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Mixed Carboxylic-Sulfonic Anhydride in Reactions with Imines: A Straightforward Route to Water-Soluble β-Lactams via a Staudinger-Type Reaction

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Abstract

The first example of employing a mixed carboxylic-sulfonic anhydride in reactions with imines is reported. Unlike with its well-studied isostere homophthalic anhydride, benzo[*c*][1,2]oxathiin-3(4*H*)-one 1,1-dioxide gave no product of a formal [4+2] cycloaddition an only followed an alternative reaction path toward β-lactams, presumably, via a formal [2+2] cycloaddition (a Staudinger-type reaction). Optimized reaction conditions involve the use of triethylamine as a base promoter, which also allows isolating the product β-lactam benzene sulfonic acids as respective triethylammonium salt by conventional column chromatography. The reaction shows some preference to *trans*-isomer formation; pure diastereomers can be isolated in some cases.

Introduction

β-Lactams (2-azetidinones) can be confidently regarded as privileged motifs[1] in drug design. Indeed, their successful application in constructing bioactive compounds continue to extend beyond antibiotics (falling into four major classes - penicillins, cephalosporins, carbapenems and monobactams)[2] and serine β-lactamase inhibitors (exemplified by clavulanic acid, sulbactam and tazobactam).[3] Although the general acceptance of β-lactams as scaffolds for non-antibacterial drug design was somewhat retarded by a misconception about their chemical reactivity,[4] their recent resurgence in the context of numerous important biological targets is evident. This is eloquently illustrated by the approved cholesterol-lowering drug ezetimibe (**1**)[5] acting as an inhibitor of acyl-CoA cholesterol acylatransferase enzyme. The development, in the early 2000*s* of this pioneering application of the β-lactam motif to the design of a chemically stable small molecule drug was accompanied by the discovery of compounds with functional activity against such targets as tryptase (**2** or BMS-363131),[6] matrix metalloprotease MMP-9 (**3**),[7] fatty acid amide hydrolase (**4**)[8] and many others (Figure 1).[9]

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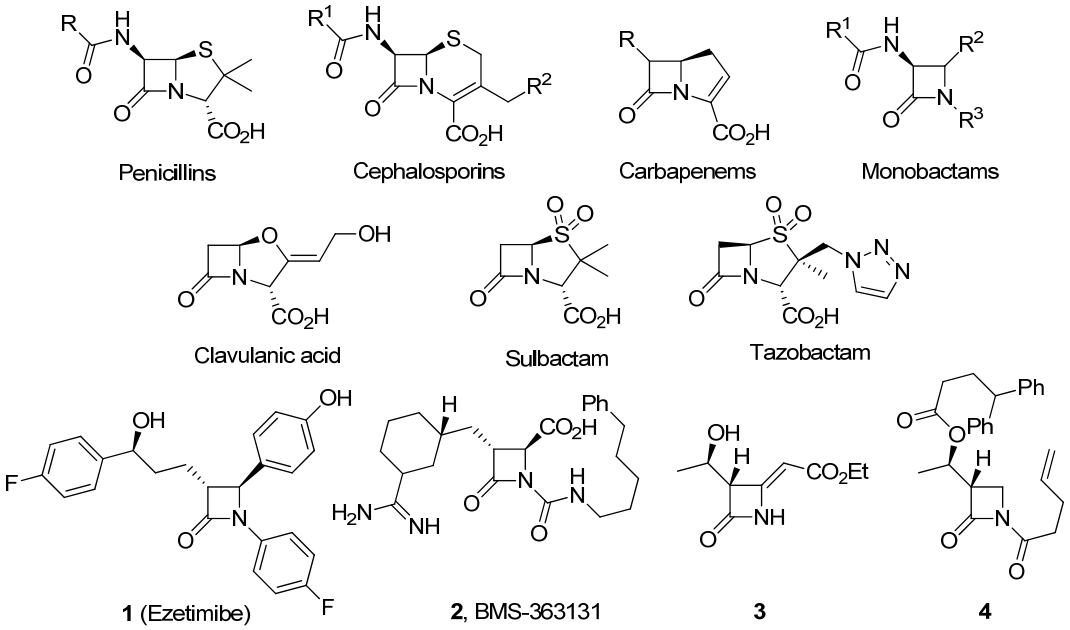
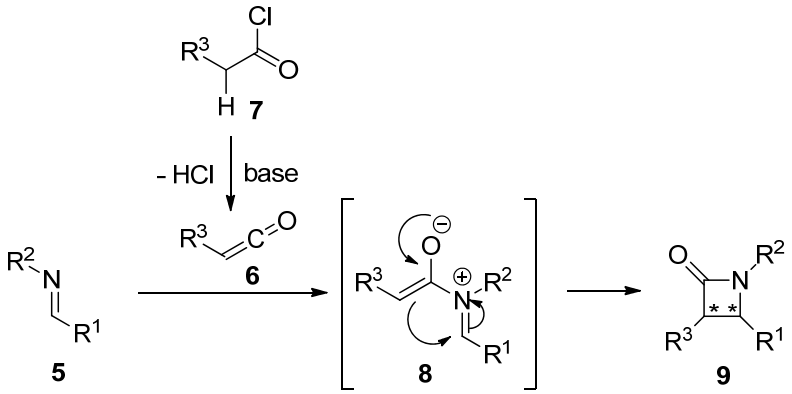
Figure 1. Prominent β-lactam antibiotics, β-lactamase inhibitors and examples of non-antibacterial β-lactams (**1**-**4**).



