2 × 250 mL). The combined organic layer was washed with saturated aqueous citric acid (2 × 20 mL), water (1 × 20 mL), and brine (1 × 10 mL), dried (Na_2SO_4), and evaporated at reduced pressure. Thus obtained crude product was distilled in a vacuum to give β-chloro esters **2b–i**.

Methyl 4-chloro-2-ethyl-2-methylbutanoate (2b) was obtained from **1b** (17.4 g). Yield 23 g (129 mmol, 86%); colorless oil; bp 44–47 °C (1 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 7.6 Hz, 3H, $(CH_3)_{Et}$), 1.13 (s, 3H, CH_3), 1.47 (dq, *J* = 14.9, 7.6 Hz, 1H, H^a-$(CH_2)_{Et}$), 1.65 (dq, *J* = 14.9, 7.6 Hz, 1H, H^b-$(CH_2)_{Et}$), 1.87 (ddd, *J* = 13.8, 10.5, 5.5 Hz, 1H, H^a-(CH_2C_q)), 2.16 (ddd, *J* = 13.8, 10.5, 5.5 Hz, 1H, H^b-(CH_2C_q)), 3.35–3.53 (m, 2H, CH_2Cl), 3.65 (s, 3H, CO_2CH_3) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 8.2, 20.3, 31.7, 40.2, 40.9, 45.3, 51.3, 176.3 ppm. GCMS (EI): *m/z* = 178 $[M]^+$, 150 $[M - C_2H_4]^+$, 116 $[M - C_2H_3Cl]^+$. Anal. Calcd. for $C_8H_{15}ClO_2$: C 53.78, H 8.46; Found: C 53.96, H 8.37.

Ethyl 4-chloro-2,2-diethylbutanoate (2c) was obtained from **1c** (21.6 g). Yield 27.6 g (134 mmol, 89%); colorless oil; bp 74–77 °C (1 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.6 Hz, 6H, $(CH_3)_{Et}$), 1.26 (t, *J* = 7.2 Hz, 3H, $(CH_3)_{OEt}$), 1.60 (q, *J* = 7.6 Hz, 4H, $(CH_2)_{Et}$)), 2.03–2.10 (m, 2H, CH_2C_q), 3.40–3.48 (m, 2H, CH_2Cl), 4.14 (q, *J* = 7.2 Hz, 2H, $(CH_2)_{OEt}$) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 7.8 (2C), 13.8, 26.4 (2C), 36.3, 40.0, 48.7, 60.0, 175.5 ppm. GCMS (EI): *m/z* = 206 $[M]^+$, 178 $[M - C_2H_4]^+$, 144 $[M - C_2H_3Cl]^+$. Anal. Calcd. for $C_{10}H_{19}ClO_2$: C 58.11, H 9.27; Found: C 58.38, H 9.45.

Methyl 4-chloro-2-methyl-2-phenylbutanoate (2d) was obtained from **1d** (24.6 g). Yield 31.6 g (139.5 mmol, 93%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.60 (s, 3H, CH_3), 2.39–2.53 (m, 2H, CH_2C_q), 3.33–3.44 (m, 2H, CH_2Cl), 3.67 (s, 3H, CO_2CH_3), 7.23–7.29 (m, 3H, 1,4,6-H_{Ph}), 7.33 (t, *J* = 7.6 Hz, 2H, 3,5-H_{Ph}) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 22.3, 40.2, 42.0, 49.3, 51.9, 125.3 (2C), 126.7, 128.2 (2C), 141.7, 175.3 ppm. GCMS (EI): *m/z* = 226 $[M]^+$, 167 $[M - CO_2CH_3]^+$. Anal. Calcd. for $C_{12}H_{15}ClO_2$: C 63.58, H 6.67; Found: C 63.90, H 6.46.

Ethyl 1-(2-chloroethyl)cyclobutane-1-carboxylate (2e) was obtained from **1e** (19.2 g). Yield 12.9 g (67.5 mmol, 45%); colorless oil; bp 65–68 °C (1 mm Hg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3H, $(CH_3)_{Et}$), 1.85–2.01 (m, 4H, CH_2), 2.22–2.29 (m, 2H, CH_2C_q), 2.36–2.49 (m, 2H, CH_2), 3.38–3.45 (m, 2H, CH_2Cl), 4.14 (q, *J* = 7.1 Hz, 2H, $(CH_2)_{Et}$) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 13.7, 15.4, 29.7 (2C), 40.0, 40.2, 46.1, 60.2, 175.6 ppm. GCMS (EI): *m/z* = 190 $[M]^+$, 128 $[M - C_2H_3Cl]^+$. Anal. Calcd. for $C_9H_{15}ClO_2$: C 56.69, H 7.93; Found: C 56.92, H 8.09.

Methyl 1-(2-chloroethyl)cyclopentane-1-carboxylate (2f) was obtained from **1f** (19.2 g). Yield 23.2 g (122 mmol, 81%); colorless oil; bp 67–70 °C (1 mm Hg). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.47–1.67 (m, 6H, CH_2), 1.96–2.04 (m, 2H, CH_2), 2.05 (t, *J* = 7.6 Hz, 2H, CH_2C_q), 3.53 (t, *J* = 7.6 Hz, 2H, CH_2Cl), 3.61 (s, 3H, CO_2CH_3) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 24.3 (2C), 35.7 (2C), 40.8, 41.3, 51.5, 52.5, 176.7 ppm. GCMS (EI): *m/z* = 190 $[M]^+$, 128 $[M - C_2H_3Cl]^+$. Anal. Calcd. for $C_9H_{15}ClO_2$: C 56.69, H 7.93; Found: C 56.71, H 8.06.

Methyl 1-(2-chloroethyl)cyclohexane-1-carboxylate (2g) was obtained from **1g** (21.3 g). Yield 26.1 g (128 mmol, 85%); colorless oil; bp 81–84 °C (1 mm Hg). ^{1}H NMR (500 MHz,

$CDCl_3$): δ = 1.20–1.37 (m, 5H, CH_2), 1.46–1.60 (m, 3H, CH_2), 1.94–2.01 (m, 2H, CH_2C_q), 2.05 (d, *J* = 12.4 Hz, 2H, CH_2), 3.37–3.46 (m, 2H, CH_2Cl), 3.67 (s, 3H, CO_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 22.5 (2C), 25.2, 33.5 (2C), 39.7, 42.4, 46.1, 51.3, 175.8 ppm. GCMS (EI): *m/z* = 204 $[M]^+$, 142 $[M - C_2H_3Cl]^+$. Anal. Calcd. for $C_{10}H_{17}ClO_2$: C 58.68, H 8.37; Found: C 58.65, H 8.23. Spectra data were found to be identical to the ones described previously [84].

Methyl 4-(2-chloroethyl)tetrahydro-2H-pyran-4-carboxylate (2h) was obtained from **1h** (21.6 g). Yield 26 g (130.5 mmol, 87%); colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.51 (td, *J* = 13.8, 4.3 Hz, 2H, CH_2), 1.98–2.04 (m, 2H, CH_2C_q), 2.06 (d, *J* = 12.6 Hz, 2H, CH_2), 3.36–3.44 (m, 4H, CH_2), 3.71 (s, 3H, CO_2CH_3), 3.79 (dt, *J* = 11.9, 3.3 Hz, 2H, CH_2) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 33.5 (2C), 38.9, 42.7, 44.0, 51.7, 64.6 (2C), 174.7 ppm. GCMS (EI): *m/z* = 206 $[M]^+$, 162 $[M - C_2H_4O]^+$. Anal. Calcd. for $C_9H_{15}ClO_3$: C 52.31, H 7.32; Found: C 52.27, H 7.08. Spectra data were found to be identical to the ones described previously [84].

1-tert-Butyl 4-ethyl 4-(2-chloroethyl)piperidine-1,4-dicarboxylate (2i) was obtained from **1i** (36.5 g). Yield 43.2 g (135 mmol, 90%); yellowish oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3H, $(CH_3)_{Et}$), 1.34–1.46 (m, 2H 3^a-$(CH_2)_{piperidine}$), 1.46 (s, 9H, Boc), 2.04 (t, *J* = 7.8 Hz, 2H, CH_2C_q), 2.13 (d, *J* = 13.3 Hz, 2H, 3^{eq}-$(CH_2)_{piperidine}$), 2.83–2.95 (m, 2H, 2^{ax}-$(CH_2)_{piperidine}$), 3.46 (t, *J* = 7.8 Hz, 2H, CH_2Cl), 3.88 (d, *J* = 13.3 Hz, 2H, 2^a-$(CH_2)_{piperidine}$), 4.21 (q, *J* = 7.1 Hz, 2H, $(CH_2)_{Et}$) ppm. Anal. Calcd. for $C_{15}H_{26}ClNO_4$: C 56.33, H 8.19, N 4.38; Found: C 56.67, H 7.95, N 3.98. Spectra data were found to be identical to the ones described previously [85].

General procedure for the synthesis of sulfonamides 3a and 4a (Method A). The solution of *N*-methylmethanesulfonamide or *N*-(*p*-methoxybenzyl)methanesulfonamide (20 mmol, 1.0 equiv) in DMF (10 mL) was added dropwise to the precooled (−10 °C) dispersion of NaH (60% w/w in mineral oil; 880 mg, 22 mmol, 1.1 equiv) in DMF (75 mL) over 15 min. After the addition was complete the reaction mixture was warmed to rt and stirred for 1 h. Then it was cooled to −10 °C again and the solution of β-bromo esters **2a** (4.16 g, 20 mmol, 1.0 equiv) in DMF (20 mL) was added dropwise over 15 min. After the addition was complete the reaction mixture was allowed to reach rt and left to stir overnight. Then it was poured into ice water (400 mL) and extracted with EtOAc (3 × 75 mL). The combined organic layer was washed with water (2 × 75 mL), brine (1 × 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was subjected to silica gel flash chromatography (gradient elution with hexanes – *t*-BuOMe) to give the target sulfonamides **3a**, **4a**.

