Tetrahedron 154 (2024) 133890

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Direct assembly of *N*-sulfamoyl lactam scaffolds bearing a zinc-binding group for inhibiting metalloenzymes based on desymmetrization of sulfamide and the Castagnoli-Cushman reaction☆

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ARTICLE INFO

Keywords:
Sulfamide
Sulfamoyl
Lactams
Tetrahydroisoquinoline
Castagnoli-cushman reaction

ABSTRACT

Sulfamide was desymmetrized by a reaction with aldehydes to give *N*-sulfamoylimines. The latter reagents were successfully introduced into diastereo- and chemoselective transformation with cyclic anhydride using the Castagnoli-Cushman reaction to give unprotected *N*-sulfamoyl tetrahydroisoquinolonic (THIQ) acids under simple metal-free protocol. Thereby, the first general approach to the direct assembly of six-membered *N*-sulfamoyl lactams was developed. The synthesized compounds belong to representative, drug-like chemotypes with their well-defined three-dimensional structures and tunable physicochemical properties. In an attempt to probe their pharmacological potential, the newly synthesized lactams were screened against therapeutically relevant human and bacterial carbonic anhydrases, with some derivatives showing low micromolar enzyme inhibitory profiles.

1. Introduction

Exploration of structural diversity around sulfamide functionality ($R_2NSO_2NR_2$) gains a lot of attention nowadays due to the discovery of numerous bioactive sulfamide derivatives [1] endowed with inhibitory activities against carbonic anhydrases [2,3], proteases [4–6], and proving useful in cancer cell growth suppression and tumor imaging, [7,8]. Marketed sulfamide-containing drugs include doripenem (antibiotic; Fig. 1a), quinagolide (reduces the level of prolactin), macitentan (an orphan drug for the treatment of pulmonary arterial hypertension), and famotidine (decreases stomach acid production). The role of sulfamide moiety in drug discovery is significant as it serves as an efficient metal-binding group, and can mimic multiple functionalities (e.g.: urea, amide, sulfonamide, carbamate, ester, ketoamide *etc*.) as a bioisoster [9].

For the generation of the screening libraries within the drug discovery projects, sulfamide-containing imines are attractive reagents. In fact, their application in various reactions allows to rapidly achieve molecular complexity which is undeniably a crucial factor in drug discovery research programs [10,11]. Recent publications demonstrate the use of readily available sulfamide imines such as symmetrical bisimines **1** and N-substituted monoimines **2**. They were involved in reductive cyclizations [12], introduced into reduction reactions with hydrides [13], metal-catalysed C-arylation [14–18] or C-alkylation [19], Biginelli [20] reaction and were also used for construction of aziridines [21] or imidazoles [22].

In the above-mentioned studies, however, no general way for the preparation of primary *N*-sulfamoylimines was suggested, and moreover, their potential in constructive reactions has not been evaluated. To fill this void, we became interested in generating primary sulfamide imines **3**, and investigating their reactivity in a Castagnoli-Cushman reaction (CCR) [23–26] with homophthalic anhydride (HPA). This approach could pave the way to a one-step assembly of *N*-sulfamoyl lactams **4** with tetrahydroisoquinoline backbone (Fig. 2, a). Interestingly, the preparation of rare known examples of five-membered *N*-sulfamoyl lactams involved post-condensational modifications of

☆ †In memory of Professor Mikhail Krasavin (30.05.1975–16.02.2023).

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https://doi.org/10.1016/j.tet.2024.133890
Received 11 October 2023; Received in revised form 7 February 2024; Accepted 10 February 2024
Available online 15 February 2024

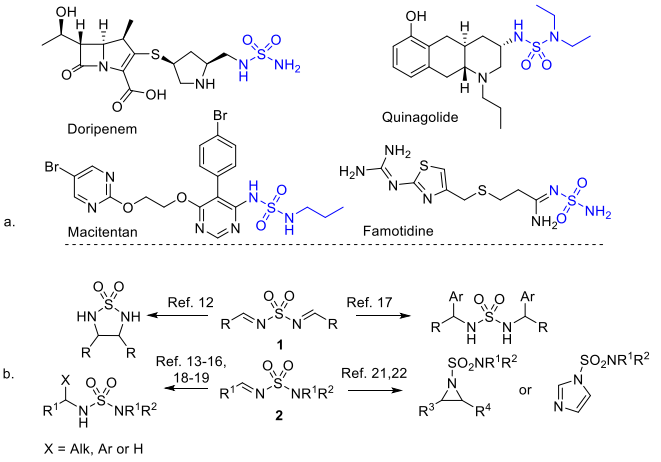


Fig. 1. a) Examples of biologically active organic sulfamide derivatives b) The structures of known *N*-sulfamoylimines and their reactivity.

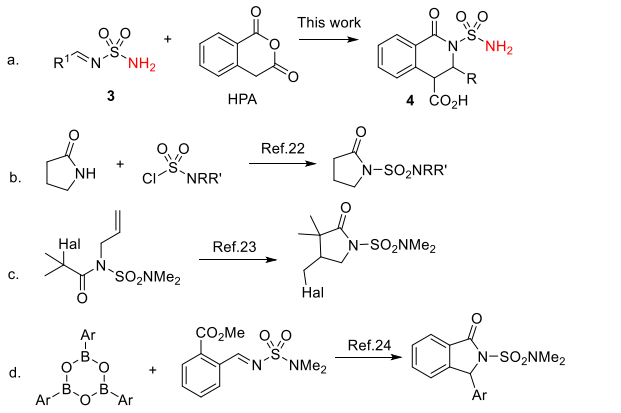


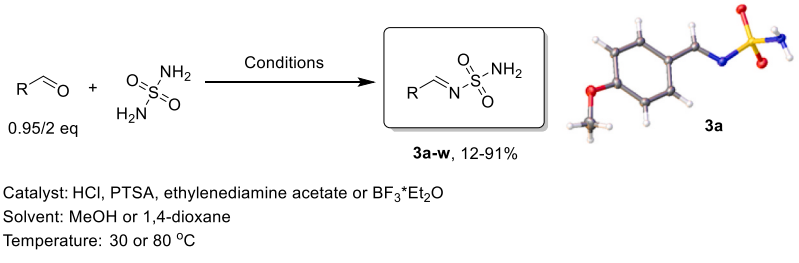
Fig. 2. a) Novel general approach to *N*-sulfamoyl lactams via Castagnoli-Cushman reaction b)-d) Previously reported examples of *N*-sulfamoyl lactams prepared according this pathway.

NH-pyrrolidones (Fig. 2, b) [27] or cyclization of functionalized substituents within linear sulfamides (Fig. 2c and d) [28,29]. Furthermore, none of the methods provided direct access to primary sulfamide derivatives. In this context, herein we report our findings on the preparation of unprotected *N*-sulfamoylimines and their reactions with homophthalic anhydride representing the first general way for the preparation of six-membered *N*-sulfamoyl lactams. We also provide the results of probing the biological activities of the latter compounds, namely their enzyme inhibitory profiles.