Perhaps the most popular way of synthesizing β-lactams is the formal [2+2] cycloaddition of imines (**5**) with ketene intermediates (**6**) generated *in situ* from α-C-H carboxylic acid derivatives containing a good leaving group at the carbonyl carbon: e. g., acyl chlorides (**7**). In the latter case, the process (known as the Staudinger reaction[10]) is essentially triggered by elimination of HCl from **7** in the presence of a base promoter, acylation of **5** by a highly reactive **6** thus formed and a closure of the 2-azetidinone ring in zwitter-ionic intermediate **8** yielding β-lactam **9** (Scheme 1) with two new stereogenic centers.[11]

Scheme 1. The Staudinger reaction as a popular way of accessing β-lactams **9**.



Recently, Knapp and co-workers described an interesting variant of the Staudinger reaction which was observed on addition of 5% methanolic sodium hydroxide solution to the reaction

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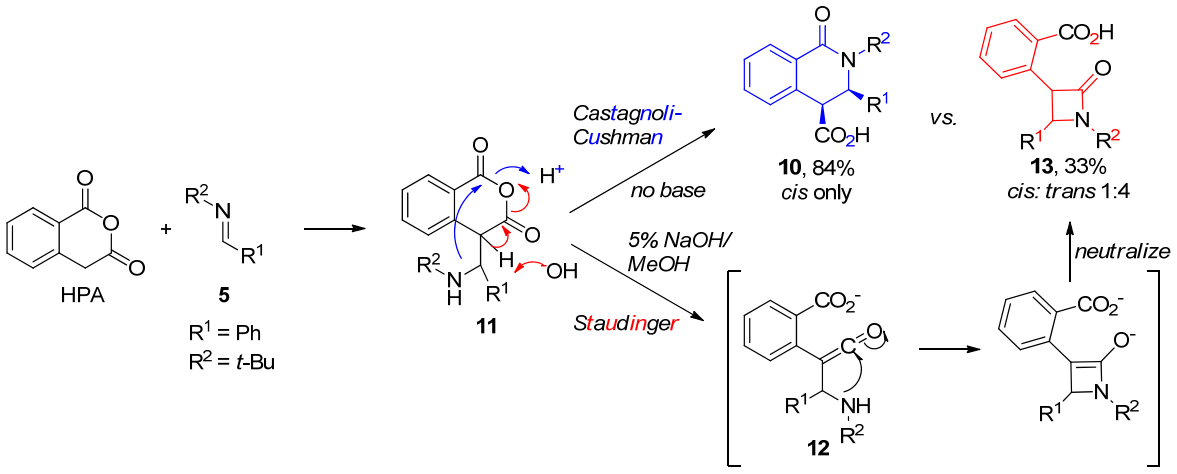
mixture containing homophthalic anhydride (HPA) and an imine **5**.[12] Although the latter combination, in the absence of any base, is a proven pathway to δ-lactams **10** via the so-called Castagnoli-Cushman reaction[13] (involving a *6-exo-dig* intramolecular lactone ring opening by a secondary amino group in the initial Mannich-type adduct **11**),[14] addition of a base triggered the intramolecular carboxylate elimination in **11** leading to the formation of highly reactive ketene intermediate **12** in which the formation of 2-azetidinone via a *4-exo-trig* process was a preferred course of the reaction. This led not only to an intriguing reactivity switch (much in the spirit of diversity oriented synthesis,[15] considering the skeletal divergence between δ- an β-lactams observed in this case) but also provided the first example of an 'intramolecular' ketene formation – the process in which the leaving group on the ketene carbon precursor remained a part of the product molecule. Due to the intramolecular character of two postulated steps in the latter transformation (**11→12** and **12→13**), the formation of **13** occurred at low temperature, in contrast to conventional Staudinger reactions typically requiring prolonged heating (Scheme 2).[12]

Scheme 2. The Staudinger and the Castagnoli-Cushman reaction between HPA and **5**: an example of diversity-oriented synthesis.



Results and discussion

Inspired by this important result, we were curious to see whether any substantial preference toward the Staudinger *vs.* the Castagnoli-Cushman course of the reaction would be displayed under similar conditions by an isostere of HPA, namely, benzo[*c*][1,2]oxathiin-3(4*H*)-one 1,1-dioxide (**14**), which is essentially a mixed cyclic carboxylic-sulfonic anhydride. Its preparation from sodium 2-formylbenzenesulfonate (**15**) via sultone **16**[16] had been described (in the context of subsequent thermolysis reactions)[17] and worked rather well in our hands. Sultone **16** was ring-opened by cyanide anion to give nitrile **17**. The latter was hydrolyzed to mixed carboxylic-