Methyl 2,2-dimethyl-4-[methyl(methylsulfonyl)amino]butanoate (3a) was obtained from $MeNHSO_2Me$ (2.18 g). Yield 3.18 g (13.4 mmol, 67%); colorless microcrystals; mp 40–42 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.17 (s, 6H, CH_3), 1.80 (dd, *J* = 9.1, 6.7 Hz, 2H, CH_2C_q), 2.74 (s, 3H, SO_2CH_3), 2.78 (s, 3H, NCH_3), 3.07 (dd, *J* = 9.1, 6.7 Hz, 2H, CH_2N), 3.63 (s, 3H, CO_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 24.7 (2C), 34.0, 35.0, 37.5, 40.4, 46.1, 51.4, 177.0 ppm. LCMS (CI): *m/z* = 238 $[M + H]^+$. Anal. Calcd. for $C_9H_{19}NO_4S$: C 45.55, H 8.07, N 5.90, S 13.51; Found: C 45.70, H 8.04, N 5.89, S 13.53.

Methyl 4-[(4-methoxybenzyl)(methylsulfonyl)amino]-2,2-dimethylbutanoate (4a) was obtained from *p*-$MeOC_6H_4NHSO_2Me$ (4.31 g). Yield 5.7 g (16.6 mmol, 83%); white powder; mp 63–65 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 6H, CH_3), 1.71–1.85 (m, 2H, CH_2C_q), 2.78 (s, 3H, SO_2CH_3), 3.03–3.15 (m, 2H, CH_2N), 3.61 (s, 3H, CO_2CH_3), 3.79 (s, 3H, OCH_3), 4.29 (s, 2H, CH_2Ar), 6.86 (d, *J* = 8.2 Hz, 2H, 3,5-H_{Ar}), 7.25 (d, *J* = 8.2 Hz, 2H, 2,6-H_{Ar}) ppm. LCMS (CI): *m/z* = 366 $[M + Na]^+$. Anal. Calcd. for $C_{16}H_{25}NO_5S$: C 55.96, H 7.34, N 4.08, S 9.33; Found: C 55.74, H 7.17, N 4.47, S 9.27.

General procedure for the synthesis of sulfonamides 3i and 4a–i (Method B). Cs_2CO_3 (9.8 g, 30 mmol, 1.5 equiv) and KI (170 mg, 1 mmol, 5 mol%) were added to the solution of β-chloro ester **2b–i** (20 mmol, 1.0 equiv) and *N*-methylmethanesulfonamide or *N*-(*p*-methoxybenzyl)methanesulfonamide (20 mmol, 1.0 equiv) and the resulting reaction mixture was stirred at 120 °C for 18 h. Then it was cooled, diluted with ice water (400 mL) and extracted with EtOAc (3 × 75 mL). The combined organic layer was washed with water (3 × 75 mL) and brine (1 × 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was subjected to flash chromatography or recrystallized to give the target sulfonamides **3i**, **4b–i**.

1-tert-Butyl 4-ethyl 4-{2-[methyl(methylsulfonyl)amino]-ethyl}piperidine-1,4-dicarboxylate (3i) was obtained from **2i** (6.4 g) and $MeNHSO_2Me$ (2.18 g); was purified by silica gel flash chromatography (gradient elution with hexanes – EtOAc). Yield 5.57 g (14.2 mmol, 71%); yellowish oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3H, $(CH_3)_{Et}$), 1.32–1.51 (m, 11H, Boc and 3^{ax}-$(CH_2)_{piperidine}$), 1.85 (t, *J* = 7.9 Hz, 2H, CH_2C_q), 2.11 (d, *J* = 13.5 Hz, 2H, 2H, 3^{eq}-$(CH_2)_{piperidine}$), 2.76 (s, 3H, SO_2CH_3), 2.80 (s, 3H, NCH_3), 2.93 (m, 2H, 2^{ax}-$(CH_2)_{piperidine}$), 3.09 (t, *J* = 7.9 Hz, 2H, CH_2N), 3.84 (d, *J* = 13.5 Hz, 2H, 2^{eq}-$(CH_2)_{piperidine}$), 4.20 (q, *J* = 7.1 Hz, 2H, $(CH_2)_{Et}$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 14.4, 28.6 (3C), 33.4 (2C), 34.9, 35.7, 37.9, 41.1 (br, 2C), 44.2, 46.0, 61.2, 79.7, 154.9, 175.1 ppm. LCMS (CI): *m/z* = 393 $[M + H]^+$. Anal. Calcd. for $C_{17}H_{32}N_2O_6S$: C 52.02, H 8.22, N 7.14, S 8.17; Found: C 52.40, H 8.00, N 7.00, S 7.77.

Methyl 2-ethyl-4-[(4-methoxybenzyl)(methylsulfonyl)amino]-2-methylbutanoate (4b) was obtained from **2b** (3.57 g) and *p*-$MeOC_6H_4NHSO_2Me$ (4.31 g); was purified by recrystallization from *t*-BuOMe. Yield 4.65 g (13 mmol, 65%); white powder; mp 72–74 °C. ^1H NMR (500 MHz, DMSO-d_6): δ = 0.67 (t, *J* = 7.5 Hz, 3H, $(CH_3)_{Et}$), 0.95 (s, 3H, CH_3), 1.35 (dq, *J* = 14.7, 7.4 Hz, 1H, H^a-$(CH_2)_{Et}$), 1.46 (dt, *J* = 14.7, 7.4 Hz, 2H, H^b-$(CH_2)_{Et}$), 1.53 (td, *J* = 12.5, 4.7 Hz, 1H, H^a-(CH_2C_q)), 1.70 (td, *J* = 12.6, 4.5 Hz, 1H, H^b-(CH_2C_q)), 2.92 (s, 4H, H^a-(CH_2N) and SO_2CH_3), 2.97–3.07 (m, 1H, H^b-(CH_2N)), 3.52 (s, 3H, CO_2CH_3), 3.73 (s, 3H, OCH_3), 4.20 (s, 2H, CH_2Ar), 6.92 (d, *J* = 8.5 Hz, 2H, 3,5-H_{Ar}), 7.24 (d, *J* = 8.5 Hz, 2H, 2,6-H_{Ar}) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = δ 8.1, 20.3, 31.4, 35.7, 38.9, 42.6, 44.4, 49.6, 51.2, 54.8, 113.5 (2C), 127.4, 129.5 (2C), 158.9, 176.5 ppm. LCMS (CI): *m/z* = 380 $[M + Na]^+$. Anal. Calcd. for $C_{17}H_{27}NO_5S$: C 57.12, H 7.61, N 3.92, S 8.97; Found: C 57.46, H 7.48, N 4.21, S 9.30.

Ethyl 2,2-diethyl-4-[(4-methoxybenzyl)(methylsulfonyl)-amino]butanoate (4c) was obtained from **2c** (3.85 g) and *p*-$MeOC_6H_4NHSO_2Me$ (4.31 g); was purified by silica gel flash chromatography (gradient elution with hexanes – *t*-BuOMe). Yield 3.7 g (9.6 mmol, 48%); white powder; mp 38–40 °C. ^1H NMR (500 MHz, DMSO-d_6): δ = 0.60 (t, *J* = 7.4 Hz, 6H, $(CH_3)_{Et}$), 1.10 (t, *J* = 7.1 Hz, 3H, $(CH_3)_{OEt}$), 1.39 (q, *J* = 7.4 Hz, 4H, $(CH_2)_{Et}$), 1.56–1.62 (m, 2H, CH_2C_q), 2.87–2.92 (m, 2H, CH_2N), 2.93 (s, 3H, SO_2CH_3), 3.72 (s, 3H, OCH_3), 3.99 (q, *J* = 7.1 Hz, 2H, $(CH_2)_{OEt}$), 4.21 (s, 2H, CH_2Ar), 6.91 (d, *J* = 8.5 Hz, 2H, 3,5-H_{Ar}), 7.24 (d, *J* = 8.5 Hz, 2H, 2,6-H_{Ar}) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 7.9 (2C), 14.1, 26.3 (2C), 31.2, 37.9, 42.9, 47.8, 50.4, 55.1, 59.9, 113.9 (2C), 128.6, 129.6 (2C), 158.8, 175.4 ppm. LCMS (CI): *m/z* = 408 $[M + Na]^+$. Anal.

Calcd. for $C_{19}H_{31}NO_5S$: C 59.20, H 8.11, N 3.63, S 8.32; Found: C 59.05, H 8.44, N 3.25, S 8.07.

Methyl 4-[(4-methoxybenzyl)(methylsulfonyl)amino]-2-methyl-2-phenylbutanoate (4d) was obtained from **2d** (4.53 g) and *p*-$MeOC_6H_4NHSO_2Me$ (4.31 g); was used in the next step without purification. Yield 3.49 g (8.6 mmol, 43%); beige powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (s, 3H, CH_3), 2.18 (ddd, *J* = 13.2, 10.1, 6.4 Hz, 1H, H^a-(CH_2C_q)), 2.26 (ddd, *J* = 13.2, 10.1, 6.4 Hz, 1H, H^b-(CH_2C_q)), 2.77 (s, 3H, SO_2CH_3), 3.04 (m, 2H, CH_2N), 3.64 (s, 3H, CO_2CH_3), 3.80 (s, 3H, OCH_3), 4.24 (d, *J* = 14.7 Hz, 1H, H^a-(CH_2Ar)), 4.29 (d, *J* = 14.7 Hz, 1H, H^b-(CH_2Ar)), 6.83 (d, *J* = 8.6 Hz, 2H, 3,5-H_{Ar}), 7.16 (d, *J* = 8.6 Hz, 2H, 2,6-H_{Ar}), 7.21 (d, *J* = 7.6 Hz, 2H, 2,6-H_{Ph}), 7.25 (t, *J* = 7.6 Hz, 1H, 4-H_{Ph}), 7.32 (t, *J* = 7.6 Hz, 2H, 3,5-H_{Ph}) ppm. LCMS (CI): *m/z* = 428 $[M + Na]^+$. Anal. Calcd. for $C_{21}H_{27}NO_5S$: C 62.20, H 6.71, N 3.45, S 7.91; Found: C 61.86, H 7.04, N 3.56, S 7.83.