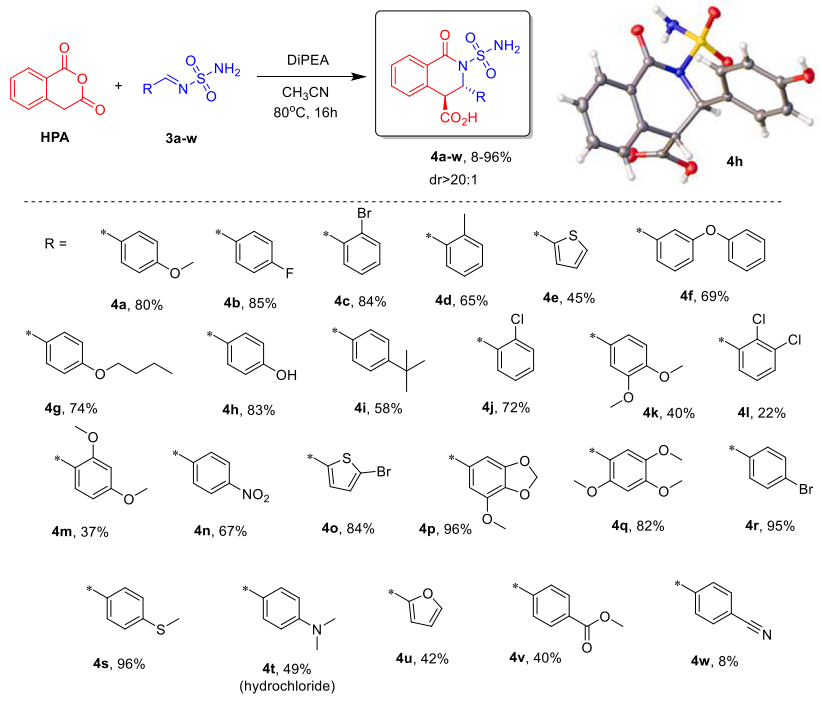
2. Results and discussion

Although multiple articles and patents describe the preparation of fully substituted *N*-sulfamoylimines, most of the reported procedures are not applicable to the synthesis of analogs with free NH_2-group. To obtain a series of primary *N*-sulfamoylimines we employed condensation of sulfuric acid diamide and aromatic aldehydes (Scheme 1). To our delight, this strategy allowed for the successful preparation of twenty-three *N*-sulfamoylimines **3a-w** in 12–91% yields, although the conditions were not universal for the selected aldehydes. Indeed, the reactivities of the carbonyl compounds varied significantly, requiring some changes in the reactant ratios, reaction temperatures, and sometimes the use of different solvents and catalysts. Moreover, the separation from unreacted sulfamide was challenging in some cases, due to the low solubility in organic solvents and high water solubility of the resulting compounds. Finally, some *N*-sulfamoylimines showed poor stability in aqueous solution and on silica (see ESI for more detail). It is these complications that gave rise to the notable difference in isolated yields for structurally close compounds. The structures of **3a-w** were confirmed using conventional NMR and HRMS methods, whereas the structure and *E*-configuration of a model compound **3a** were additionally supported with X-ray crystallographic data (Scheme 1 and CCDC 2165217).

Having prepared a series of imine substrates **3** we proceeded with evaluating their applicability in the preparation of *N*-sulfamoyl lactams via CCR with homophthalic anhydride (Scheme 2). We performed a brief reaction conditions screening starting with simple stirring 1-to-1 mixture of reactants at room temperature in acetonitrile, but no conversion was observed. Due to the low solubility of *N*-sulfamoyimines we only tried DMSO as an alternative solvent, which gave a full conversion of **3** and afforded **4a** as a single isomer at room temperature. The disadvantages of using DMSO as a reaction solvent were related to a more complicated drying procedure and more difficult product isolation. In the meantime, performing the reaction in acetonitrile in presence of a catalytic amount (5 %mol) of DIPEA also afforded full conversion of **3** according to ^{1}H NMR, however, the product **4a** was formed in 3.8:1 diastereomeric ratio. Increasing the reaction temperature to 80 °C improved *dr* to >20:1, and we finally chose these conditions for further work. Using the developed protocol, we have successfully transformed all twenty-three prepared *N*-sulfamoylimines **3a-w** into *N*-sulfamoyl lactams **4a-w** with the highest yield of 96% (**4p**). In most cases, products were isolated without chromatography using extraction. All compounds **4** were obtained as single *trans*-configured isomers, which was supported by X-ray crystallographic data for compound **4h** (CCDC 2165216, Scheme 2) and by correlation of characteristic ^{1}H NMR data, where the values of vicinal coupling constants for methine protons from lactam cycle fell within typical range (1–5 Hz) for *trans*-tetrahydroisoquinolones [30,31] (see ESI, Table S1 for detail). It was found that different types of substituents in *N*-sulfamoylimines are suitable for this reaction, including either electron-rich or electron-deficient aromatics (e.g. NO_2 (**4n**, 67%) and CO_2Me (**4v**, 40%), which are known to give very low or zero yields in other CCR-type protocols), as well as heterocycles (thiophene (**4o**, 84%), furane (**4u**, 42%)). Moreover, we managed to employ reagents with ionizable or nucleophilic functional groups, like OH (**4h**, 83%) and NMe_2 (**4t**, 49%), which is a very rare case for the CCR-type transformations with HPA.



Scheme 1. General scheme for the preparation of *N*-sulfamoylimines **3** and crystal structure of compound **3a**.

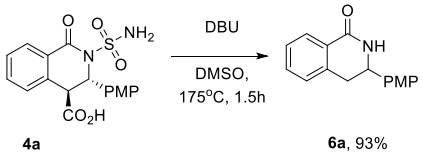


Scheme 2. Preparation of *N*-sulfamoylactams **4a-w** via Castagnoli-Cushman reaction of homophthalic anhydride with sulfamide Schiff base.

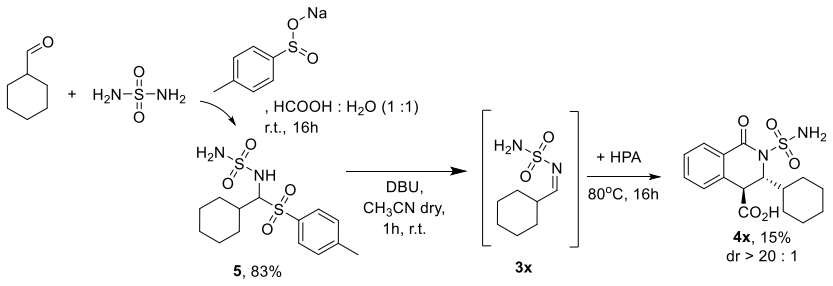
We also became interested in extending the reaction scope to aliphatic *N*-sulfamoylimines. Our developed protocol for direct condensation of sulfamide with aldehydes failed and there were no examples of the preparation of such compounds reported in the literature. In light of these facts, we tried an alternative approach [32] to imine generation implying the isolation of a sulfamide, aldehyde, and sodium *p*-tolylsulfinate adduct (namely compound **5**, Scheme 3) followed by *in situ* generation of imine **3x** via base-promoted sulfinate elimination and its reaction with homophthalic anhydride. This approach allowed the synthesis of compound **4x** with an alkyl group at position 3 of the lactam ring in a 15% yield. We treated this as a remarkable success since low to zero yields are common for CCR with similar poorly nucleophilic imines, namely *N*-hydroxyimines [31] or *N*-sulfonylimines [32]. Thereby, we identified the synthetic approach for *in situ* generation of previously unknown and unavailable aliphatic *N*-sulfonylimines and provided an example of their reactivity.

Having established an efficient protocol for the preparation of *N*-sulfamoyl lactams **4** we proceeded with the investigation of their properties. First, we tested their thermal stability (in DMSO solution) and found that compound **4a** easily undergoes decarboxylation at 110°C (15% conversion within 1h, monitored by ^{1}H NMR spectroscopy), which is quite unusual for other HPA-derived lactams [33]. The decarboxylation process was also accompanied by partial loss of the sulfamoyl group. Heating samples of **4a** at 130, 150 and 175 °C for 1h, always yielded mixtures of the corresponding products. Full conversion of compound **4a** into the known [34] *NH*-lactam **6a** was achieved after heating it for 1.5h at 175 °C in the presence of a base (isolated yield 93%, Scheme 4). Therefore, we can conclude that while stable at temperatures below 80 °C, *N*-sulfamoyl lactams **4** are prone to thermal decomposition, which involves both decarboxylation and desulfamoylation processes.

The synthetic approach developed in this work provides convenient access to highly functionalized lactams, which possess well-defined three-dimensional structures and tunable physicochemical properties. Such characteristics are of great interest to the field of drug design and discovery [35,36]. Drug-like molecules bearing primary sulfamide group are highly desired in research programs targeting various therapeutically relevant proteins, especially metalloenzymes [9,37]. Indeed, it is well-known that screening libraries of primary sulfamides are enriched with potent and selective inhibitors of carbonic anhydrases,



Scheme 4. Thermal decomposition of compound **4a**.



Scheme 3. An alternative approach for *in situ* preparation of aliphatic *N*-sulfamoyl imine **3x** from precursor **5** and its reaction with homophthalic anhydride.

histone deacetylases, and metalloproteases [37,38]. In the active sites of the carbonic anhydrases, primary sulfamides typically coordinate the zinc ion in the depth of the catalytic cavity thus blocking the enzymatic activity [39]. Inspired by these facts we have evaluated the inhibitory effect of compounds **4a-x** against therapeutically relevant isoforms of human and bacterial carbonic anhydrases. Specifically, **4a-x** were profiled versus human carbonic anhydrases I, II (antiglaucoma drug target), and IX (anticancer drug target), as well as *VhCAβ*-carbonic anhydrase from *vibrio cholerae* (VhCAβ, recently suggested antibacterial drug target) [40–42]. The enzyme-blocking activities of **4a-x** were determined via the stopped-flow kinetic technique which is a golden standard method for the discovery of carbonic anhydrase inhibitors [43]. Marketed pan-isoform inhibitor acetazolamide (AAZ) was used as a reference compound. The results are outlined in Table 1 (see also ESI, p.S16 for details).