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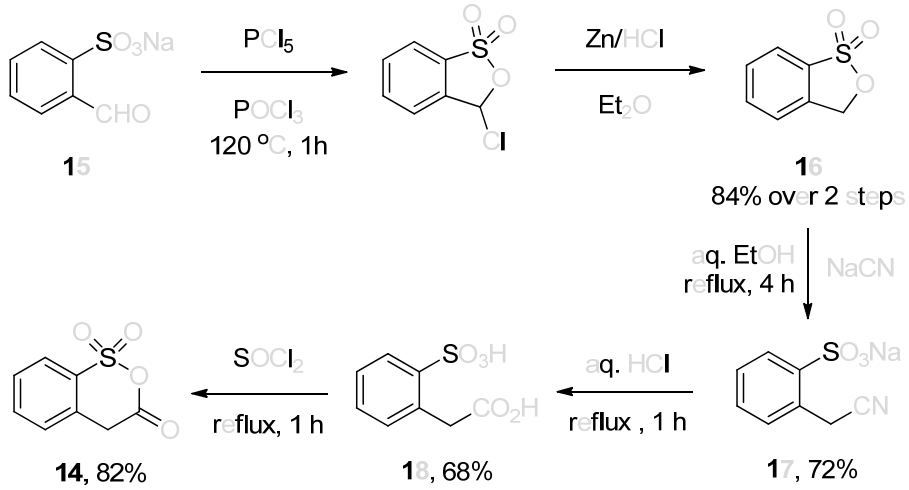
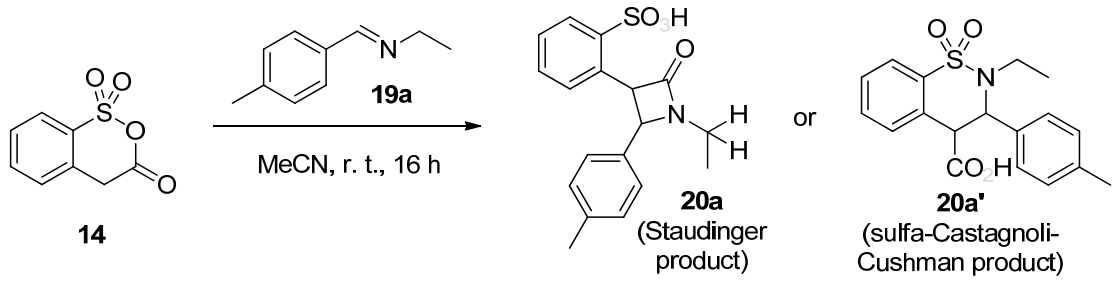
sulfonic diacid **18** and cyclodehydrated by $SOCl_2$ to provide the target mixed anhydride **14** (Scheme 3).

Scheme 3. Preparation of mixed carboxylic-sulfonic anhydride **14**.



The initial uncatalyzed model reaction of **14** with imine **19a** conducted in acetonitrile over 16 h led to a nearly complete consumption of the starting materials and a formation of a mixture of multiple products among which one product clearly predominated and was isolated in a pure form and low yield by repeated column chromatography. Drawing an analogy with the analogous reaction involving HPA (Scheme 2), we anticipated that the product thus obtained could have either the β-lactam structure (**20a**) or be indeed a sultam isostere of the traditional Castagnoli-Cushman δ-lactam adducts (**20a′**). Although the ^{1}H and ^{13}C NMR spectra did not allow assigning the structure to either **20a** or **20a′** unambiguously, it was done based on a clear heteronuclear correlation between the carbonyl carbon and the ethyl group's CH_2 observed in the product's HMBC spectrum (Scheme 4).

Scheme 4. Initial reaction of **14** with an imine (**19a**).



In our view, this clearly attested to the Staudinger-type reaction pathway being the only favored course of the reaction of **14** with imines, which can be rationalized by a substantially higher

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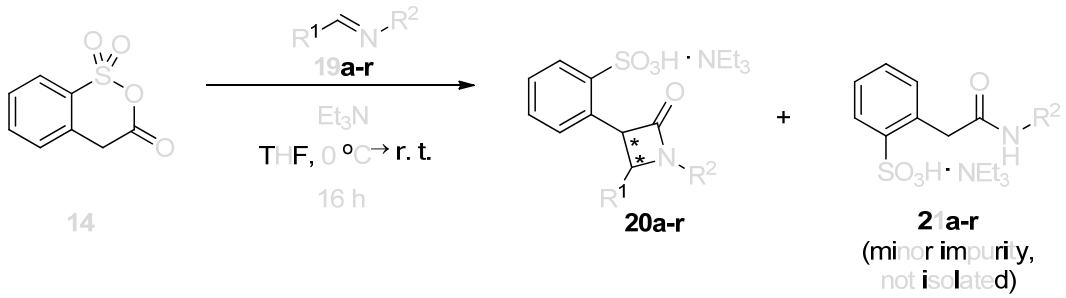
tendency of the sulfonate anion to act as a leaving group (compared to carboxylate anion in **11**) and to give rise to ketene-type intermediates (similar to **12**). Therefore, we set off to improve the yield of β-lactam product **20a** in order to develop a practically sound approach to this new type of benzenesulfonic acid-containing adducts.