Ethyl 1-{2-[(4-methoxybenzyl)(methylsulfonyl)amino]ethyl}-cyclobutane-1-carboxylate (4e) was obtained from **2e** (3.81 g) and *p*-$MeOC_6H_4NHSO_2Me$ (4.31 g); was purified by silica gel flash chromatography (gradient elution with hexanes – *t*-BuOMe). Yield 3.32 g (9 mmol, 45%); beige powder; mp 63–65 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.09 (t, *J* = 7.1 Hz, 3H, $(CH_3)_{Et}$), 1.63–1.81 (m, 4H, CH_2), 1.81–1.93 (m, 2H, CH_2C_q), 2.15–2.25 (m, 2H, CH_2), 2.82–2.90 (m, 2H, CH_2N), 2.92 (s, 3H, SO_2CH_3), 3.72 (s, 3H, OCH_3), 3.99 (q, *J* = 7.1 Hz, 2H, $(CH_2)_{Et}$), 4.22 (s, 2H, CH_2Ar), 6.91 (d, *J* = 8.5 Hz, 2H, 3,5-H_{Ar}), 7.25 (d, *J* = 8.5 Hz, 2H, 2,6-H_{Ar}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 14.0, 15.2, 29.2 (2C), 35.6, 38.1, 43.0, 45.1, 50.2, 55.1, 60.0, 113.9 (2C), 128.5, 129.7 (2C), 158.8, 175.4 ppm. LCMS (CI): *m/z* = 392 $[M + Na]^+$. Anal. Calcd. for $C_{18}H_{27}NO_5S$: C 58.51, H 7.37, N 3.79, S 8.68; Found: C 58.15, H 7.66, N 3.83, S 8.29.

Methyl 1-{2-[(4-methoxybenzyl)(methylsulfonyl)amino]-ethyl}cyclopentane-1-carboxylate (4f) was obtained from **2f** (3.81 g) and *p*-$MeOC_6H_4NHSO_2Me$ (4.31 g); was purified by recrystallization from *t*-BuOMe. Yield 5.17 g (14 mmol, 70%); beige powder; mp 74–76 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.26–1.40 (m, 2H, CH_2), 1.43–1.55 (m, 4H, CH_2), 1.66–1.77 (m, 2H, CH_2), 1.83–1.97 (m, 2H, CH_2), 2.85–2.97 (m, 5H, CH_2N and SO_2CH_3), 3.52 (s, 3H, CO_2CH_3), 3.74 (s, 3H, OCH_3), 4.21 (s, 2H, CH_2Ar), 6.93 (d, *J* = 8.1 Hz, 2H, 3,5-H_{Ar}), 7.25 (d, *J* = 8.1 Hz, 2H, 2,6-H_{Ar}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 24.3 (2C), 35.3 (2C), 36.6, 38.1, 43.8, 50.0, 51.6, 51.7, 55.1, 113.8 (2C), 128.4, 129.7 (2C), 158.8, 176.5 ppm. LCMS (CI): *m/z* = 392 $[M + Na]^+$. Anal. Calcd. for $C_{18}H_{27}NO_5S$: C 58.51, H 7.37, N 3.79, S 8.68; Found: C 58.70, H 7.45, N 3.93, S 8.78.

Methyl 1-{2-[(4-methoxybenzyl)(methylsulfonyl)amino]-ethyl}cyclohexane-1-carboxylate (4g) was obtained from **2g** (4.09 g) and *p*-$MeOC_6H_4NHSO_2Me$ (4.31 g); was purified by silica gel flash chromatography (gradient elution with hexanes – *t*-BuOMe). Yield 3.91 g (10.2 mmol, 56%); beige powder; mp 90–92 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.10–1.18 (m, 5H, CH_2), 1.36–1.46 (m, 3H, CH_2), 1.52–1.63 (m, 2H, CH_2C_q), 1.72–1.86 (m, 2H, CH_2), 2.86–2.90 (m, 2H, CH_2N), 2.91 (s, 3H, SO_2CH_3), 3.52 (s, 3H, CO_2CH_3), 3.73 (s, 3H, OCH_3), 4.18 (s, 2H, CH_2Ar), 6.91 (d, *J* = 8.5 Hz, 2H, 3,5-H_{Ar}), 7.21 (d, *J* = 8.5 Hz, 2H, 2,6-H_{Ar}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 22.4 (2C), 25.2, 33.1 (2C), 37.3, 38.2, 42.5, 45.0, 50.0, 51.5, 55.1, 113.9 (2C), 128.4, 129.7 (2C), 158.8, 175.6 ppm. LCMS (CI): *m/z* = 406 $[M + Na]^+$. Anal. Calcd. for $C_{19}H_{29}NO_5S$: C 59.51, H 7.62, N 3.65, S 8.36; Found: C 59.40, H 7.40, N 3.74, S 8.03.

Methyl 4-{2-[(4-methoxybenzyl)(methylsulfonyl)amino]-ethyl}tetrahydro-2H-pyran-4-carboxylate (4h) was obtained from **2h** (4.13 g) and *p*-$MeOC_6H_4NHSO_2Me$ (4.31 g); was purified by silica gel flash chromatography (gradient elution with hexanes – *t*-BuOMe). Yield 3.86 g (10.0 mmol, 50%); white powder; mp 103–105 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.33 (ddd, *J* = 13.6, 10.5, 3.9 Hz, 2H, 3^{ax}-$(CH_2)_{pyran}$), 1.58–1.66 (m, 2H, CH_2C_q), 1.79 (d, *J* = 13.6 Hz, 2H, 3^{eq}-$(CH_2)_{pyran}$), 2.87–2.95 (m, 5H, CH_2N and SO_2CH_3), 3.21 (ddd, *J* = 11.9, 10.5, 2.8 Hz, 2H, 2^{ax}-$(CH_2)_{pyran}$), 3.56 (s, 3H, CO_2CH_3), 3.60 (dt, *J* = 11.9, 3.9 Hz, 2H, 2^{eq}-$(CH_2)_{pyran}$), 3.73 (s, 3H, OCH_3), 4.19 (s, 2H, CH_2Ar), 6.92 (d, *J* = 8.5 Hz, 2H,), 4.19 (s, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H, 2,6-H_{Ar}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 33.2 (2C), 37.3, 38.1, 42.1, 42.9, 50.1, 51.8, 55.1, 64.1 (2C), 113.9 (2C), 128.4, 129.8 (2C), 158.8 ppm. LCMS (CI): *m/z* = 408 $[M + Na]^+$. Anal. Calcd. for $C_{18}H_{27}NO_6S$: C 56.09, H 7.06, N 3.63, S 8.32; Found: C 55.80, H 6.94, N 3.89, S 8.40.

1-tert-Butyl 4-ethyl 4-{2-[(4-methoxybenzyl)(methylsulfonyl)amino]ethyl}piperidine-1,4-dicarboxylate (4i) was obtained from **2i** (6.4 g) and *p*-$MeOC_6H_4NHSO_2Me$ (4.31 g); was purified by silica gel flash chromatography (gradient elution with hexanes – EtOAc). Yield 4.79 g (9.6 mmol, 48%); white powder; mp 65–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 3H, $(CH_3)_{Et}$), 1.28 (ddd, *J* = 13.7, 12.2, 5.1 Hz, 2H, 3^{ax}-$(CH_2)_{piperidine}$)), 1.42 (s, 9H, Boc), 1.72 (dd, *J* = 8.2 Hz, 2H, CH_2C_q), 1.98 (d, *J* = 13.5 Hz, 2H, 3^{eq}-$(CH_2)_{piperidine}$), 2.77 (m, 3H, SO_2CH_3), 2.84 (dd, *J* = 15.7, 12.2 Hz, 2H, 2^{ax}-$(CH_2)_{piperidine}$), 3.05 (dd, *J* = 8.2 Hz, 2H, CH_2N), 3.75 (d, *J* = 13.4 Hz, 2H, 2^{eq}-$(CH_2)_{piperidine}$), 3.79 (s, 3H, OCH_3), 4.10 (q, *J* = 7.1 Hz, 2H, $(CH_2)_{Et}$), 4.25 (s, 2H, CH_2Ar), 6.85 (d, *J* = 8.0 Hz, 2H, 3,5-H_{Ar}), 7.20 (d, *J* = 8.0 Hz, 2H, 2,6-H_{Ar}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 13.9, 28.0 (3C), 32.3 (br, 2C), 36.7, 38.1, 40.9 (br, 2C), 42.2, 43.4, 50.0, 55.0, 60.3, 78.6, 113.8 (2C), 128.4, 129.7 (2C), 153.8, 158.8, 174.1 ppm. LCMS (CI): *m/z* = 521 $[M + Na]^+$. Anal. Calcd. for $C_{24}H_{38}N_2O_7S$: C 57.81, H 7.68, N 5.62, S 6.43; Found: C 57.91, H 7.53, N 5.80, S 6.18.

General procedure for the synthesis of ε-sultams 5a,i and 6a–h. The solution of sulfonamide **3a,i, 4a–h** (8 mmol, 1.0 equiv) in DMF (15 mL) was added dropwise to the precooled (−10 °C) solution of *t*-BuOK (2.24 g, 20 mmol, 2.5 equiv) in DMF (50 mL) under an argon atmosphere. After the addition was complete the reaction mixture was allowed to reach rt and left to stir overnight. Then it was diluted with ice water (200 mL), acidified with 1 M aqueous HCl to pH 5–6, and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with water (2 × 50 mL) and brine (1 × 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was subjected to flash chromatography or recrystallized to give the target ε-sultams **5a,i, 6a–h**.