As seen from Table 1, most of the generated sulfamides did not exhibit detectable activity against human carbonic anhydrase isoforms. This is likely due to the presence of a bulky substituent in position 3 of the tetrahydroisoquinoline scaffold. In fact, according to the literature data, substitution pattern around the zinc-binding group significantly affects the compounds' affinity towards human carbonic anhydrases [44]. The latter phenomenon stems from the positioning of the catalytic zinc atom at the very bottom of a deep cavity, therefore bulky substituents can prevent sulfamide moiety from reaching metal ion unless they accommodate in a hydrophobic pocket nearby [45]. Interestingly, only a few lactams inhibited *h*CA II, whose active site is considered the most hydrophobic among human isoforms of the enzymes [46]. These comprised aromatically substituted molecules **4h**, **4i**, **4v**, and **4w**, as well as furan-bearing **4u**, and cyclohexane-containing **4x**. Inhibition constant (K_I) values of these substances were in the single-to double--digit micromolar range. The same compounds were active against cancer-related *h*CA IX isoform with K_I values in the range of tens of micromoles. **4u-x** also inhibited *h*CA I, which is typically considered an off-target protein, however, compounds **4h** and **4i** did not show noticeable activities against this isozyme.

Bacterial *β*-carbonic anhydrases often have less deep catalytic cavities compared to human isoforms, thus the catalytic zinc ion can be considered more available for binding [41,47]. However, sulfamide-bearing lactams **4a-s** did not show detectable inhibition of *β*-carbonic anhydrase from *vibrio cholerae*, whereas the K_I's of **4u-x** were in the double-digit micromolar range, thus significantly underperforming the reference FDA-approved drug. All in all, the observed micromolar activities of **4u-x** against all four enzymes demonstrated the applicability of the synthetic approach for the design of biologically active compounds. Despite the fact that enzyme inhibition demonstrated by **4a-x** is generally modest, it can likely be further improved, primarily by optimizing the substituent at position **3**. On the other hand, the discovered chemotype looks attractive to inhibit other metalloenzymes with larger active site cavities, whereas current substitution patterns can confer selectivity over ubiquitous carbonic anhydrase isoforms (such as *h*CA I and II) and prevent compounds' accumulation in red blood cells [48,49].

Table 1
Inhibition of *h*CA I, II, IX and *VhCAβ* with compounds **4a-x**.

K_I (μM)[a]				
Cmp	**hCA I**	**hCAII**	**hCA IX**	**VhCAβ**
4a	>100	>100	>100	>100
4b	>100	>100	>100	>100
4c	>100	>100	>100	>100
4d	>100	>100	>100	>100
4e	>100	>100	>100	>100
4f	>100	>100	>100	>100
4g	>100	>100	>100	>100
4h	>100	35.1	41.7	>100
4i	>100	55.0	53.5	>100
4j	>100	96.4	>100	>100
4k	>100	>100	>100	>100
4l	>100	>100	>100	>100
4m	>100	>100	>100	>100
4n	>100	>100	>100	>100
4o	>100	>100	>100	>100
4p	>100	>100	>100	>100
4q	>100	>100	>100	>100
4r	>100	>100	>100	>100
4s	>100	>100	>100	>100
4t	>100	>100	>100	>100
4u	23.6	95.9	53.4	93.0
4v	53.4	8.6	37.5	83.9
4w	17.7	18.1	38.1	84.8
4x	39.8	16.5	60.8	93.9
AAZ	0.25	0.012	0.026	0.45

[a] Mean from 3 different assays, by a stopped flow technique (errors were in the range of ± 5–10 % of the reported values).

3. Conclusions

In summary, we have prepared a series of structurally diverse *N*-sulfamoyl imines (sulfamide monoimines) and investigated their reaction with homophthalic anhydride (Castagnoli-Cushman reaction, CCR), which afforded previously unknown *N*-sulfamoyl δ-lactams, namely 1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids **4a-x**. The reaction demonstrated a broad substrate scope including such challenging for the CCR reagents as imines bearing nucleophilic, ionizable, enolizable or strong electron-withdrawing groups. The developed methodology also offers the advantage of high yields (up to 96%) and diastereoselectivity (for all dr's > 20:1, relative *trans*-configuration was supported by X-ray crystallography) simple isolation (19 out of 24 products were isolated pure after simple extraction, without chromatography) as well as direct and metal-free access to unprotected *N*-sulfamoyl lactams. Furthermore, the drug-like character of the obtained structures, as well as their polyfunctional molecular periphery the new chemotype has obvious potential in the field of drug discovery. To probe the pharmacological properties of the novel *N*-sulfamoyl tetrahydroisoquinoline-4-carboxylic acids we have screened **4a-x** against therapeutically relevant human and bacterial carbonic anhydrase isoforms. Despite the modest activities, with the most potent derivatives showing low micromolar K_I values, the compounds can be considered candidates for iterational optimization. Indeed, fine-tuning the substitution patterns, while being synthetically tractable and straightforward, can help generate both more potent carbonic anhydrase inhibitors or selective blockers of other metalloenzymes devoid of CA-inhibitory properties. In this context, a more extensive investigation of the new chemotypes' biological activities will be reported in due course.

4. Experimental part

4.1. General information

All reagents were obtained from commercial sources and used without further purification. HPLC grade acetonitrile and dimethylformamide were dried and stored over MS 4 Å (>48h). Mass spectra were recorded with a Bruker Maxis HRMS-ESI-qTOF spectrometer (electrospray ionization). NMR data were recorded with Bruker Avance 400 spectrometer (400.13 MHz for ^{1}H, 100.61 MHz for ^{13}C and 376.50 MHz for ^{19}F) in DMSO-d_6 and were referenced to residual solvent proton peaks ($\delta_H = 2.51$) and solvent carbon peaks ($\delta_C = 39.52$). Melting points were determined with RD-MP (REACH Devices) melting point apparatus in open capillary tubes. Preparative HPLC was carried out on Shimadzu LC-20AP chromatograph, equipped with spectrophotometric detector (monitoring at 214/254 nm). Column: Agilent Zorbax prepHT XDB-C18, 5 μm, 21.2 × 150 mm, mobile phase: water (A)/acetonitrile (B) + 0.1% TFA, flowrate 12 mL/min, temperature 40 °C. X-ray Single Crystal analysis was performed on Agilent Technologies (Oxford Diffraction) SuperNova diffractometer with monochromated CuKα radiation. The

crystal was kept at 100 K during data collection. Using Olex2 [50], the structures were solved with the SHELXT [51] structure solution program using Intrinsic Phasing and refined with the SHELXL [52] refinement package using Least Squares minimization.

General Procedure 1.1 for preparation of imines 3a-e,j, 3n, 3t, 3v, 3w.

Sulfuric diamide (2.5 mmol, 1 mol equiv.) was added to the aromatic aldehyde (5 mmol, 2 mol equiv.), then the mixture was dissolved in the respective solvent* and acid catalyst** was added. After that the resulting suspension was left at 80 °C while stirring for another 16 h***

*methanol (6 mL) was used for the substances **3a-e,j** and **3t**; 1,4-dioxane (6 mL) was used for the **3n**, **3v** and **3w.**

concentrated hydrochloric acid (10 μL) was used for **3a and **3b**; 4-methylbenzenesulfonic acid hydrate (0.125 mmol, 0.05 mol equiv.) was used for **3c-e,j**, **3t** and **3w**; BF_3*Et_2O (0.5 mmol, 0.01 mol equiv.) was used for **3n**, **3v.**

***for **3v** and **3w** the mixture was stirring during 32 h (^{1}H NMR control).

After that the mixture was cooled to r.t.*, solvent was evaporated, then the precipitate was washed with diethyl ether (3 × 15 mL) and partitioned between ethylacetate and water (25 mL of ethylacetate was washed with 2 × 15 mL of water), the organic layer was separated, dried with anhydrous sodium sulfate, the solvent was evaporated, the residue was dried in vacuo to give pure title product.**

*for products **3a**, **3j** and **3t** crystals were formed immediately after cooling to r.t., therefore these mixtures were refrigerated for an hour, then they were filtered and the solid residues were dried in vacuo.