Since the formation of **20a** most likely required deprotonation of the α-position in **14** or its initial Mannich adduct with **19a** (analogous to **11**), we tried to employ sodium acetate (1.1 equiv.) as a relatively weak base promoter which, as we had hoped, could also transform **20a** to the respective sodium salt and thus facilitate its isolation. Experiments with AcONa were conducted in parallel in different solvents (DMF, toluene, chlorobenzene, 1,2-dichloroethane, ethyl acetate, THF and methyl *tert*-butyl ether. The crude reaction mixtures were concentrated and analyzed by ^{1}H NMR. Although no noticeable improvement compared to the uncatalyzed reaction was observed, the screening of solvents revealed that the use of THF markedly suppressed by-product formation and led to the cleanest crude reaction mixture of all with respect to target compound **20a**. Further capitalizing on this finding, we performed subsequent reactions in THF and employed triethylamine as a stronger base. To our delight, it not only improved the yield of **20a** but also permitted convenient isolation of the respective triethylammonium salts of the product sulfonic acid by column chromatography on silica gel. Several manipulations with the reaction's temperature regimen showed that the best isolated yield (66%) of **20a** was obtained after column chromatography when the reaction started at 0 ºC, gradually allowed to warm up to ambient temperature and continued at that temperature overnight. The only persistent minor (<5%) by-product observed by ^{1}H NMR (though not isolated characterized) was monoamide **21a** whose formation is fully justified (*vide infra*) based on the mechanistic understanding of the reaction. The protocol optimized for the synthesis of **20a** was subsequently applied to the synthesis of other 2-azetidinones (**20b-r**) studied in this work (Scheme 5).

Scheme 5. Optimized protocol for the synthesis of 2-azetidinones **20a-r**.



β-Lactam products **20a-r** obtained as triethylammonium salts according to the protocol reported herein are shown in Table 1. ^{1}H NMR analysis of the crude reaction mixtures prior to product

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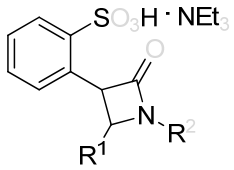
isolation demonstrated that in the majority of cases (except for **20q-r** derived from imines of aliphatic aldehydes) *trans*-isomer predominated over *cis*. The vicinal coupling constant (^3J) between H-3 and H-4 of the 2-azetidinone ring is an established and reliable criterion for relative stereochemistry assignment in 3,4-disubstituted 2-azetidinones.[18-24] It was successfully applied in our case and further confirmed by a single-crystal X-ray analysis of a representative compound (*trans*-**20h**, see ESI for details). Chromatographic isolation of the products generally either improved the diastereomeric ratios compared to the initial ones observed in the crude reaction mixtures or, in some cases, even allowed isolating and characterizing pure *trans*- and/or *cis*-isomers. The isolated yields were generally good, except for two cases **20n** and **20o** which provided unexpectedly low yields due to the formation of a complex product mixture (Table 1).

Table 1. β-Lactams synthesized via condensation of **14** with imines **19a-r**.



20a-r

Entry		R^1	R^2	dr[a]	^3J (Hz) *trans/cis*	Isolated yield, %[b]
1	**20a**	*p*-Tol	Et	5:1	1.8/5.6	66 (7.7:1)
2	**20b**	*p*-Tol	PMB	*trans*	2.0/5.9	78 (*trans*)
3	**20c**	4-$MeOC_6H_4$	Me	5.8:1	1.7/5.6	63 (9:1)
4	**20d**	4-FC_6H_4	cyclohexyl	2:1	2.1/5.7	58[c]
5	**20e**	3,4-$(MeO)_2C_6H_3$	*n*-Bu	4.6:1	<1.0/5.5	64 (5:1)
6	**20f**	2-$MeOC_6H_4$	Bn	7.5:1	2.2/5.8	65 (8.5:1)
07	**20g**	4-ClC_6H_4	*n*-Pr	4.5:1	2.0/5.7	50 (10:1)
8	**20h**	4-$O_2NC_6H_4$	*n*-Pr	2.3:1	2.0/5.5	51[d,e]
9	**20i**	4-$MeO_2CC_6H_4$	*i*-Pr	1.8:1	2.0/5.9	60[f]
10	**20j**	4-$MeOC_6H_4$	CH_2CO_2Me	8:1	2.2/5.7	66 (*trans*)
11	**20k**	3-$O_2NC_6H_4$	Me	2:1	2.1/5.7	50% (4:1)[g]
12	**20l**	3-$BnOC_6H_4$	(2-furyl)CH_2	4.3:1	2.0/5.8	64 (*trans*)
13	**20m**	2-thienyl	cyclopropyl	8:1	2.1/5.7	59 (*trans*)
14	**20n**	5-nitrofur-2-yl	PMB	9:1	2.3/5.6	21 (*trans*)
15	**20o**	3-thienyl	(pyrid-3-yl)CH_2	*trans*	2.2/ND	29 (*trans*)

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16	**20p**	pyrid-3-yl	*n*-Pr	2.2:1	1.9/5.6	61 (2.8:1)[h]
17	**20q**	Et	cyclohexyl	1:1.8	2.1/5.4	64[i]
18	**20r**	*i*-Pr	*n*-Bu	1:1.6	2.2:5.6	48 (1:1.1)

[a]Diastereomeric ratio (*trans/cis*) in reaction mixture (determined by crude ^{1}H NMR). [b]The dr of isolated products is given in parentheses. [c]A 6:1 *trans/cis* mixture (48%) and the pure *cis*-isomer (10%) were isolated by column chromatography. [d]The pure *trans*-isomer (39%) and a 1:8 *trans/cis* mixture (12%) were isolated by column chromatography. [e]Structure of *trans*-**20h** was confirmed by single-crystal X-ray analysis. [f]The pure *trans*-isomer (26%) and a 1:1.1 *trans/cis* mixture (34%) were isolated by column chromatography. [g]The pure *trans*-isomer (30%) was isolated by column chromatography and characterized. [h]The pure *cis*- (10%) and *trans*- (28%) isomers were isolated after repeated column chromatography. [i]The pure *cis*-isomer (30%) and a 8:1 *trans/cis* mixture (11%) were isolated by column chromatography.