2,5,5-Trimethyl-1,2-thiazepan-6-one 1,1-dioxide (5a) was obtained from **3a** (1.9 g); was purified by recrystallization from hexanes – *t*-BuOMe, 1:1 (v/v). Yield 1.07 g (5.2 mmol, 65%); colorless microcrystals; mp 88–90 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (s, 6H, CH_3), 1.88–2.16 (m, 2H, CH_2C_q), 2.91 (s, 3H, NCH_3), 3.25–3.63 (m, 2H, CH_2N), 4.29 (s, 2H, CH_2SO_2) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ = 25.5 (2C), 35.6, 36.2, 47.0, 47.1, 63.1, 201.3 ppm. LCMS (CI): *m/z* = 206 $[M + H]^+$. Anal. Calcd. for $C_8H_{15}NO_3S$: C 46.81, H 7.37, N 6.82, S 15.62; Found: C 47.07, H 7.06, N 6.62, S 15.84.

tert-Butyl 10-methyl-7-oxo-9-thia-3,10-diazaspiro[5.6]dodecane-3-carboxylate 9,9-dioxide (5i) was obtained from **3i** (3.14 g); was purified by recrystallization from hexanes – EtOAc, 1:1 (v/v). Yield 1.69 g (4.9 mmol, 61%); white powder; mp 160–

162 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.37 (s, 9H, Boc), 1.48 (ddd, J = 13.9, 6.1, 3.3 Hz, 2H, 3^{eq}-$(CH_2)_{piperidine}$), 1.72 (ddd, J = 13.9, 9.1, 4.3 Hz, 2H, 3^{ax}-$(CH_2)_{piperidine}$), 2.08 (m, 2H, CH_2C_q), 2.85 (s, 3H, NCH_3), 3.19 (br m, 2H, 2^{ax}-$(CH_2)_{piperidine}$), 3.31 (m, 2H, CH_2N), 3.41 (ddd, J = 13.4, 6.1, 4.3 Hz, 2H, 2^{eq}-$(CH_2)_{piperidine}$), 4.56 (s, 2H, CH_2SO_2) ppm. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ = 28.5 (3C), 28.6, 32.0 (2C), 35.8, 40.0 (br, 2C), 45.9, 48.9, 62.6, 79.2, 154.3, 202.8 ppm. LCMS (CI): m/z = 345 [M − H]$^-$. Anal. Calcd. for $C_{15}H_{26}N_2O_5S$: C 52.00, H 7.56, N 8.09, S 9.25; Found: C 52.19, H 7.72, N 7.75, S 9.56.

2-(4-Methoxybenzyl)-5,5-dimethyl-1,2-thiazepan-6-one 1,1-dioxide (6a) was obtained from **4a** (5.5 g, 16 mmol) and *t*-BuOK (4.48 g, 40 mmol); was purified by recrystallization from hexanes – EtOAc, 8:2 (v/v). Yield 4.13 g (13.3 mmol, 83%); white powder; mp 93–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.13 (s, 6H, CH_3), 2.03 (t, J = 6.1 Hz, 2H, CH_2C_q), 3.22 (t, J = 6.1 Hz, 2H, CH_2N), 3.81 (s, 3H, OCH_3), 4.31 (s, 2H, CH_2Ar), 4.41 (s, 2H, CH_2SO_2), 6.89 (d, J = 8.1 Hz, 2H, 3,5-H_{Ar}), 7.21 (d, J = 8.1 Hz, 2H, 2,6-H_{Ar}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 25.8 (2C), 33.9, 43.0, 47.1, 50.8, 55.6, 64.2, 114.4 (2C), 128.5, 130.2 (2C), 159.3, 203.2 ppm. LCMS (CI): m/z = 334 [M + Na]$^+$. Anal. Calcd. for $C_{15}H_{21}NO_4S$: C 57.86, H 6.80, N 4.50, S 10.30; Found: C 57.84, H 6.57, N 4.79, S 10.42.

5-Ethyl-2-(4-methoxybenzyl)-5-methyl-1,2-thiazepan-6-one 1,1-dioxide (6b) was obtained from **4b** (2.86 g); was purified by recrystallization from *t*-BuOMe – EtOAc, 10:1 (v/v). Yield 1.82 g (5.6 mmol, 70%); white powder; mp 67–69 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.74 (t, J = 7.5 Hz, 3H, $(CH_3)_{Et}$), 0.99 (s, 3H, CH_3), 1.40–1.60 (m, 2H, $(CH_2)_{Et}$), 1.76 (dd, J = 15.7, 5.0 Hz, 1H, H^{eq}-(CH_2C_q)), 2.26 (dd, J = 15.7, 9.9 Hz, 1H, H^{ax}-(CH_2C_q)), 3.08 (dd, J = 15.1, 5.0 Hz, 1H, H^{eq}-(CH_2N)), 3.21 (dd, J = 15.1, 9.9 Hz, 1H, H^{ax}-(CH_2N)), 3.75 (s, 3H, OCH_3), 4.27 (d, J = 14.6 Hz, 1H, H^{a}-(CH_2Ar)), 4.35 (d, J = 13.1 Hz, 1H, H^{a}-(CH_2SO_2)), 4.40 (d, J = 14.6 Hz, 1H, H^{b}-(CH_2Ar)), 4.88 (d, J = 13.1 Hz, 1H, H^{b}-(CH_2SO_2)), 6.94 (d, J = 8.6 Hz, 2H, 3,5-H_{Ar}), 7.24 (d, J = 8.5 Hz, 2H, 2,6-H_{Ar}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 7.9, 20.7, 31.1, 31.3, 42.4, 50.0, 50.4, 55.1, 64.0, 114.0 (2C), 128.1, 129.7 (2C), 158.9, 202.3 ppm. GCMS (EI): m/z = 325 [M]$^+$. Anal. Calcd. for $C_{16}H_{23}NO_4S$: C 59.05, H 7.12, N 4.30, S 9.85; Found: C 58.91, H 6.72, N 4.32, S 9.79.

5,5-Diethyl-2-(4-methoxybenzyl)-1,2-thiazepan-6-one 1,1-dioxide (6c) was obtained from **4c** (2.97 g); was purified by silica gel flash chromatography (gradient elution with hexanes – *t*-BuOMe). Yield 1.60 g (4.7 mmol, 59%); white solid; mp 73–75 °C. ^{1}H NMR (500 MHz, DMSO-d_6): = δ 0.65 (t, J = 7.4 Hz, 6H, $(CH_3)_{Et}$), 1.37 (dq, J = 14.7, 7.3 Hz, 2H, H^{a}-$(CH_2)_{Et}$), 1.59 (dq, J = 14.7, 7.3 Hz, 2H, H^{b}-$(CH_2)_{Et}$), 1.91–2.02 (m, 2H, CH_2C_q), 3.01–3.14 (m, 2H, CH_2N), 3.73 (s, 3H, OCH_3), 4.31 (s, 2H, CH_2Ar), 4.57 (s, 2H, CH_2SO_2), 6.91 (d, J = 8.4 Hz, 2H, 3,5-H_{Ar}), 7.22 (d, J = 8.4 Hz, 2H, 2,6-H_{Ar}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 7.6 (2C), 25.6 (2C), 28.4, 42.3, 50.5, 52.8, 55.1, 64.2, 114.0 (2C), 128.1, 129.7 (2C), 158.9, 201.8 ppm. LCMS (CI): m/z = 338 [M − H]$^-$. Anal. Calcd. for $C_{17}H_{25}NO_4S$: C 60.15, H 7.42, N 4.13, S 9.44; Found: C 60.48, H 7.73, N 3.94, S 9.24.

2-(4-Methoxybenzyl)-5-methyl-5-phenyl-1,2-thiazepan-6-one 1,1-dioxide (6d) was obtained from **4d** (3.24 g); was purified by silica gel flash chromatography (gradient elution with hexanes – *t*-BuOMe). Yield 1.49 g (4.0 mmol, 50%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (s, 3H, CH_3), 2.19 (dt, J = 15.5, 4.1 Hz, 1H, H^{eq}-(CH_2C_q)), 3.01 (ddd, J = 15.5, 11.7, 4.1 Hz, 1H, H^{ax}-(CH_2C_q)), 3.18 (ddd, J = 13.6, 11.7, 4.1 Hz, 1H, H^{ax}-(CH_2N)), 3.38 (dt, J = 13.6, 4.1 Hz, 1H, H^{eq}-(CH_2N)), 3.79 (s, 3H, OCH_3), 4.14 (d, J = 12.6 Hz, 1H, H^{a}-(SO_2CH_3)), 4.20 (d, J = 14.5 Hz, 1H, H^{a}-(CH_2Ar)), 4.42 (d, J = 12.6 Hz, 1H, H^{b}-(SO_2CH_3)), 4.44 (d, J = 14.5 Hz, 1H, H^{a}-(CH_2Ar)), 6.88 (d, J = 8.3 Hz, 2H, 3,5-H_{Ar}), 7.21 (d, J = 8.3 Hz, 2H, 2,6-H_{Ar}), 7.23 (d, J = 7.5 Hz, 2H, 2,6-H_{Ph}), 7.26 (t, J = 7.5 Hz, 1H, 4-H_{Ph}), 7.33 (t, J = 7.5 Hz, 2H, 3,5-H_{Ph}) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 24.1, 33.0, 43.3, 52.2, 54.2, 55.3, 65.6, 114.1 (2C), 126.1 (2C), 127.4, 127.7, 129.1 (2C), 130.1 (2C), 141.0, 159.5, 196.7 ppm. LCMS (CI): m/z = 372 [M − H]$^-$. Anal. Calcd. for $C_{20}H_{23}NO_4S$: C 64.32, H 6.21, N 3.75, S 8.58; Found: C 64.49, H 6.46, N 3.67, S 8.46.