** for **3n** the mixture was refrigerated, then the cloudy precipitate was filtered off, the filtrate was evaporated, solid residue was recrystallized from a solution of tetrahydrofuran and diethyl ether (10 mL: 20 mL respectively), after that the crystals were filtered and dried in vacuo. For **3v** solvent was evaporated and precipitate was recrystallized from a solution of acetone and hexane (18 mL: 33 mL respectively). For **3w** solvent was evaporated, the residue was washed with methyl *tert*-butyl ether (3 × 3 mL) and with diethyl ether (3 × 7 mL). After that the residue was dried in vacuo.

4.2. General Procedure 1.2 for preparation of imines 3f,k,l,m,o,p,q,r,s

To a stirred mixture of sulfamide (1.25 equiv) and corresponding aldehyde (1 equiv.) in 3 mL of methanol an aliquote of 300 μL of ethylenediamine acetate was added. The resulting mixture was stirred for 16 h at room temperature followed by filtration of precipitate, washing it with small amount of cold methanol and drying in air.

***N*-(4-Methoxybenzyliden)sulfamide (3a):** Yield 481 mg, 90%. Colorless solid, mp 177–179 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 7.84–7.78 (m, 2H), 6.99–6.92 (m, 2H), 6.87 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 164.5, 133.1, 125.6, 115.3, 56.2. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_8H_{10}N_2O_3S^+$ 237.0304; Found 237.0308.

***N*-(4-Fluorobenzyliden)sulfamide (3b):** Yield 162 mg, 32%. Colorless solid, mp 160–162 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.13–8.06 (m, 2H), 7.48–7.38 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0 (d, J = 253.3 Hz), 165.9, 133.6 (d, J = 9.6 Hz), 129.8 (d, J = 2.7 Hz), 117.1 (d, J = 22.2 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ −104.2. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_7H_7FN_2O_2SNa^+$ 225.0104; Found 225.0116.

***N*-(2-*B*romobenzyliden)sulfamide (3c):** Yield 335 mg, 51%. Colorless solid, mp 180–182 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.08 (dd, J = 7.5, 2.1 Hz, 1H), 7.85 (dd, J = 7.8, 1.4 Hz, 1H), 7.66–7.55 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.4, 136.3, 134.4, 131.2, 130.1, 129.2, 127.8. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_7H_8BrN_2O_2S^+$ 262.9484; Found 262.9477.

***N*-(2-Methylbenzyliden)sulfamide (3d):** prepared as E/Z-mixture. Yield 252 mg, 51%. Colorless solid, mp 136–138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H min), 9.14 (s, 1H maj), 8.09–8.04 (m, 1H min), 7.96 (dd, J = 8.1, 1.5 Hz, 1H maj), 7.62 (td, J = 7.5, 1.5 Hz, 1H min), 7.56 (td, J = 7.5, 1.5 Hz, 1H), 7.42–7.36 (m, 4H maj+4H min), 2.62 (s, 3H min), 2.58 (s, 3H maj). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.3, 165.4, 143.0, 141.6, 135.5, 134.2, 132.2, 132.0, 130.8, 130.8, 130.7, 129.6, 127.2, 127.1, 19.7, 19.5. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_8H_{10}N_2O_2SNa^+$ 221.0355; Found 221.0350.

***N*-(2-Thienylmethyliden)sulfamide (3e):** Yield 342 mg, 72%. Beige solid, mp 159–161 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H, min), 9.05 (s, 1H, maj), 8.34–8.17 (m, 2H, min + maj), 8.14–8.01 (m, 2H, min + maj), 7.45–7.17 (m, 5H, min + maj). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3 (min), 160.2 (maj), 142.5 (maj), 139.9 (maj), 139.2 (min), 138.4 (min), 138.1 (min), 136.3 (maj), 130.2 (min), 129.7 (maj). HRMS (ESI/Q-TOF) *m/z*: $[M+K]^+$ Calcd for $C_5H_6N_2O_2S_2K^+$ 228.9502; Found 228.9514.

***N*-sulfamoyl-(3-phenoxyphenyl)methanimine (3f):** Yield 749 mg, 90%. Yellow crystals, 153.5 °C–156 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 7.78–7.72 (m, 1H), 7.60 (t, J = 7.9 Hz, 1H), 7.53–7.50 (m, 1H), 7.48–7.41 (m, 2H), 7.39 (s, 2H), 7.38–7.33 (m, 1H), 7.26–7.18 (m, 1H), 7.14–7.07 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.6, 158.2, 156.2, 134.9, 131.7, 130.9, 126.5, 124.9, 124.5, 120.0, 118.0. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{12}N_2O_3SNa^+$ 299.0461; Found 299.0454.

***N*-(4-Butoxybenzyliden)sulfamide (3g):** Yield 410 mg, 64%. Colorless solid, mp 147–149 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 7.97–7.91 (m, 2H), 7.27 (s, 2H), 7.16–7.08 (m, 2H), 4.09 (t, J = 6.5 Hz, 2H), 1.73 (p, J = 6.6 Hz, 2H), 1.45 (h, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.2, 164.0, 133.1, 125.4, 115.7, 68.2, 31.0, 19.1, 14.1. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{11}H_{16}N_2O_3SNa^+$ 279.0774; Found 279.0787.

***N*-(4-Hydroxybenzyliden)sulfamide (3h):** Yield 70 mg, 14%. Colorless glassy solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 8.75 (s, 1H), 7.87–7.80 (m, 2H), 7.21 (s, 2H), 6.96–6.89 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 163.8, 133.4, 124.0, 116.7. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_7H_8N_2O_3SNa^+$ 223.0148; Found 223.0136.

***N*-(4-*tert*-Butylbenzyliden)sulfamide (3i):** Yield 162 mg, 27%. Colorless solid, mp 100–102 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (s, 1H), 7.95–7.91 (m, 2H), 7.64–7.60 (m, 2H), 7.37 (s, 2H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.7, 157.9, 130.8, 130.5, 126.7, 35.5, 31.2. HRMS (ESI/Q-TOF) *m/z*: $[M+K]^+$ Calcd for $C_{11}H_{16}N_2O_2SK^+$ 241.1005; Found 241.1002.

***N*-(2-Chlorobenzyliden)sulfamide (3j):** Yield 65 mg, 12%. Colorless solid, mp 160–162 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.75–7.65 (m, 2H), 7.57 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.0, 137.3, 136.1, 131.1, 129.8, 129.7, 128.7. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_7H_8ClN_2O_2S^+$ 218.9990; Found 218.9989.

***N*-Sulfamoyl-(3,4-dimethoxyphenyl)methanimine (3k):** Yield 392.7 mg, 54%. Beige solid, 149.8 °C–156 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.80 (s, 1H), 7.60 (dd, J = 8.3, 2.0 Hz, 1H), 7.50 (d, J = 1.9 Hz, 1H), 7.27 (s, 2H), 7.15 (d, J = 8.3 Hz, 1H), 3.93 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 154.5, 149.7, 127.6, 125.6, 112.0, 110.6, 56.3, 56.0. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_9H_{12}N_2O_4SNa^+$ 267.0410; found 267.0411.

***N*-Sulfamoyl-(2,3-dichlorophenyl)methanimine (3l):** Yield 390 mg, 51%. Colorless solid, 174.5 °C–177.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.04 (dd, J = 7.9, 1.6 Hz, 1H), 7.97 (dd, J = 8.1, 1.6 Hz, 1H), 7.62 (s, 2H), 7.57 (t, J = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.5, 135.4, 134.5, 133.0, 131.7, 129.0, 127.9. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_7H_6Cl_2N_2O_2S^+$ 252.9600; found 252.9598.

***N*-Sulfamoyl-(2,4-dimethoxyphenyl)methanimine (3m)** Yield 376.2 mg, 51%. Beige solid, 176.4 °C–181 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.19 (s, 2H), 6.75–6.67 (m, 2H), 3.93 (s, 1H), 3.89 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.8, 163.3, 161.3, 130.1, 113.6, 108.0, 98.7, 56.7, 56.3.

HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_9H_{12}N_2O_4S^+$ 267.0410; found 267.0410

***N*-(4-Nitrobenzyliden)sulfamide (3n):** Yield 218 mg, 38%. Beige solid, mp 224–226 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.43–8.37 (m, 2H), 8.30–8.24 (m, 2H), 7.57 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.5, 150.9, 138.5, 131.9, 124.7. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_7H_7N_3O_4SNa^+$ 252.0049; Found 252.0031

***N*-sulfamoyl-(2-bromothiophene)methanimine (3o):** Yield 407 mg, 51 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.91 (d, $J = 4.0$ Hz, 1H), 7.49 (d, $J = 4.0$ Hz, 1H), 7.40 (s, 2H). 13C NMR (101 MHz, DMSO-d_6) δ 159.5, 140.6, 140.0, 133.3, 123.0. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_5H_5BrN_2O_2S_2^+$ 268.9049; found 268.8878.

***N*-sulfamoyl-(7-methoxybenzo [d] [1,3] dioxol-5-yl)methanimine (3p)** Yield 590 mg, 76%. Beige solid, 183.8 °C–190 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 7.40 (d, $J = 1.4$ Hz, 1H), 7.32 (s, 2H), 7.22 (d, $J = 1.4$ Hz, 1H), 6.17 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 149.6, 144.0, 140.7, 127.6, 112.3, 103.6, 103.1, 56.9. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_9H_{12}N_2O_4S^+$ 267.0410; found 267.0410.

***N*-sulfamoyl-(2,4,5-trimethoxyphenyl)methanimine (3q):** Yield 751 mg, 91%. Yellow solid, 226 °C–230.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 7.34 (s, 1H), 7.20 (s, 2H), 6.82 (s, 1H), 3.94 (s, 3H), 3.94 (s, 3H), 3.77 (s, 3H). 13C NMR (101 MHz, DMSO-d_6) δ 161.2, 158.3, 156.8, 143.9, 111.7, 108.8, 97.9, 57.1, 56.6, 56.2. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{14}N_2O_5S^+$ 275.0696; found 275.0700.

***N*-sulfamoyl-(4-bromophenyl)methanimine (3r):** Yield 538 mg, 68%. Colorless solid, 185 °C–191.4 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.93 (s, 1H), 7.97–7.90 (m, 2H), 7.83–7.77 (m, 2H), 7.43 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.2, 132.9, 132.5, 132.2, 128.6. HRMS (ESI/Q-TOF) *m/z*: $[M-H]^-$ calcd for $C_7H_6BrN_2O_2S^-$ 260.9339; found 260.9337.

***N*-sulfamoyl-((4-(methylthio)phenyl))methanimine (3s)** Yield 513 mg, 74%. Yellow solid, 176.5 °C–182 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 7.96–7.87 (m, 2H), 7.48–7.40 (m, 2H), 7.34 (s, 2H), 2.56 (s, 3H). 13C NMR (101 MHz, DMSO-d_6) δ 166.4, 147.4, 131.1, 129.1, 125.9, 14.4. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_8H_{10}N_2O_2S_2^+$ 253.0076; found 253.0075.

***N*-(4-(Dimethylamino)benzyliden)sulfamide (3t):** Yield 493 mg, 87%. Yellow solid, mp 206–208 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.77 (d, $J = 8.6$ Hz, 2H), 7.05 (s, 2H), 6.81 (d, $J = 8.9$ Hz, 2H), 3.06 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 154.6, 133.0, 119.6, 112.0, 40.1. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_9H_{13}N_3O_2SNa^+$ 250.0621; Found 250.0620.

***N*-sulfamoyl-(furan-2-yl)methanimine (3u)** Yield 334 mg, 64%. Beige solid, 149 °C–170 °C (decomp.).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.14 (d, $J = 1.7$ Hz, 1H), 7.59 (d, $J = 3.6$ Hz, 1H), 7.31 (s, 2H), 6.82 (dd, $J = 3.6$, 1.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.5, 150.3, 149.0, 125.22, 114.0. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_5H_6N_2O_3S^+$ 175.0172; found 175.0174.

N-(4-Carbomethoxybenzylidene)sulfamide (3v): Yield 393 mg, 65%. Colorless solid, mp 235–237 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 8.14 (s, 4H), 7.50 (s, 2H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.2, 166.0, 137.0, 134.4, 130.9, 130.3, 53.0. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_9H_{10}N_2O_4S$ 243.0434; Found 243.0435.

***N*-(4-Cyanobenzyliden)sulfamide (3w):** Yield 105 mg, 20%. Colorless solid, mp 226–228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.18 (d, $J = 8.0$ Hz, 2H), 8.05 (d, $J = 8.1$ Hz, 2H), 7.55 (s, 2H).^{13}C NMR (101 MHz, DMSO-d_6) δ 165.9, 137.0, 133.6, 131.2, 118.6, 116.2. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_8H_7N_3O_2S$ 210.0332; Found 210.0337.

4.3. General Procedure 2 for preparation of lactams 4a-w

Imine **3a-w** (0.62 mmol, 1 equiv.) and homophthalic anhydride (0,62 mmol, 1 equiv.) were placed in a screw-cap vial and the mixture was suspended in dry acetonitrile (1 mL), then DIPEA was added dropwise (0.03 mmol, 0.05 equiv.).* After stirring for 16 h at 80 °C (pre-heated metal heating block; bath temperature) the mixture was concentrated under reduced pressure and dissolved in ethylacetate (10 mL). The product was extracted into the sodium hydrocarbonate saturated solution (15 mL), the aqueous layer was separated, washed with ethyl acetate, then acidified with concentrated hydrochloric acid (pH control; end point: pH∼1).** The resulting suspension was extracted again with ethyl acetate (2 × 15 mL), combined organics were dried with anhydrous sodium sulfate, concentrated in vacuo give pure title product.

*for the substances **4p-t** 1 mL of dry DMF was added after stirring for 10 min to dissolve reaction components.

for the substances **4k, **4l**, **4v**, **4w** the resulting suspension was filtered, then the filtrate was purified by preparative RP HPLC (see General information); Gradient: 5% B (0–5 min), 5–60% B (5–50 min), 60% B (50–60 min), 60%–90% B (60–70 min); for **4t**: after acidification of $NaHCO_3$ extract the resulting aqueous solution was left overnight in a beaker at room tempearture. The crystals were formed, collected and dried in vacuo to give pure compound **4t.**

***(rac)*-(3*S*,4*S*)-3-(4-methoxyphenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4a):** Yield 186 mg, 80%. Colorless solid, mp 77–79 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (br. s, 1H), 7.99–7.95 (m, 1H), 7.79 (s, 2H), 7.50 (td, $J = 7.5$, 1.5 Hz, 1H), 7.43 (td, $J = 7.5$, 1.3 Hz, 1H), 7.28 (d, $J = 7.6$ Hz, 1H), 7.09 (d, $J = 8.4$ Hz, 2H), 6.78 (d, $J = 8.9$ Hz, 2H), 6.12 (d, $J = 1.9$ Hz, 1H), 4.31 (d, $J = 2.0$ Hz, 1H), 3.65 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.8, 163.1, 158.8, 135.2, 133.7, 131.4, 130.3, 128.7, 128.6, 127.7, 127.5, 114.3, 60.7, 55.5, 51.5. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{16}N_2O_6S$ 377.0802; Found 377.0803.

***(rac)*-(3*S*,4*S*)-3-(4-fluorophenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4b):** Yield 192 mg, 85%. Colorless solid, mp 176–178 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (br.s, 1H), 7.98 (d, $J = 7.7$ Hz, 1H), 7.87 (s, 2H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.45 (t, $J = 7.5$ Hz, 1H), 7.30 (d, $J = 7.5$ Hz, 1H), 7.22 (dd, $J = 8.6$, 5.2 Hz, 2H), 7.08 (t, $J = 8.7$ Hz, 2H), 6.17 (s, 1H), 4.38 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.6, 162.9, 135.7 (d, $J = 2.9$ Hz), 134.9, 133.9, 130.3, 128.8, 128.5, 128.4 (d, $J = 8.4$ Hz), 127.8, 115.8 (d, $J = 21.6$ Hz), 60.5, 51.3.^{19}F NMR (376 MHz, DMSO-d_6) δ −115.4. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}FN_2O_5S^+$ 365.0602; Found 365.0610.