Quite surprising was also our inability to obtain any β-lactam product from reactions of **14** with imines derived from aromatic amines. This however, can be given the following explanation from the mechanistic standpoint. Obviously, the reduced reactivity of the *N*-aryl imines in reaction with **14** implies that interaction of the imine nitrogen atom with an electrophilic entity is critically important for the formation of β-lactam product. Considering the much higher reactivity of the carbonyl group of **14** compared to the analogous functionality in HPA, it is not illogical to suppose that the interaction of **14** with the imine *via* direct imine acylation[25] could be the first, triggering event *en route* to the β-lactam product **20**. *N*-acylation of the imine will likely facilitate the α-deprotonation of the phenacetyl component in putative *N*-acyl iminium intermediate **22** with triethylamine or, in case of the less productive uncatalyzed reaction (*vide supra*), by the weakly basic unreacted imine. α-Deprotonation, in turn, inevitably leads to the closure of the 2-azetinone ring and provides **20**, which may even occur in a concerted fashion with α-deprotonation. Of course, the postulated highly electrophilic **22** could also rapidly react with any adventitious water and this would give the observed minor carboxamide by-product **21** (Scheme 6). It should be noted that performing reaction in presence of 4Å molecular sieves failed to suppress the formation of **21**.

Scheme 6. Proposed mechanism for the formation of **20** in the reaction of **14** an **19**.

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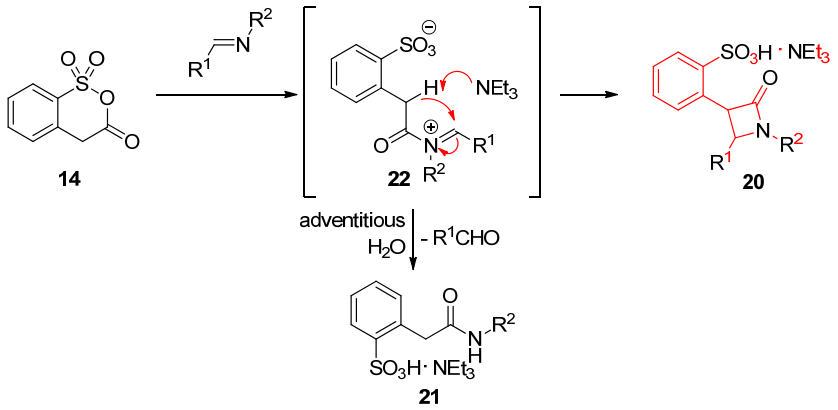

The proposed mechanism appears to be fully consistent with the experimental observations. At the same time, if we consider the mechanism shown in Scheme 2 for an analogous reaction of HPA, it would not fully justify the observed inertness of *N*-aryl imines in the triethylamine-promoted reaction with **14**. Indeed, the secondary amino group in **11** (or its hypothetical sulfa-analog), even bearing an aryl substituent, is very likely to be acylated by ketene since even intermolecular reactions of anilines with ketenes are known to proceed quite well.[26] At the same time, we cannot completely rule out the possibility that introduction of aryl substituents at the imine nitrogen atom could be detrimental to β-lactam formation because it retards subsequent acylation of the same nitrogen atom by a ketene moiety (using the HPA analogy shown in Scheme 2). Although the proposed formation of **20** *via* the direct imine acylation/intramolecular Mannich ring closure does not involve the formation of a ketene intermediate the net result of this transformation (despite the proposed reversed order of events, which is also a subject of ongoing debate[27]) is the Staudinger-type, formal [2+2] cycloaddition reaction of an imine **19** with **14** (a reactive equivalent of a ketene) which yields β-lactam **20**.

Poor aqueous solubility is a major issue that hinders drug development[28] and necessitates invention of costly drug delivery strategies.[29] Unfortunately, this problem has also affected the field of β-lactam antibiotics: recent examples include cephalosporins ceftobiprole[30] and ceftaroline[31] both of which are approved for clinical use and are administered as prodrugs due to extremely low solubility of the principal active component. The triethylammonium sulfonate-bearing β-lactams **20** synthesized in this work are essentially free from any solubility issues. Besides being distinctly well-soluble in organic solvents (such as methanol, chloroform, acetonitrile), compounds **20a-r** all display excellent solubility in aqueous medium (estimated to be >500 μM). This is, most likely, a consequence of them containing the triethylammmoniun sulfonate moiety, a unique feature resulting from the use of **14** in the reaction with imines.