8-(4-Methoxybenzyl)-7-thia-8-azaspiro[3.6]decan-5-one 7,7-dioxide (6e) was obtained from **4e** (2.96 g); was purified by silica gel flash chromatography (gradient elution with hexanes – *t*-BuOMe). Yield 1.65 g (5.1 mmol, 67%); white powder; mp 57–59 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.72–1.94 (m, 4H, $(CH_2)_{butane}$), 2.19–2.25 (m, 2H, CH_2C_q), 2.25–2.34 (m, 2H, $(CH_2)_{butane}$), 3.09–3.22 (m, 2H, CH_2N), 3.73 (s, 3H, OCH_3), 4.23 (s, 2H, CH_2Ar), 4.58 (s, 2H, CH_2SO_2), 6.91 (d, J = 8.2 Hz, 2H, 3,5-H_{Ar}), 7.21 (d, J = 8.2 Hz, 2H, 2,6-H_{Ar}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 14.3, 30.2 (2C), 31.9, 42.6, 49.9, 52.0, 55.1, 64.0, 114.0 (2C), 128.0, 129.6 (2C), 158.9, 202.5 ppm. LCMS (CI): m/z = 322 [M − H]$^-$. Anal. Calcd. for $C_{16}H_{21}NO_4S$: C 59.42, H 6.55, N 4.33, S 9.91; Found: C 59.67, H 6.86, N 4.73, S 10.28.

9-(4-Methoxybenzyl)-8-thia-9-azaspiro[4.6]undecan-6-one 8,8-dioxide (6f) was obtained from **4f** (2.96 g); was purified by recrystallization from *t*-BuOMe – EtOAc, 10:1 (v/v). Yield 2.35 g (7.0 mmol, 87%); white powder; mp 102–104 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.40–1.51 (m, 2H, $(CH_2)_{pentane}$), 1.50–1.63 (m, 4H, $(CH_2)_{pentane}$), 1.73–1.92 (m, 2H, $(CH_2)_{pentane}$), 1.99–2.13 (m, 2H, CH_2C_q), 3.04–3.18 (m, 2H, CH_2N), 3.74 (s, 3H, OCH_3), 4.29 (s, 2H, CH_2Ar), 4.64 (s, 2H, CH_2SO_2), 6.93 (d, J = 8.2 Hz, 2H, 3,5-H_{Ar}), 7.22 (d, J = 8.2 Hz, 2H, 2,6-H_{Ar}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 25.0 (2C), 32.4, 36.6 (2C), 43.6, 50.5, 55.1, 57.9, 64.6, 113.9 (2C), 128.0, 129.6 (2C), 158.8, 202.7 ppm. LCMS (CI): m/z = 336 [M − H]$^-$. Anal. Calcd. for $C_{17}H_{23}NO_4S$: C 60.51, H 6.87, N 4.15, S 9.50; Found: C 60.78, H 7.11, N 4.23, S 9.34.

10-(4-Methoxybenzyl)-9-thia-10-azaspiro[5.6]dodecan-7-one 9,9-dioxide (6g) was obtained from **4g** (3.07 g); was purified by silica gel flash chromatography (gradient elution with hexanes – *t*-BuOMe). Yield 2.02 g (5.8 mmol, 72%); white powder; mp 87–89 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.19–1.46 (m, 8H, $(CH_2)_{hexane}$), 1.56–1.69 (m, 2H, $(CH_2)_{hexane}$), 2.03–2.10 (m, 2H, CH_2C_q), 3.03–3.13 (m, 2H, CH_2N), 3.72 (s, 3H, OCH_3), 4.27 (s, 2H, CH_2Ar), 4.59 (s, 2H, CH_2SO_2), 6.90 (d, J = 8.4 Hz, 2H, 3,5-H_{Ar}), 7.21 (d, J = 8.4 Hz, 2H, 2,6-H_{Ar}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 20.9 (2C), 25.1, 29.4, 31.9 (2C), 42.0, 50.0, 50.4, 55.1, 64.1, 113.9 (2C), 128.1, 129.7 (2C), 158.8, 202.6 ppm. GCMS (EI): m/z = 351 [M]$^+$. Anal. Calcd. for $C_{18}H_{25}NO_4S$: C 61.51, H 7.17, N 3.99, S 9.12; Found: C 61.71, H 7.52, N 3.74, S 8.87.

10-(4-methoxybenzyl)-3-oxa-9-thia-10-azaspiro[5.6]dodecan-7-one 9,9-dioxide (6h) was obtained from **4h** (3.08 g); was purified by silica gel flash chromatography (gradient elution with hexanes – *t*-BuOMe). Yield 2.12 g (6.0 mmol, 75%); white solid; mp 116–118 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (ddd, J = 13.8, 9.4, 4.1 Hz, 2H, 3^{ax}-$(CH_2)_{pyran}$), 1.97–2.04 (m, 2H, CH_2C_q), 2.10 (dt, J = 13.8, 3.8 Hz, 2H, 3^{eq}-$(CH_2)_{pyran}$), 3.18–3.37 (m, 2H, CH_2N), 3.52 (ddd, J = 12.1, 9.4, 3.8 Hz, 2H, 2^{ax}-$(CH_2)_{pyran}$), 3.72 (dt, J = 12.1, 4.1 Hz, 2H, 2^{eq}-$(CH_2)_{pyran}$), 4.25 (s, 2H, CH_2Ar), 4.45 (s, 2H, CH_2SO_2), 6.85 (d, J = 8.6 Hz, 2H, 3,5-H_{Ar}), 7.17 (d, J = 8.6 Hz, 2H, 2,6-H_{Ar}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ = 30.3, 32.0 (2C), 41.9, 47.6, 50.4, 55.1, 62.6 (2C), 64.2, 114.0 (2C), 128.1, 129.7 (2C), 158.9, 201.7 ppm. LCMS (CI):

m/z = 352 $[M - H]^-$. Anal. Calcd. for $C_{17}H_{23}NO_5S$: C 57.77, H 6.56, N 3.96, S 9.07; Found: C 57.90, H 6.85, N 3.59, S 9.26.

General procedure for the synthesis of alcohols 7a,b. $NaBH_4$ (45 mg, 1.2 mmol, 1.2 equiv) was added portion-wise to the stirred solution of ketosultam **5a**,**6a** (1 mmol, 1 equiv) in MeOH (15 mL) and THF (15 mL). After the addition was complete the mixture was left to stir overnight and then evaporated under reduced pressure. The residue was triturated with water (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (1 × 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give the title compound **7a,b**.

6-Hydroxy-2,5,5-trimethyl-1,2-thiazepane 1,1-dioxide (7a) was obtained from **5a** (205 mg). Yield 180 mg (0.87 mmol, 87%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.47 (dt, *J* = 15.6, 4.3 Hz, 1H, H^{eq}-(CH_2C_q)), 2.26 (ddd, *J* = 15.6, 9.6, 6.5 Hz, 1H, H^{ax}-(CH_2C_q)), 3.13–3.22 (m, 2H, CH_2N), 3.39–3.52 (m, 2H, CH_2SO_2), 3.59–3.70 (m, 1H, CH_{OH}) ppm; exchangeable proton (OH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 24.2, 27.7, 33.4, 36.7, 38.7, 46.5, 57.4, 73.4 ppm. LCMS (CI): *m/z* = 208 $[M + H]^+$. Anal. Calcd. for $C_8H_{17}NO_3S$: C 46.35, H 8.27, N 6.76, S 15.47; Found: C 46.44, H 8.21, N 6.65, S 15.79.

6-Hydroxy-2-(4-methoxybenzyl)-5,5-dimethyl-1,2-thiazepane 1,1-dioxide (7b) was obtained from **6a** (311 mg); was purified by HPLC (gradient elution with MeCN – water). Yield 280 mg (0.9 mmol, 90%); white powder; mp 78–80 °C. ^{1}H NMR (500 MHz, CD_3CN): δ = 0.99 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.49 (ddd, *J* = 15.3, 6.6, 3.8 Hz, 1H, H^{eq}-(CH_2C_q)), 2.04 (ddd, *J* = 15.3, 9.6, 4.0 Hz, 1H, H^{ax}-(CH_2C_q)), 2.92 (m, 1H, H^{eq}-(CH_2N)), 3.23 (ddd, *J* = 14.5, 9.6, 3.8 Hz, 1H, H^{ax}-(CH_2N)), 3.46 (br s, 1H, OH), 3.46 (dd, *J* = 14.7, 7.0 Hz, 1H, H^a-(CH_2SO_2)), 3.54 (dd, *J* = 14.7, 3.2 Hz, 1H, H^b-(CH_2SO_2)), 3.70 (dd, *J* = 7.0, 3.2 Hz, 1H, CH_{OH}), 4.28 (d, *J* = 15.3 Hz, 1H, H^a-(CH_2Ar)), 4.50 (d, *J* = 15.3 Hz, 1H, H^b-(CH_2Ar)), 6.92 (d, *J* = 8.6 Hz, 2H, 3,5-H_{Ar}), 7.28 (d, *J* = 8.6 Hz, 2H, 2,6-H_{Ar}) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, CD_3CN): δ = 25.7, 25.9, 35.1, 39.1, 43.4, 52.2, 55.9, 60.4, 74.3, 114.9 (2C), 130.5 (3C), 160.2 ppm. LCMS (CI): *m/z* = 336 $[M + Na]^+$. Anal. Calcd. for $C_{15}H_{23}NO_4S$: C 57.49, H 7.40, N 4.47, S 10.23; Found: C 57.10, H 7.46, N 4.23, S 10.56.

2-(4-Methoxybenzyl)-5,5-dimethyl-1,2-thiazepan-6-one 1,1-dioxide (8). The solution of ketosultam **6a** (310 mg, 1 mmol, 1 equiv.), N_2H_4•H_2O (150 mg, 3 mmol, 3 equiv.) and 10 M aqueous HCl (0.02 mL, 0.2 mmol, 0.2 equiv.) in MeOH (50 mL) was refluxed for 3 h. Then the reaction mixture was evaporated under reduced pressure, triturated with water (50 mL) and filtered to give the title product **8**. Yield 310 mg (0.95 mmol, 95%); white powder; mp 103–105°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.03 (s, 6H, CH_3), 1.65–1.79 (m, 2H, CH_2C_q), 2.93–3.02 (m, 2H, CH_2N), 3.70 (s, 3H, OCH_3), 4.24 (s, 2H, CH_2Ar), 4.31 (s, 2H, CH_2SO_2), 6.22 (s, 2H, NH_2), 6.88 (d, *J* = 8.5 Hz, 2H, 3,5-H_{Ar}), 7.17 (d, *J* = 8.5 Hz, 2H, 2,6-H_{Ar}) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 27.7 (2C), 36.2, 40.4, 42.2, 48.5, 49.9, 55.0, 113.9 (2C), 128.6, 129.4 (2C), 142.7, 158.7 ppm. LCMS (CI): *m/z* = 326 $[M + H]^+$. Anal. Calcd. for $C_{15}H_{23}N_3O_3S$: C 55.36, H 7.12, N 12.91, S 9.85; Found: C 55.25, H 6.99, N 12.79, S 9.58.