***(rac)*-(3*S*,4*S*)-3-(2-bromophenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4c):** Yield 221 mg, 84%. Colorless solid, mp 212–214 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.16 (br.s, 1H), 8.05 (dd, $J = 6.9$, 2.2 Hz, 1H), 7.91 (s, 2H), 7.69–7.61 (m, 1H), 7.51 (ddt, $J = 10.8$, 7.4, 3.8 Hz, 2H), 7.33 (dd, $J = 6.9$, 2.0 Hz, 1H), 7.17 (p, $J = 5.5$ Hz, 2H), 6.83–6.76 (m, 1H), 6.45–6.43 (m, 1H), 4.20 (d, $J = 1.7$ Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.3, 163.2, 137.7, 134.0, 134.0, 133.8, 130.6, 130.2, 129.1, 128.5, 128.3, 127.9, 127.8, 121.8, 60.7, 49.1. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}BrN_2O_5^+$ 424.9801; Found 424.9805.

***(rac)*-(3*S*,4*S*)-1-oxo-2-sulfamoyl-3-(o-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4d):** Yield 145 mg, 65%. Colorless solid, mp 209–211 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (br.s, 1H), 8.06 (dd, $J = 7.2$, 2.0 Hz, 1H), 7.81 (s, 2H), 7.51 (m, $J = 7.6$, 1.9 Hz, 2H), 7.28 (dd, $J = 7.1$, 1.9 Hz, 1H), 7.20 (d, $J = 7.6$ Hz, 1H), 7.13–7.06 (m, 1H), 6.94 (t, $J = 7.4$ Hz, 1H), 6.65 (d, $J = 7.7$ Hz, 1H), 6.35–6.32 (m, 1H), 4.16 (d, $J = 1.5$ Hz, 1H), 2.47 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) 13C NMR (101 MHz, DMSO-d_6) δ 172.0, 163.4, 137.4, 134.7, 134.5, 133.7, 131.3, 130.6, 128.8, 128.7, 127.8, 127.6, 126.3, 125.5, 58.6, 49.4, 19.0. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{17}N_2O_5S^+$ 361.0853; Found 361.0858.

***(rac)*-(3*S*,4*S*)-1-oxo-2-sulfamoyl-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4e):** Yield 98 mg, 45%. Beige solid, mp 66–68 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.19 (br.s, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.81 (s, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.48 (q, J = 8.0 Hz, 2H), 7.36–7.25 (m, 1H), 6.93 (s, 1H), 6.86 (s, 1H), 6.38 (s, 1H), 4.43 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.1, 162.4, 143.0, 135.5, 133.9, 130.7, 128.9, 128.4, 127.9, 127.1, 126.7, 126.0, 57.7, 51.3. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{13}N_2O_5S_2^+$ 353.0260; Found 353.0264.

***(rac)*-(3*S*,4*S*)-1-oxo-3-(3-phenoxyphenyl)-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4f):** Yield 187 mg, 69%. Yellow glassy solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (br.s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.85 (s, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.37–7.23 (m, 4H), 7.12 (t, J = 7.3 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.80 (q, J = 9.1, 7.0 Hz, 4H), 6.17 (s, 1H), 4.36 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.5, 163.0, 156.9, 156.7, 141.8, 134.9, 133.8, 130.7, 130.5, 130.3, 128.7, 128.6, 127.7, 123.9, 121.6, 118.8, 117.8, 116.9, 60.8, 51.4. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{18}N_2O_6SNa^+$ 461.0778; Found 461.0779.

***(rac)*-(3*S*,4*S*)-3-(4-butoxyphenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4g):** Yield 192 mg, 74%. Yellow solid, mp 70–72 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (br.s, 1H), 7.98 (dd, J = 7.7, 1.5 Hz, 1H), 7.80 (s, 2H), 7.52 (td, J = 7.5, 1.5 Hz, 1H), 7.45 (td, J = 7.5, 1.3 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.12 (d, J = 1.8 Hz, 1H), 4.33 (d, J = 2.0 Hz, 1H), 3.87 (t, J = 6.4 Hz, 2H), 1.67–1.58 (m, 2H), 1.43–1.33 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.7, 163.0, 158.3, 135.1, 133.7, 131.2, 130.3, 128.7, 127.7, 127.5, 114.8, 67.5, 60.7, 51.4, 31.2, 19.2, 14.1. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{22}N_2O_6SNa^+$ 441.1091; Found 441.1095.

***(rac)*-(3*S*,4*S*)-3-(4-hydroxyphenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4h):** Yield 186 mg, 83%. Beige solid, mp 217–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (br.s, 1H), 9.35 (s, 1H), 7.96 (dd, J = 7.8, 1.4 Hz, 1H), 7.79 (s, 2H), 7.52 (td, J = 7.5, 1.5 Hz, 1H), 7.44 (td, J = 7.6, 1.3 Hz, 1H), 7.29 (dd, J = 7.6, 1.3 Hz, 1H), 6.95 (d, J = 8.6 Hz, 2H), 6.60 (d, J = 8.6 Hz, 2H), 6.07 (d, J = 1.8 Hz, 1H), 4.30 (d, J = 1.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.8, 163.1, 157.0, 135.2, 133.7, 130.3, 129.6, 128.7, 128.6, 127.7, 127.4, 115.6, 60.8, 51.5. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{15}N_2O_6S^+$ 363.0645; Found 363.0651.

***(rac)*-(3*S*,4*S*)-3-(4-(*tert*-butyl)phenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4i):** Yield 145 mg, 58%. Colorless solid, mp 202–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.09 (br.s, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.82 (s, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.15 (s, 1H), 4.38 (d, J = 1.8 Hz, 1H), 1.20 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.7, 163.0, 150.0, 136.6, 135.1, 133.8, 130.4, 128.7, 128.6, 127.8, 126.0, 125.8, 60.9, 51.3, 34.6, 31.5. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{23}N_2O_5S$ 403.1322; Found 403.1322.

***(rac)*-(3*S*,4*S*)-3-(2-chlorophenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4j):** Yield 170 mg, 72%. Colorless solid, mp 182–184 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (br.s, 1H), 8.05 (dd, J = 7.3, 1.5 Hz, 1H), 7.92 (s, 2H), 7.50 (ddd, J = 13.5, 7.2, 1.6 Hz, 3H), 7.33 (dd, J = 6.8, 1.9 Hz, 1H), 7.25 (td, J = 7.7, 1.7 Hz, 1H), 7.14 (td, J = 7.6, 1.3 Hz, 1H), 6.81 (dd, J = 7.9, 1.6 Hz, 1H), 6.49 (d, J = 1.7 Hz, 1H), 4.22 (d, J = 1.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.4, 163.2, 136.3, 134.2, 133.9, 131.3, 130.5, 130.5, 129.9, 129.0, 128.5, 127.8, 58.6, 49.0. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}ClN_2O_5S^+$ 381.0306; Found 381.0308.

***(rac)*-(3*S*,4*S*)-3-(3,4-dimethoxyphenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4k):** Yield 101 mg, 40%. Colorless solid, mp 86–88 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (br.s, 1H), 7.97 (dd, J = 7.8, 1.4 Hz, 1H), 7.83 (s, 2H), 7.52 (td, J = 7.5, 1.5 Hz, 1H), 7.44 (td, J = 7.6, 1.3 Hz, 1H), 7.31–7.27 (m, 1H), 6.82 (d, J = 2.2 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.61 (dd, J = 8.4, 2.2 Hz, 1H), 6.12 (d, J = 1.8 Hz, 1H), 4.41 (d, J = 2.0 Hz, 1H), 3.66 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.8, 163.1, 149.0, 148.3, 135.2, 133.7, 131.7, 130.4, 128.6, 127.6, 118.3, 111.9, 110.1, 60.8, 55.8, 55.7, 51.4. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{19}N_2O_7S^+$ 407.0907; Found 407.0909.

***(rac)*-(3*S*,4*S*)-3-(2,3-dichlorophenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4l):** Yield 57 mg, 22%. Colorless solid, mp 88–90 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.29 (br.s, 1H), 8.04 (dd, J = 7.6, 1.6 Hz, 1H), 7.97 (s, 2H), 7.53 (dqd, J = 14.9, 7.3, 1.5 Hz, 3H), 7.36 (dd, J = 7.4, 1.5 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 6.75 (dd, J = 8.0, 1.4 Hz, 1H), 6.51 (d, J = 1.6 Hz, 1H), 4.27 (d, J = 1.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.3, 163.1, 138.9, 134.0, 134.0, 130.7, 130.3, 129.1, 128.7, 128.3, 127.8, 126.4, 59.0, 48.5. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{13}Cl_2N_2O_5S^+$ 414.9917; Found 414.9921.