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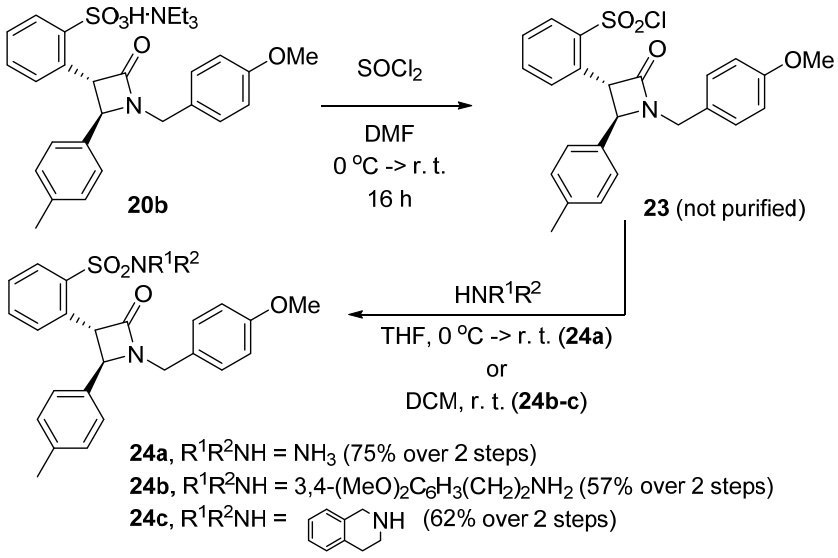
Besides being the guarantor of high aqueous solubility of β-lactams **20**, the benzenesulfonate moiety can be transformed into the respective sulfonyl chloride and subsequently, to various sulfonamides, which constitute an important class of pharmacophores.[32] To illustrate this possibility, we converted a representation product **20b** (obtained as a pure *trans*-isomer) into respective sulfonyl chloride **23** which, without further purification, was split into three equal portions and reacted with ammonia, a primary and a secondary amine providing the respective primary, secondary and tertiary sulfonamides **24a-c** in good yields over two steps (Scheme 7).

Scheme 7. Transformation of compound **20b** into sulfonyl chloride **23** and a series of sulfonamides **24a-c**.



Conclusions

In summary, we have investigated, for the first time, the use of a mixed carboxylic-sulfonic anhydride in base-promoted reaction with imines. The reaction was shown to follow the only productive course both in uncatalyzed and based-promoted format, namely, providing a product of a Staudinger-type formal [2+2] cycloaddition between the anhydride and imine partners. The use of triethylamine as a base not only gave a clean and high-yielding conversion into product β-lactam bearing a triethylammonium benzenesulfonate moiety, it also enabled straightforward purification of the latter by conventional column chromatography. The newly established variant of a Staudinger-type reaction was found to work only for *N*-alkyl imines and to fail for *N*-aryl counterparts, which was justified by a propose reaction mechanism. The presence of a unique triethylammonium benzenesulfonate moiety in the β-lactam products thus obtained not only

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endows them with a marked aqueous solubility but also provides a reactive handle for introducing various sulfonamides, which are important pharmacophoric groups from drug design perspective. The medicinal chemistry potential of the new water-soluble β-lactams is currently investigated in our laboratories and will be reported in due course.

Experimental

General information. NMR spectroscopic data were recorded with a 400 MHz spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) in $CDCl_3$ and in DMSO-d_6 and were referenced to residual solvent proton signals (δ_H = 7.26 and 2.50 ppm, respectively) and solvent carbon signals (δ_C = 77.0 and 39.5 ppm, respectively). Melting points were determined with a Melting Point Apparatus in open capillary tubes. Mass spectra were recorded with a HRMS-ESI-qTOF spectrometer (electrospray ionization mode). Chlorobenzene was distilled over P_2O_5 and stored over molecular sieves 4Å. Imines **19a-p,r** were prepared from corresponding aldehydes and amines by stirring with anhydrous $MgSO_4$ at room temperature in DCM for 24-48 h and subsequent concentration *in vacuo*. Imine **19q** was prepared according to known procedure.[33] All imines **19** and anhydride **14** were stored at 5 °C in darkness.

Preparation of anhydride 14

3*H*-Benzo[*c*][1,2]oxathiole 1,1-dioxide (16). Sultone **16** was prepared from **15** in 2 steps according to literature procedures.[16] To a mixture of sodium 2-formylbenzenesulfonate monohydrate **15** (34.0 g, 0.15 mol) and phosphorus pentachloride (34.0 g, 0.16 mol) phosphorus oxychloride (30 mL, 0.32 mol) was slowly added. After initial vigorous reaction (HCl evolution!) the mixture was stirred at 120 °C for 1 hour. The excess of $POCl_3$ was removed under reduced pressure and the solidified residue was triturated with crashed ice (300 g). After stirring for 30 min in ice water the white crystals were filtered off, washed with water (2× 100 mL) and dried in air to give 32 g of 3-chloro-3*H*-benzo[*c*][1,2]oxathiole 1,1-dioxide which was used in the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.80 (m, 2H), 7.75 (td, *J* = 7.6, 1.0 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.25 (s, 1H).

To a stirred mixture of substance obtained in previous step (20.0 g), zinc dust (30.0 g) and diethyl ether (230 mL) conc. aq. HCl was added dropwise at such a rate that the mixture slightly boiled. After approximately 30 min (when TLC showed the full consumption of starting material) the mixture was filtered through a pad of Celite, washed with ether (2×80 mL) and evaporated. The obtained light yellow oil was triturated with cold water (250 mL), the crystals formed were filtered, washed with water (150 mL) and *n*-hexane (100 mL) and dried in air to afford 13.4 g pure title compound **16** (84% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.73 (td, *J* = 7.6, 1.1 Hz, 1H), 7.63 (td, *J* = 7.6, 1.0 Hz, 1H), 7.45 (dt, *J* = 7.7, 1.0 Hz, 1H), 5.55 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 133.7, 131.7, 130.0, 123.3, 121.9, 71.1.