5,5-Dimethyl-1,2-thiazepan-6-one 1,1-dioxide (9). CF_3CO_2H (10 mL) was added to the stirred solution of sultam **6a** (500 mg, 1.6 mmol) in CH_2Cl_2 (10 mL) and thus obtained mixture was left to react at rt overnight. Then it was evaporated under reduced pressure and the residue was subjected to silica gel flash chromatography (gradient elution with hexanes – *t*-BuOMe) to give the title compound **9**. Yield 220 mg (1.15 mmol, 72%); white powder; mp 35–37 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.06 (s, 6H, CH_3), 1.89–2.03 (m, 2H, CH_2C_q), 3.00–3.15 (m, 2H, CH_2N), 4.46 (s, 2H, CH_2SO_2), 7.65 (br s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 25.1 (2C), 38.1, 38.5, 46.7, 65.4, 203.3 ppm. LCMS (CI): *m/z* = 190 $[M - H]^-$. Anal. Calcd. for $C_7H_{13}NO_3S$: C 43.96, H 6.85, N 7.32, S 16.76; Found: C 44.32, H 7.15, N 6.92, S 16.87.

General procedure for the synthesis of enaminoketones 10i, 11a,b,e–g. The stirred solution of ketosultam **5i**, **6a,b,e–g** (4 mmol, 1 equiv.) and DMFDMA (1.43 g, 1.6 mL, 12 mmol, 3 equiv.) in 1,4-dioxane (25 mL) was refluxed for 12 h. After the scheduled time the reaction mixture was evaporated under reduced pressure and the residue was dissolved in EtOAc (100 mL). The organic layer was washed with water (2 × 50 mL) and brine (1 × 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. Thus obtained crude product was recrystallized from the appropriate solvent to give the title compound **10i**, **11a,b,e–g**.

tert-Butyl 8-[(dimethylamino)methylidene]-10-methyl-7-oxo-9-thia-3,10-diazaspiro[5.6]dodecane-3-carboxylate 9,9-dioxide (10i) was obtained from **5i** (1.39 g); was purified by recrystallization from hexanes – EtOAc, 1:1 (v/v). Yield: 1.35 g (3.4 mmol, 84%); mp 171–173 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.39 (s, 9H, Boc), 1.56 (d, *J* = 13.6 Hz, 2H, CH_2), 1.84–2.00 (m, 4H, CH_2), 2.50–3.20 (br s, 6H, $N(CH_3)_2$), 2.63 (s, 3H, NCH_3), 3.11 (br m, 2H, CH_2), 3.37–3.52 (m, 4H, CH_2), 7.32 (s, 1H, CH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 27.1, 28.0 (3C), 33.0 (2C), 34.6, 42.4 (br s, 2C), 45.9, 46.9 (br s, 2C), 49.2, 78.5, 105.8, 153.5, 153.9, 200.1 ppm. LCMS (CI): *m/z* = 402 $[M + H]^+$. Anal. Calcd. for $C_{18}H_{31}N_3O_5S$: C 53.84, H 7.78, N 10.47, S 7.98; Found: C 53.67, H 7.57, N 10.41, S 8.34.

7-[(Dimethylamino)methylidene]-2-(4-methoxybenzyl)-5,5-dimethyl-1,2-thiazepan-6-one 1,1-dioxide (11a) was obtained from **6a** (1.25 g); was purified by recrystallization from hexanes – EtOAc, 1:1 (v/v). Yield: 1.35 g (3.7 mmol, 92%); white powder; mp 168–170 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.15 (s, 6H, CH_3), 1.72–1.96 (m, 2H, CH_2C_q), 2.50–3.20 (br s, 6H, $N(CH_3)_2$), 3.16–3.22 (m, 2H, CH_2N), 3.75 (s, 3H, OCH_3), 4.04 (s, 2H, CH_2Ar), 6.92 (d, *J* = 7.8 Hz, 2H, 3,5-H_{Ar}), 7.28 (d, *J* = 7.8 Hz, 2H, 2,6-H_{Ar}), 7.33 (s, 1H, CH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 28.4 (2C), 33.9, 42.8, 47.2 (2C), 48.1, 49.6, 55.6, 107.7, 114.4 (2C), 128.9, 130.2 (2C), 152.5, 159.2, 202.0 ppm. LCMS (CI): *m/z* = 367 $[M + H]^+$. Anal. Calcd. for $C_{18}H_{26}N_2O_4S$: C 58.99, H 7.15, N 7.64, S 8.75; Found: C 58.76, H 7.54, N 7.31, S 8.62.

7-[(Dimethylamino)methylidene]-5-ethyl-2-(4-methoxybenzyl)-5-methyl-1,2-thiazepan-6-one 1,1-dioxide (11b) was obtained from **6b** (1.3 g); was purified by recrystallization from MeOH. Yield: 1.25 g (3.3 mmol, 82%); white powder; mp 140–142 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.77 (t, *J* = 7.4 Hz, 3H, $(CH_3)_{Et}$), 1.07 (s, 3H, CH_3), 1.56–1.82 (m, 3H, H^{eq}-(CH_2C_q) and $(CH_2)_{Et}$), 1.89 (dd, *J* = 15.9, 9.1 Hz, 1H, H^{ax}-(CH_2C_q)), 2.50–3.20 (br s, 6H, $N(CH_3)_2$), 3.10 (dd, *J* = 15.3, 8.0 Hz, 1H, H^{eq}-(CH_2N)), 3.25 (dd, *J* = 15.3, 9.1 Hz, 1H, H^{ax}-(CH_2N)), 3.75 (s, 3H, OCH_3), 3.99 (d, *J* = 14.1 Hz, 1H, H^a-(CH_2Ar)), 4.09 (d, *J* = 14.2 Hz, 1H, H^b-(CH_2Ar)), 6.93 (d, *J* = 8.4 Hz, 2H, 3,5-H_{Ar}), 7.28 (d, *J* = 8.4 Hz, 2H, 2,6-H_{Ar}), 7.36 (s, 1H, CH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 8.0, 24.5, 29.9, 30.7, 41.9, 47.9 (br s, 2C), 49.0, 50.5, 55.0, 107.6, 113.8 (2C), 128.3, 129.7 (2C), 152.4, 158.6, 201.2 ppm. LCMS (CI): *m/z* = 381 $[M + H]^+$. Anal. Calcd. for $C_{19}H_{28}N_2O_4S$: C 59.98, H 7.42, N 7.36, S 8.43; Found: C 60.32, H 7.74, N 7.58, S 8.29.

7-[(Dimethylamino)methylidene]-9-(4-methoxybenzyl)-8-thia-9-azaspiro[4.6]undecan-6-one 8,8-dioxide (11e) was obtained

from **6e** (1.29 g); additional purification was not required. Yield 1.13 g (3.0 mmol, 75%); yellowish powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66–1.90 (m, 4H, CH_2), 1.95–2.07 (m, 2H, CH_2), 2.45 (q, *J* = 9.7 Hz, 2H, CH_2), 2.72 (br s, 3H, $N(CH_3)_2$), 3.19 (br s, 3H, $N(CH_3)_2$), 3.38 (br s, 2H, CH_2), 3.73 (s, 3H, OCH_3), 3.94 (s, 2H, NCH_2Ar), 6.79 (d, *J* = 8.5 Hz, 2H, 3,5-H_{Ar}), 7.19 (d, *J* = 8.5 Hz, 2H, 2,6-H_{Ar}), 7.53 (s, 1H, CH) ppm. LCMS (CI): *m/z* = 379 $[M + H]^+$. Anal. Calcd. for $C_{19}H_{26}N_2O_4S$: C 60.29, H 6.92, N 7.40, S 8.47; Found: C 60.62, H 6.97, N 7.24, S 8.25.

7-[(Dimethylamino)methylidene]-9-(4-methoxybenzyl)-8-thia-9-azaspiro[4.6]undecan-6-one 8,8-dioxide (11f) was obtained from **6f** (1.35 g); was purified by recrystallization from MeOH. Yield 1.3 g (3.3 mmol, 83%); white powder; mp 155–157 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.46–1.69 (m, 6H, CH_2), 1.74–1.88 (m, 2H, CH_2C_q), 1.91–2.08 (m, 2H, CH_2), 2.50–3.20 (br s, 6H, $N(CH_3)_2$), 3.11–3.22 (m, 2H, CH_2N), 3.74 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2Ar), 6.91 (d, *J* = 8.5 Hz, 2H, 3,5-H_{Ar}), 7.26 (d, *J* = 8.5 Hz, 2H, 2,6-H_{Ar}), 7.36 (s, 1H, CH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 24.6 (2C), 32.0, 37.9 (2C), 42.4, 46.8 (br s, 2C), 48.9, 54.8, 59.2, 109.2, 113.5 (2C), 127.5, 129.2 (2C), 153.3, 158.7, 201.4 ppm. LCMS (CI): *m/z* = 393 $[M + H]^+$. Anal. Calcd. for $C_{20}H_{28}N_2O_4S$: C 61.20, H 7.19, N 7.14, S 8.17; Found: C 61.36, H 7.23, N 7.32, S 8.20.