***(rac)*-(3*S*,4*S*)-3-(2,4-dimethoxyphenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4m):** Yield 93 mg, 37%. Grey solid, mp 95–97 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (br.s, 2H maj + min), 8.01 (dd, J = 7.5, 1.6 Hz, 1H maj), 7.95–7.88 (m, 1H min), 7.75 (s, 2H maj), 7.55–7.40 (m, 3H maj), 7.42–7.30 (m, 1H min), 7.30–7.23 (m, 1H maj), 6.59 (d, J = 8.5 Hz, 1H maj), 6.56 (d, J = 2.4 Hz, 1H maj), 6.31 (d, J = 2.0 Hz, 2H maj), 6.29 (d, J = 2.6 Hz, 1H min), 4.13 (d, J = 1.8 Hz, 1H maj), 3.94 (s, 1H min), 3.88 (s, 3H maj), 3.67 (s, 3H maj), 3.58 (s, 1H min). ^{13}C NMR (101 MHz, DMSO-d_6) 172.9, 171.9, 163.5, 160.4, 156.9, 137.0, 135.3, 133.7, 132.8, 132.2, 130.8, 130.4, 128.6, 128.6, 127.7, 127.4, 127.4, 119.0, 104.8, 99.2, 56.6, 56.3, 55.6, 49.3. Some signals of second rotamer are missing due to spectrum broadening. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{19}N_2O_7S^+$ 407.0907; Found 407.0904.

According to analytical RP-HPLC (on C18 silica) there was only one peak in the sample of compound **2m**, which supports that two sets of signals in NMR arise from rotamers and not from diastereomers (they were always separable on analytical column in our previous studies for HPA-derived lactams). This conclusion is also supported by the fact that both sets of signals have small $^3J_{HH}$ values for methine lactam protons (for *cis*-isomers they are usually 5–10Hz). We also heated the NMR sample to 80 °C, but coalescence was not achieved. At higher temperatures we observed decomposition.

***(rac)*-(3*S*,4*S*)-3-(4-nitrophenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4n):** Yield 162 mg, 67%. Yellow solid, mp 151–153 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (br.s, 1H), 8.12 (d, J = 8.8 Hz, 2H), 8.00 (dd, J = 7.7, 1.5 Hz, 1H), 7.97 (s, 2H), 7.56–7.43 (m, 4H), 7.32–7.28 (m, 1H), 6.30 (d, J = 1.7 Hz, 1H), 4.48 (d, J = 1.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.3, 162.8, 147.3, 147.1, 134.5, 134.0, 130.3, 129.0, 128.3, 127.9, 127.8, 124.1, 60.7, 50.8. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}N_3O_7S^+$ 392.0547; Found 392.0550.

***(rac)*-(3*S*,4*S*)-3-(5-bromothiophen-2-yl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4o):** Yield 224 mg, 84%. Yellow solid, mp 67–69 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 (br.s, 1H), 7.97 (dd, J = 7.8, 1.4 Hz, 1H), 7.86 (s, 2H), 7.64 (td, J = 7.5, 1.4 Hz, 1H), 7.52 (td, J = 7.7, 1.3 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 3.9 Hz, 1H), 6.80 (d, J = 3.9 Hz, 1H), 6.31–6.29 (m, 1H), 4.44 (d, J = 2.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.9, 162.2, 144.6, 135.3, 134.2, 130.8, 130.3, 129.1, 128.2, 128.1, 127.8, 111.1, 57.6, 50.6. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{12}BrN_2O_5S_2^+$ 430.9366; Found 430.9372.

***(rac)*-(3*S*,4*S*)-3-(7-methoxybenzo[d] [1,3] dioxol-5-yl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4p):** Yield 250 mg, 96%. Orange glassy solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 1H), 7.97 (dd, J = 7.8, 1.4 Hz, 1H), 7.85 (s, 2H), 7.54 (td, J = 7.5, 1.5 Hz, 1H), 7.45 (td, J = 7.5, 1.3 Hz, 1H), 7.31 (dd, J = 7.7, 1.3 Hz, 1H), 6.50 (d, J = 1.7 Hz, 1H), 6.36 (d, J = 1.7 Hz, 1H), 6.10–6.08 (m, 1H), 5.90 (dd, J = 5.8, 1.1 Hz, 2H), 4.39 (d, J = 2.1 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.6, 163.0, 148.9, 143.4, 135.2, 134.3, 134.2, 133.8, 130.4, 128.7, 128.5, 127.7, 106.4, 101.8, 100.5,

60.9, 56.6, 51.4. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{17}N_2O_8S^+$ 421.0700; Found 421.0698.

***(rac)*-(3*S*,4*S*)-1-oxo-2-sulfamoyl-3-(2,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4q):** Yield 222 mg, 82%. Beige solid, mp 134–136 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 8.02 (dd, J = 7.5, 1.7 Hz, 1H), 7.80 (s, 2H), 7.54–7.41 (m, 2H), 7.26 (dd, J = 7.4, 1.5 Hz, 1H), 6.69 (s, 1H), 6.32 (d, J = 1.8 Hz, 1H), 6.25 (s, 1H), 4.12 (d, J = 1.9 Hz, 1H), 3.88 (s, 3H), 3.74 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.9, 163.6, 150.2, 149.5, 142.4, 135.4, 133.7, 130.4, 128.7, 128.6, 127.5, 117.9, 112.3, 98.9, 56.9, 56.8, 56.4, 56.3, 49.5. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{21}N_2O_8S^+$ 437.1013; Found 437.1016.

***(rac)*-(3*S*,4*S*)-3-(4-bromophenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4r):** Yield 250 mg, 95%. Yellow glassy solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98–7.94 (m, 1H), 7.83 (s, 2H), 7.51 (td, J = 7.5, 1.5 Hz, 1H), 7.47–7.40 (m, 3H), 7.28 (d, J = 7.4 Hz, 1H), 7.14 (d, J = 8.3 Hz, 2H), 6.14 (s, 1H), 4.32 (d, J = 2.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.7, 163.0, 139.2, 135.2, 133.8, 131.8, 130.2, 128.7, 128.6, 128.5, 127.8, 121.0, 60.8, 51.4. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}BrN_2O_5S^+$ 424.9801; Found 424.9804.

***(rac)*-(3*S*,4*S*)-3-(4-(methylthio)phenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4s):** Yield 233 mg, 96%. Yellow glassy solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (dd, J = 7.7, 1.5 Hz, 1H), 7.80 (s, 2H), 7.51 (td, J = 7.5, 1.5 Hz, 1H), 7.44 (td, J = 7.6, 1.3 Hz, 1H), 7.30–7.26 (m, 1H), 7.12 (s, 4H), 6.13 (d, J = 1.8 Hz, 1H), 4.32 (d, J = 2.0 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.8, 163.0, 137.7, 136.2, 135.3, 133.8, 130.3, 128.6, 128.6, 127.7, 126.9, 126.3, 60.9, 51.5, 14.9. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{17}N_2O_5S_2^+$ 393.0573; Found 393.0575.

4-((*rac*)-(3*S*,4*S*)-4-carboxy-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinolin-3-yl)-N,N-dimethylbenzenaminium chloride (4t): Yield 129 mg, 49%. Beige solid, mp 203–205 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (dd, J = 7.8, 1.5 Hz, 1H), 7.81 (s, 2H), 7.52 (td, J = 7.5, 1.5 Hz, 1H), 7.44 (td, J = 7.5, 1.3 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 7.13 (d, J = 8.1 Hz, 2H), 7.05–6.90 (m, 2H), 6.12 (d, J = 1.9 Hz, 1H), 4.35 (d, J = 2.0 Hz, 1H), 2.89 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) ^{13}C NMR (101 MHz, DMSO-d_6, 353K) δ 171.6, 163.2, 149.8, 135.4, 133.6, 130.2, 129.0, 128.6, 127.8, 127.1, 113.2, 60.8, 60.8, 51.6. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{21}N_3O_5SCl^+$ 390.1118; Found 390.1120.