Sodium 2-(cyanomethyl)benzenesulfonate (17). Anhydride **14** was prepared from sultone **16** via intermediates **17** and **18** according to modified literature procedures.[17] To a stirred solution of sodium cyanide (3.7 g, 0.075 mol) in water (38 mL) a solution of sultone **16** (12.5 g, 0.073 mol) in ethanol (400 mL) was added within 20 min. The mixture was refluxed for 4 hours. The

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solvents were removed *in vacuo*, the residue was refluxed with 60 mL of acetonitrile, cooled in ice and the precipitated white crystals were filtered off and dried in air to give 11.6 g (72%) of compound (**17**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (dd, J = 7.6, 1.5 Hz, 1H), 7.48 – 7.37 (m, 2H), 7.32 (td, J = 7.4, 1.7 Hz, 1H), 4.37 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 134.5, 133.0, 130.5, 127.3, 127.0, 124.8, 119.4, 23.6.

2-(2-Sulfophenyl)acetic acid (18). To a solution of substance from previous step (2.8 g, 0.013 mol) in water (25 ml) conc. aq. HCl (25 mL) was added and the mixture was refluxed for 1 hour. After cooling to ambient temperature the resulting mixture was filtered through a pad of Celite and evaporated to dryness. The residue was dissolved in water (20 mL) and passed through a column with Amberlyst(H) ion exchange resin. The collected fractions with product (detected by pH) were evaporated at *in vacuo* and the resulting crude material was recrystallized from acetonitrile to give 1.88 g (68%) of compound **18**; mp 149–152 °C (MeCN). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (dd, J = 8.0, 1.6 Hz, 1H), 7.33 (td, J = 7.2, 1.5 Hz, 1H), 7.31 – 7.14 (m, 2H), 4.03 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5, 146.0, 132.5, 131.7, 129.6, 127.0, 126.7, 39.4.

Benzo[*c*][1,2]oxathiin-3(4*H*)-one 1,1-dioxide (14). Thionyl chloride (30 mL) was added to 2-(2-sulfophenyl)acetic acid (864 mg, 4.0 mmol) and the mixture was stirred under reflux for 1 hour. After cooling to ambient temperature the clear yellow solution was decanted from small amount of dark oil and evaporated to dryness under reduced pressure at 30–35 °C. The crystalline residue was triturated with *n*-hexane (25 mL), filtered and dried *in vacuo* to give 650 mg (82%) of anhydride **14**; mp 150–153 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.8, 1.3 Hz, 1H), 7.73 (td, J = 7.6, 1.4 Hz, 1H), 7.69 – 7.56 (m, 1H), 7.47 (d, J = 7.6 Hz, 1H), 4.28 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 134.6, 133.6, 129.3, 129.0, 128.9, 125.0, 37.0.

General procedure for preparation of β-lactams 20. To an ice cooled solution of appropriate imine **19** (0.5 mmol) in absolute THF (2 mL) anhydride **14** (99 mg, 0.5 mmol) was added. After stirring for 5 min triethyl amine (56 mg, 0.55 mmol) was added and the mixture was stirred for 30 min in ice-bath and then at ambient temperature for overnight. The solvent was removed in *vacuo* and the resulting crude material was subjected to column chromatography on silica gel.

2-(*trans/cis*-1-Ethyl-2-oxo-4-(*p*-tolyl)azetidin-3-yl)benzenesulfonic acid triethylammonium salt (*trans/cis*-20a). Eluent for chromatography EtOAc/MeOH/Et_3N (80 : 15 : 5); yield 147 mg (66%), *dr* 7.7:1; colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) of major *trans*-isomer δ 10.00 (br.s, 1H), 8.05 (dd, J = 7.7, 1.0 Hz, 1H), 7.47 (dd, J = 7.7, 1.5 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.32 – 7.27 (m, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 5.47 (d, J = 1.3 Hz, 1H), 4.52 (d, J = 1.8 Hz, 1H), 3.63 (dq, J = 14.7, 7.4 Hz, 1H), 2.95 (qd, J = 7.3, 4.8 Hz, 6H), 2.94 – 2.87 (m, 1H), 2.33 (s, 3H), 1.18 (t, J = 7.4 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) of major *trans*-isomer δ 169.3, 144.2, 137.8, 134.7, 133.6, 130.6, 129.2, 127.8, 127.3, 127.2, 127.1, 64.1, 60.7, 46.0, 35.0, 21.2, 13.2, 8.5. HRMS *m/z* $[M–H]^-$ calcd for $C_{18}H_{18}NO_4S$ 344.0962, found 344.0968.