8-[(Dimethylamino)methylidene]-10-(4-methoxybenzyl)-9-thia-10-azaspiro[5.6]dodecan-7-one 9,9-dioxide (11g) was obtained from **6g** (1.41 g); additional purification was not required. Yield: 1.43 g (3.5 mmol, 88%); beige powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.18–1.64 (m, 8H, CH_2), 1.64–1.85 (m, 2H, CH_2), 1.85–2.00 (m, 2H, CH_2C_q), 2.50–3.20 (br s, 6H, $N(CH_3)_2$), 3.14–3.24 (m, 2H, CH_2N), 3.75 (s, 3H, OCH_3), 4.02 (s, 2H, CH_2Ar), 6.93 (d, *J* = 8.3 Hz, 2H, 3,5-H_{Ar}), 7.28 (d, *J* = 8.3 Hz, 2H, 2,6-H_{Ar}), 7.35 (s, 1H, CH) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ = 21.4 (2C), 25.8, 34.1 (2C), 37.9, 41.9, 47.5 (2C), 49.4, 51.5, 55.6, 108.3, 114.4 (2C), 128.8, 130.2 (2C), 152.8, 159.2, 202.4 ppm. LCMS (CI): *m/z* = 407 $[M + H]^+$. Anal. Calcd. for $C_{21}H_{30}N_2O_4S$: C 62.04, H 7.44, N 6.89, S 7.89; Found: C 61.85, H 7.79, N 6.80, S 7.70.

General procedure for the synthesis of fused pyrazoles 12i and 13a,b,e–g. The stirred solution of enaminoketone **10i**, **11a,b,e–g** (2 mmol, 1 equiv.) and N_2H_4•H_2O (500 mg, 0.49 mL, 10 mmol, 5 equiv.) in MeOH (50 mL) was refluxed for 6 h. After the scheduled time the reaction mixture was evaporated under reduced pressure, triturated with water (50 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (1 × 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. Thus obtained crude product was recrystallized from MeOH to give the title compound **12i**, **13a,b,e–g**.

tert-Butyl 5'-methyl-6',7'-dihydro-1'H(2'H),5'H-spiro[piperidine-4,8'-pyrazolo[3,4-f][1,2]thiazepine]-1-carboxy-late 4',4'-dioxide (12i) was obtained from **10i** (803 mg). Yield 580 mg (1.58 mmol, 79%); white powder; mp 223–225 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.39 (s, 9H, Boc), 1.59 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 2.22 (d, *J* = 11.1 Hz, 2H, CH_2), 2.55 (s, 3H, NCH_3), 3.25–3.32 (m, 2H, CH_2), 3.53 (d, *J* = 13.0 Hz, 2H, CH_2), 3.63 (m, 2H CH_2), 8.19 (s, 1H, CH), 13.26 (s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 28.0 (3C), 30.9, 34.0, 34.4 (2C), 37.3, 40.4 (2C), 46.1, 78.4, 117.7, 133.1, 152.1, 154.0 ppm. LCMS (CI): *m/z* = 369 $[M - H]^-$. Anal. Calcd. for $C_{16}H_{26}N_4O_4S$: C 51.87, H 7.07, N 15.12, S 8.65; Found: C 52.06, H 6.74, N 15.15, S 8.61.

5-(4-Methoxybenzyl)-8,8-dimethyl-5,6,7,8-tetrahydro-1H (2H)-pyrazolo[3,4-f][1,2]thiazepine 4,4-dioxide (13a) was obtained from **11a** (733 mg). Yield 580 mg (1.74 mmol, 87%); white powder; mp 79–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 6H, CH_3), 1.59–1.77 (m, 2H, CH_2C_q), 3.41–3.71 (m, 2H, CH_2N), 3.78 (s, 3H, OCH_3), 4.08 (s, 2H, CH_2Ar), 6.85 (d, *J* = 8.3 Hz, 2H, 3,5-H_{Ar}), 7.22 (d, *J* = 8.3 Hz, 2H, 2,6-H_{Ar}), 7.92 (s, 1H, CH), 10.93 (br s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 28.1 (2C), 34.2, 36.3, 42.3, 48.9, 55.3, 114.1 (2C), 120.6, 127.3, 129.7 (2C), 135.2, 152.5, 159.3 ppm. LCMS (CI): *m/z* = 334 $[M - H]^-$. Anal. Calcd. for $C_{16}H_{21}N_3O_3S$: C 57.29, H 6.31, N 12.53, S 9.56; Found: C 57.36, H 6.62, N 12.54, S 9.24.

8-Ethyl-5-(4-methoxybenzyl)-8-methyl-5,6,7,8-tetrahydro-1H (2H)-pyrazolo[3,4-f][1,2]thiazepine 4,4-dioxide (13b) was obtained from **11b** (761 mg). Yield 640 mg (1.82 mmol, 91%); white powder; mp 125–127 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.2 Hz, 3H, $(CH_3)_{Et}$), 1.41 (s, 3H, CH_3), 1.51 (dd, *J* = 15.4, 6.2 Hz, 1H, H^{eq}-(CH_2C_q)), 1.76 (dq, *J* = 14.2, 7.2 Hz, 1H, H^a-$(CH_2)_{Et}$), 1.83–1.96 (m, 1H, H^{ax}-(CH_2C_q)), 2.13 (dq, *J* = 14.2, 7.2 Hz, 1H, H^b-$(CH_2)_{Et}$), 3.23 (dd, *J* = 16.0, 6.4 Hz, 1H, H^{eq}-(CH_2N)), 3.69–3.86 (m, 4H, H^a-(CH_2Ar) and OCH_3), 3.91 (m, 1H, H^{ax}-(CH_2N)), 4.39 (d, *J* = 14.1 Hz, 1H, H^b-(CH_2Ar)), 6.86 (d, *J* = 8.4 Hz, 2H, 3,5-H_{Ar}), 7.23 (t, *J* = 8.4 Hz, 2H, 2,6-H_{Ar}), 7.94 (s, 1H, CH), 11.13 (br s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 7.9, 24.5, 30.7, 31.3, 39.0, 41.2, 48.5, 54.8, 113.6 (2C), 120.2, 126.8, 129.3 (2C), 135.1, 150.9, 158.8 ppm. LCMS (CI): *m/z* = 348 $[M - H]^-$. Anal. Calcd. for $C_{17}H_{23}N_3O_3S$: C 58.43, H 6.63, N 12.02, S 9.17; Found: C 58.68, H 6.53, N 11.88, S 8.77.

5'-(4-Methoxybenzyl)-6',7'-dihydro-1'H(2'H),5'H-spiro[cyclobutane-1,8'-pyrazolo[3,4-f][1,2]thiazepine] 4',4'-dioxide (13e) was obtained from **11e** (757 mg). Yield 580 mg (1.68 mmol, 84%); white powder; mp 148–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (t, *J* = 5.4 Hz, 2H, CH_2C_q), 2.00 (p, *J* = 7.7 Hz, 2H, CH_2), 2.11–2.24 (m, 2H, CH_2), 2.50–2.84 (m, 2H, CH_2), 3.45–3.73 (m, 2H, CH_2N), 3.82 (s, 3H, OCH_3), 4.06 (s, 2H, CH_2Ar), 6.89 (d, *J* = 8.6 Hz, 2H, 3,5-H_{Ar}), 7.25 (d, *J* = 8.6 Hz, 2H, 2,6-H_{Ar}), 7.98 (s, 1H, CH), 10.97 (br s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 15.5, 31.5 (2C), 31.7, 42.3, 43.2, 48.5, 55.5, 114.4 (2C), 118.8, 128.4, 130.0 (2C), 132.6, 153.6, 159.2 ppm. LCMS (CI): *m/z* = 346 $[M - H]^-$. Anal. Calcd. for $C_{17}H_{21}N_3O_3S$: C 58.77, H 6.09, N 12.09, S 9.23; Found: C 58.62, H 6.12, N 12.20, S 8.93.

5'-(4-Methoxybenzyl)-6',7'-dihydro-1'H(2'H),5'H-spiro[cyclopentane-1,8'-pyrazolo[3,4-f][1,2]thiazepine] 4',4'-dioxide (13f) was obtained from **11f** (785 mg). Yield 680 mg (1.88 mmol, 94%); white powder; mp 181–183 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.47–1.69 (m, 6H, CH_2), 1.68–1.77 (m, 2H, CH_2C_q), 2.20–2.44 (m, 2H, CH_2), 3.33–3.51 (m, 2H, CH_2N), 3.72 (s, 3H, OCH_3), 3.96 (s, 2H, CH_2Ar), 6.89 (d, *J* = 8.4 Hz, 2H, 3,5-H_{Ar}), 7.23 (d, *J* = 8.4 Hz, 2H, 2,6-H_{Ar}), 8.19 (s, 1H, CH), 13.13 (s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ = 24.1 (2C), 31.9, 37.8 (2C), 44.2, 47.9, 48.6, 55.5, 114.4 (2C), 119.3, 128.4, 130.1 (2C), 132.9 , 153.7, 159.2 ppm. LCMS (CI): *m/z* = 360 $[M - H]^-$. Anal. Calcd. for $C_{18}H_{23}N_3O_3S$: C 59.81, H 6.41, N 11.63, S 8.87; Found: C 59.98, H 6.55, N 11.93, S 8.65.

5'-(4-Methoxybenzyl)-6',7'-dihydro-1'H(2'H),5'H-spiro[cyclohexane-1,8'-pyrazolo[3,4-f][1,2]thiazepine] 4',4'-dioxide (13g) was obtained from **11g** (813 mg). Yield 690 mg (1.84 mmol, 92%); white powder; mp 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.71 (m, 6H, CH_2), 1.74–1.84 (m, 2H, CH_2C_q), 1.88–2.02 (m, 2H, CH_2), 2.02–2.19 (m, 2H, CH_2), 3.48–3.68 (m, 2H, CH_2N), 3.82 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2Ar), 6.89 (d, *J* = 8.5 Hz, 2H, 3,5-H_{Ar}), 7.26 (d, *J* = 8.5 Hz, 2H, 2,6-H_{Ar}), 7.98 (s, 1H, CH), 10.75 (br s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ = 21.2 (2C), 25.3, 27.8, 34.4 (2C), 38.5, 41.0, 48.6,

54.8, 113.6 (2C), 120.2, 126.8, 129.3 (2C), 137.2, 152.5, 158.8 ppm. LCMS (CI): *m/z* = 374 $[M - H]^-$. Anal. Calcd. for $C_{19}H_{25}N_3O_3S$: C 60.78, H 6.71, N 11.19, S 8.54; Found: C 60.58, H 6.89, N 11.18, S 8.79.