***(rac)*-(3*S*,4*S*)-3-(furan-2-yl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4u):** Yield 87 mg, 42%. Beige solid, mp 193–195 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (br.s, 1H), 7.97–7.92 (m, 1H), 7.84 (s, 2H), 7.59 (td, J = 7.5, 1.5 Hz, 1H), 7.51–7.43 (m, 3H), 6.28 (dd, J = 3.4, 1.8 Hz, 1H), 6.14 (t, J = 1.5 Hz, 1H), 6.09 (d, J = 3.3 Hz, 1H), 4.50 (d, J = 2.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.1, 162.5, 152.0, 143.3, 135.5, 133.8, 130.3, 128.7, 128.0, 127.9, 111.0, 108.3, 56.0, 48.1. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{13}N_2O_6S^+$ 337.0489; Found 337.0494.

***(rac)*-(3*S*,4*S*)-3-(4-(methoxycarbonyl)phenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4v):** Yield 100 mg, 40%. Colorless glassy solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H), 7.98 (dd, J = 7.7, 1.5 Hz, 1H), 7.91 (s, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.51 (td, J = 7.5, 1.6 Hz, 1H), 7.44 (td, J = 7.6, 1.4 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.30–7.26 (m, 1H), 6.24 (d, J = 1.8 Hz, 1H), 4.44 (d, J = 1.9 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.4, 166.2, 162.9, 144.9, 134.7, 133.9, 130.2, 129.8, 129.3, 128.8, 128.5, 127.8, 126.8, 61.0, 52.6, 51.0. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{17}N_2O_7S^+$ 405.0751; Found 405.0755.

***(rac)*-(3*S*,4*S*)-3-(4-cyanophenyl)-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4w):** Yield 18 mg, 8%. Colorless solid, mp 97–99 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.94 (s, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.40 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 7.5 Hz, 1H), 6.24 (s, 1H), 4.44 (d, J = 1.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.3, 162.8, 145.1, 134.5, 134.0, 133.0, 130.3, 129.0, 128.3, 127.9, 127.5, 118.9, 110.8, 60.8, 50.7. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{14}N_3O_5S^+$ 372.0649; Found 372.0643.

4.4. Preparation of compound 5

Sulfuric diamide (2 mmol, 1 mol.equiv.) was dissolved in a mixture of distilled water and formic acid (3 mL + 3 mL), then sodium 4-methylbenzenesulfinate (2.43 mmol, 1.213 mol.equiv.) was added. After that the mixture was cooled in an ice bath for 2 min, then cyclohexanecarbaldehyde (2 mmol, 1 mol.equiv.) was added dropwise. The resulting suspension was left in the bath while stirring for another 16 h. After that the mixture was filtered, the collected solid was washed with water and pentane successively and dried in vacuo to give pure title compound.

***N*-(sulfamoyl)cyclohexyl(tosyl)methanamine (5):** Yield 574 mg, 83%. Colorless solid, mp 89–91 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (br.s, 1H), 8.26 (d, J = 4.0 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.23 (s, 2H), 2.38 (s, 3H), 1.86–1.79 (m, 2H), 1.72 (dd, J = 9.0, 3.9 Hz, 2H), 1.63 (dt, J = 12.5, 3.5 Hz, 1H), 1.39–1.14 (m, 6H). The sample decomposed during ^{13}C NMR spectrum acquisition. HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{22}N_2O_4S_2Na^+$ 369.0913; Found 369.0918.

4.5. Preparation of compound 4x

Compound **5** (0.5 mmol, 1 mol equiv.) was dissolved in dry acetonitrile (0.5 ml), then DBU (0.55 mmol, 1.1 mol equiv.) was added to it dropwise. After stirring for 1 h at r.t. HPA (0.5 mmol, 1 mol equiv.) was added as well and the resulting suspension was left at 80 °C while stirring for another 16 h. After that, the suspension was cooled to −20 °C, the residue was centrifuged and dried in vacuo. Then the residue was purified by preparative RP HPLC (eluent – H_2O (0,1% trifluoroacetic acid): Acetonitrile (0,1% trifluoroacetic acid)); method: 5 min–95%: 5%, 45 min–95%: 5%–40%: 60%, 10 min–40%: 60%, 10 min–10%: 90%. Fractions containing Castagnoli-Cushman reaction product (control by analytical RP HPLC) were pooled and concentrated to give compound **4x**.

***(rac)*-(3R,4S)-3-cyclohexyl-1-oxo-2-sulfamoyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (4x):** Yield 33 mg, 15%. Colorless solid, mp 205–207 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 7.91 (dd, J = 8.0, 1.4 Hz, 1H), 7.62 (dd, J = 7.6, 1.4 Hz, 1H), 7.60 (d, J = 3.2 Hz, 2H), 7.48 (ddd, J = 7.0, 3.9, 2.7 Hz, 2H), 4.71 (dd, J = 7.0, 1.6 Hz, 1H), 4.19 (d, J = 1.6 Hz, 1H), 1.71–1.65 (m, 2H), 1.53 (t, J = 10.3 Hz, 2H), 1.42 (td, J = 8.0, 7.4, 3.2 Hz, 2H), 1.14 (td, J = 11.9, 8.5 Hz, 1H), 1.09–0.91 (m, 3H), 0.62 (qd, J = 12.6, 3.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.8, 162.8, 136.6, 133.7, 130.0, 128.7, 128.5, 127.7, 63.6, 45.3, 41.7, 30.0, 29.5, 26.1, 26.0, 26.0. HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{21}N_2O_5S^+$ 353.1166; Found 353.1168.

4.6. Preparation of compound 6a

Compound **4a** (40 mg, 0.1 mmol) was dissolved in DMSO (1 mL) followed by addition of DBU (30 mg, 0.2 mmol) and heating at 175 °C (metal heating block) for 17 h with stirring. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1 N HCl, $NaHCO_3$ (sat), water, dried over sodium sulfate, filtered and concentrated to afford pure compound **6a** in 25 mg, 93% yield. The obtained NMR data matched reported [34] before.

4.7. Bioassay

An Applied Photophysics stopped-flow instrument has been used for assaying the CA catalysed CO_2 hydration activity [43]. Phenol red (at a concentration of 0.2 mM) has been used as indicator, working at the

absorbance maximum of 557 nm, with 20 mM Hepes (pH 7.5) as buffer, and 20 mM Na_2SO_4 (for maintaining constant the ionic strength), following the initial rates of the CA-catalysed CO_2 hydration reaction for a period of 10–100 s. The CO_2 concentrations ranged from 1.7 to 17 mM for the determination of the kinetic parameters and inhibition constants. For each inhibitor at least six traces of the initial 5–10% of the reaction have been used for determining the initial velocity. The uncatalyzed rates were determined in the same manner and subtracted from the total observed rates. Stock solutions of inhibitor (0.1 mM) were prepared in distilled deionised water and dilutions up to 0.01 nM were done thereafter with the assay buffer. Inhibitor and enzyme solutions were pre-incubated together for 15 min at room temperature prior to assay, in order to allow for the formation of the EI complex. The inhibition constants were subsequently obtained by nonlinear least-squares methods using PRISM 3 and the ChengPrusoff equation, as reported earlier, and represent the mean from at least three different determinations. All CA isoforms were recombinant ones obtained in-house as reported earlier [47,53–55].

5. Crystallographic data

Deposition numbers 2165216 (**4h**) and 2165217 (**3a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

CRediT authorship contribution statement

Elizaveta Karchuganova: Investigation. **Sofiia Martynova:** Investigation. **Stanislav Kalinin:** Investigation, Writing – original draft, Methodology. **Andrea Angeli:** Investigation. **Dmitry Dar'in:** Conceptualization, Writing – review & editing. **Daniella Vullo:** Investigation. **Claudiu T. Supuran:** Conceptualization, Data curation, Project administration, Resources, Writing – review & editing. **Olga Bakulina:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

This research was funded by the Russian Science Foundation [19-75-30008-P]. We thank LLC Accellenna, Russia for continuous support. We are grateful to the Research Centre for Magnetic Resonance, the Centre for Chemical Analysis and Materials Research and the Research Centre for X-ray Diffraction Studies of Saint Petersburg State University Research Park for the analytical data. In commemoration of the 300th anniversary of St Petersburg State University's founding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2024.133890.

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