General procedure for the synthesis of fused amino pyrimidines 14i and 15a. Guanidine hydrochloride (190 mg, 1 mmol, 2 equiv.) and enaminoketone **10i**, **11a** (1 mmol, 1 equiv.) were sequentially added to the stirred solution of MeONa (110 mg, 2 mmol, 2 equiv.) in MeOH (25 mL) and the resulting reaction mixture was stirred at rt for 4 h. Then it was evaporated under reduced pressure, the residue was diluted with water (25 mL), acidified with 2 M aqueous HCl to pH 7, and filtered. Thus obtained crude product was recrystallized from MeOH to give the title compound **14i**, **15a**.

tert-Butyl 7'-amino-2'-methyl-3',4'-dihydro-2'H-spiro[piperidine-4,5'-pyrimido[4,5-f][1,2]thiazepine]-1-carboxylate 1',1'-dioxide (14i) was obtained from **10i** (402 mg). Yield 350 mg (0.88 mmol, 88%); white powder; mp >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.39 (s, 9H, Boc), 1.55–1.85 (br m, 2H, CH_2), 1.85–2.03 (m, 2H, CH_2), 2.19–2.41 (m, 2H, CH_2), 2.62 (s, 3H, NCH_3), 3.31–3.83 (br m, 4H, CH_2), 7.33 (br s, 2H, NH_2), 8.47 (s, 1H, CH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 28.1 (3C), 28.4, 31.0 (2C), 34.2, 40.4 (2C), 44.1, 45.8, 78.4, 120.2, 153.9, 159.9, 163.2, 171.6 ppm. LCMS (CI): *m/z* = 398 $[M + H]^+$. Anal. Calcd. for $C_{17}H_{27}N_5O_4S$: C 51.37, H 6.85, N 17.62, S 8.07; Found: C 51.09, H 6.46, N 17.75, S 8.36.

7-Amino-2-(4-methoxybenzyl)-5,5-dimethyl-2,3,4,5-tetrahydropyrimido[4,5-f][1,2]thiazepine 1,1-dioxide (15a) was obtained from **11a** (366 mg). Yield 340 mg (0.93 mmol, 93%); white powder; mp >250 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.38 (s, 6H, CH_3), 1.66–2.06 (m, 2H, CH_2C_q), 3.29–3.36 (m, 2H, CH_2N), 3.72 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2Ar), 6.90 (d, *J* = 8.2 Hz, 2H, 3,5-H_{Ar}), 7.24 (d, *J* = 8.2 Hz, 2H, 2,6-H_{Ar}), 7.45 (br s, 2H, NH_2), 8.51 (s, 1H, CH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 29.6 (2C), 33.4, 42.3, 43.5, 48.6, 55.0, 113.9 (2C), 122.2, 127.8, 129.6 (2C), 158.7, 163.5, 168.0, 172.6 ppm. LCMS (CI): *m/z* = 363 $[M + H]^+$. Anal. Calcd. for $C_{17}H_{22}N_4O_3S$: C 56.34, H 6.12, N 15.46, S 8.85; Found: C 56.63, H 5.73, N 15.81, S 8.59.

General procedure for the cleavage of PMB protecting group from fused pyrazoles 13a,f. The solution of fused pyrazole **13a,f** (1 mmol) in CF_3CO_2H (20 mL) was stirred at rt overnight. Then it was evaporated under reduced pressure, diluted with water (50 mL), neutralized with saturated aqueous K_2CO_3 to pH 7, and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (2 × 30 mL), dried (Na_2SO_4), and evaporated at reduced pressure to give the crude product **16a,f** which was purified as follows.

8,8-Dimethyl-5,6,7,8-tetrahydro-1H(2H)-pyrazolo[3,4-f][1,2]thiazepine 4,4-dioxide (16a) was obtained from **13a** (335 mg); was purified by HPLC (gradient elution with MeCN – H_2O). Yield 160 mg (0.74 mmol, 74%); white powder; mp 140–142 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.45 (s, 6H, CH_3), 1.69–1.87 (m, 2H, CH_2C_q), 3.47–3.66 (m, 2H, CH_2NH), 7.85 (s, 1H, CH) ppm; exchangeable protons ($NHSO_2$ and $NH_{pyrazole}$). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3OD): δ = 27.1 (2C), 35.9, 39.9, 40.9, 123.5, 136.4, 152.4 ppm. LCMS (CI): *m/z* = 216 $[M + H]^+$. Anal. Calcd. for $C_8H_{13}N_3O_2S$: C 44.64, H 6.09, N 19.52, S 14.89; Found: C 44.82, H 6.45, N 19.91, S 14.78.

6',7'-Dihydro-1H'(2'H),5'H-spiro[cyclopentane-1,8'-pyrazolo[3,4-f][1,2]thiazepine] 4',4'-dioxide (16f) was obtained from **13f** (361 mg); was purified by silica gel flash chromatography (elution with MeOH). Yield 190 mg (0.81 mmol, 81%); white powder; mp 149–151 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.42–1.68 (m, 6H, CH_2), 1.68–1.80 (m, 2H, CH_2), 2.09–2.35 (m, 2H, CH_2), 3.33–3.42 (m, 2H, CH_2NH), 7.29 (t, *J* = 6.5 Hz, 1H, $NHSO_2$), 8.03 (br s, 1H, CH), 12.94 (br s, 1H, $NH_{pyrazole}$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, CD_3OD): δ = 24.7 (2C), 38.7, 39.8, 42.5, 49.0, 124.7, 134.3, 153.6 ppm. LCMS (CI): *m/z* = 242 $[M + H]^+$. Anal. Calcd. for $C_{10}H_{15}N_3O_2S$: C 49.77, H 6.27, N 17.41, S 13.29; Found: C 49.42, H 6.23, N 17.69, S 13.29.

7-Amino-5,5-dimethyl-2,3,4,5-tetrahydropyrimido[4,5-f][1,2]thiazepine 1,1-dioxide (17a). The solution of fused amino pyrimidine **15a** (200 mg, 0.55 mmol) in CF_3CO_2H (10 mL) was stirred at rt overnight. Then it was evaporated under reduced pressure, triturated with water (30 mL), neutralized with saturated aqueous K_2CO_3 to pH 7, and filtered. Thus obtained crude product was recrystallized from MeOH to give the title compound **17a**. Yield 117 g (0.48 mmol, 88%); white powder; mp >250 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.35 (s, 6H, CH_3), 1.82–1.92 (m, 2H, CH_2C_q), 3.21–3.28 (m, 2H, CH_2N), 7.29 (br s, 2H, NH_2), 7.64 (t, *J* = 6.7 Hz, 1H, NH), 8.49 (s, 1H, CH) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ = 28.1 (2C), 38.8, 39.1, 43.3, 126.1, 157.4, 163.2, 172.3 ppm. LCMS (CI): *m/z* = 243 $[M + H]^+$. Anal. Calcd. for $C_9H_{14}N_4O_2S$: C 44.61, H 5.82, N 23.12, S 13.23; Found: C 44.67, H 5.87, N 23.04, S 13.22.

Cytotoxicity of ε-sultams and their derivatives. The biological study was carried out at the breast cancer cell line MDA-MB-231. Cell cultures were obtained from the bank of human and animal tissue cell lines of the R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology National Academy of Sciences of Ukraine. Cells were incubated in plastic plates (SPL, Pyeongtaek, Korea) in DMEM with high glutamine, 10% fetal calf serum (Biowest, France), and 40 μg/mL gentamicin (Merck, Germany) at 37 °C and 5% CO_2 atmosphere. Test ε-sultams and their derivatives were added to the incubation solution from the 50 mM stock solution in DMSO. The concentrations range of 0.25–0.039 mM was prepared by two-fold dilutions. Similarly, the polymer–small molecule conjugates were tested, the concentration range of the studied compounds was 0.125–0.0195 mM. Living cells were stained with crystal violet. The incubation medium was removed, 50 μl of 0.5% crystal violet in 70% methyl alcohol was added to each well and stained for 10 min. Excess dye was washed off with water three times after staining. The optical absorbance of the wells was measured on a tablet spectrophotometer (Labsystems Multiskan PLUS, Vantaa, Finland) at 540 nm. Cytotoxic effect was calculated according to the formula:

$$E(\%) = \left(1 - \frac{D_e}{D_c}\right) \cdot 100\ \%$$

where E – relative change of cell number, %; De – absorbance of experimental wells at 540 nm; Dc – absorbance of control wells at 540 nm. Dose–effect curves were constructed and IC_{50} was calculated according to the Hill equation (when cells death was more than 90%). Experiments were repeated five times.

Interaction between D-PAA and ε-sultams. As a polymer carrier, 1 g of star-shaped anionic Dextran-graft-Polyacrylamide copolymer with molecular weight Mw 1.3×10^6 g/mol and polydispersity index of 1.4 was dissolved in water (100 mL) during 24 hours. After that, appropriate volume of DMSO solutions of compounds **7b**, **6b**, **6e**, **6h**, and **13a** was added to adjust a final concentration of 0.125–0.195 mM and vigorously stirred for 30 min. Dynamic light scattering was measured on Brookhaven NanoBrook (USA) with 512 nm laser at scattering angle of 173 °. For each solution, 15 autocorrelation curves were collected and averaged. Hydrodynamic radii distributions were

extracted from averaged data by regularized singular value decomposition algorithm.

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Supplementary Material

The Supporting Information contains the materials and methods, experimental details, characterizations, ^{1}H and ^{13}C NMR spectra images of the synthesized compounds.