2-(*trans*-1-(4-Methoxybenzyl)-2-oxo-4-(*p*-tolyl)azetidin-3-yl)benzenesulfonic acid triethylammonium salt (*trans*-20b). The titled compound was filtered after precipitation from reaction mixture; yield 210 mg (78%); colorless solid, mp 162–164 °C (EtOAc). ^{1}H NMR (400

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MHz, DMSO-d_6) δ 8.89 (br.s, 1H), 7.77 (dd, J = 7.8, 1.4 Hz, 1H), 7.33 (td, J = 7.5, 1.5 Hz, 1H), 7.23 (td, J = 7.5, 1.3 Hz, 1H), 7.19 – 7.11 (m, 7H), 6.92 (d, J = 8.7 Hz, 2H), 5.51 (d, J = 2.0 Hz, 1H), 4.69 (d, J = 15.1 Hz, 1H), 4.19 (d, J = 2.1 Hz, 1H), 3.75 (s, 3H), 3.71 (d, J = 15.1 Hz, 1H), 3.08 (q, J = 7.3 Hz, 6H), 2.32 (s, 3H), 1.16 (t, J = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.0, 159.0, 147.4, 137.5, 134.9, 134.0, 129.9, 129.6, 129.5, 128.8, 127.6, 127.32, 127.26, 126.9, 114.5, 64.5, 60.4, 55.5, 46.2, 43.6, 21.2, 9.1. HRMS *m/z* [M–H]$^-$ calcd for $C_{24}H_{22}NO_5S$ 436.1224, found 436.1215.

2-(*trans/cis*-2-(4-Methoxyphenyl)-1-methyl-4-oxoazetidin-3-yl)benzenesulfonic acid triethylammonium salt (*trans/cis*-20c). Eluent for chromatography EtOAc/MeOH/Et_3N (75 : 20 : 5); yield 112 mg (63%), *dr* 9:1; colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) of major *trans*-isomer δ 10.10 (br.s, 1H), 8.05 (d, J = 7.4 Hz, 1H), 7.47 (dd, J = 7.5, 0.9 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.34 – 7.27 (m, 3H), 6.89 (d, J = 8.5 Hz, 2H), 5.48 (s, 1H), 4.42 (d, J = 1.7 Hz, 1H), 3.80 (s, 3H), 3.05 – 2.95 (br.m, 6H), 2.83 (s, 3H), 1.21 (br.t, J = 6.2 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) of major *trans*-isomer δ 169.7, 159.5, 144.2, 133.5, 130.5, 129.4, 128.5, 127.8, 127.6, 127.1, 114.0, 66.1, 61.7, 55.3, 46.1, 26.7, 8.7. HRMS *m/z* [M–H]$^-$ calcd for $C_{17}H_{16}NO_5S$ 346.0755, found 346.0736.

2-(*trans/cis*-1-Cyclohexyl-2-(4-fluorophenyl)-4-oxoazetidin-3-yl)benzenesulfonic acid triethylammonium salt (*trans/cis*-20d). Eluent for chromatography EtOAc/MeOH/Et_3N (80 : 15 : 5); first was isolated *trans/cis*-**20d** mixture (*dr* 6:1), yield 96 mg (48%); colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) of major *trans*-isomer δ 10.11 (br.s, 1H), 8.06 – 8.01 (m, 1H), 7.46 – 7.38 (m, 4H), 7.33 – 7.27 (m, 1H), 7.03 (t, J = 8.7 Hz, 2H), 5.41 (d, J = 2.1 Hz, 1H), 4.49 (d, J = 2.1 Hz, 1H), 3.51 – 3.44 (m, 1H), 2.99 (qd, J = 7.3, 4.8 Hz, 6H), 2.10 – 2.02 (m, 1H), 1.83 – 1.53 (m, 6H), 1.21 (t, J = 7.3 Hz, 9H), 1.32 – 1.06 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) of major *trans*-isomer δ 169.3, 162.5 (d, J = 245.9 Hz), 144.2, 135.1 (d, J = 3.1 Hz), 133.6, 130.6, 129.1 (d, J = 8.2 Hz), 127.7, 127.2, 127.1, 115.3 (d, J = 21.5 Hz), 63.4, 60.4, 52.9, 46.1, 31.5, 31.1, 25.22, 25.20, 25.0, 8.5. HRMS *m/z* [M–H]$^-$ calcd for $C_{21}H_{21}FNO_4S$ 402.1170, found 402.1156.

2-(*cis*-1-Cyclohexyl-2-(4-fluorophenyl)-4-oxoazetidin-3-yl)benzenesulfonic acid triethylammonium salt (*cis*-20d). Next was isolated *cis*-**20d,** yield 21 mg (10%); colorless solid, mp 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (br.s, 1H), 7.75 (d, J = 7.3 Hz, 1H), 7.34 – 7.25 (m, 4H), 7.17 (t, J = 7.6 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.75 (t, J = 8.7 Hz, 2H), 5.87 (d, J = 5.7 Hz, 1H), 5.30 (d, J = 5.7 Hz, 1H), 3.58 – 3.45 (m, 1H), 3.16 – 3.02 (br.m, 6H), 2.17 – 2.08 (m, 1H), 1.94 – 1.86 (m, 1H), 1.85 – 1.67 (m, 3H), 1.63 – 1.57 (m, 1H), 1.31 (t, J = 6.7 Hz, 9H), 1.36 – 1.08 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.9 (d, J = 245.0 Hz), 143.8, 132.3 (d, J = 2.9 Hz), 130.9, 130.6, 129.9 (d, J = 8.1 Hz), 129.4, 126.87, 126.85, 114.1 (d, J = 21.3 Hz), 59.7, 58.4, 53.3, 46.3, 31.5, 30.8, 25.31, 25.29, 25.1, 8.7. HRMS *m/z* [M–H]$^-$ calcd for $C_{21}H_{21}FNO_4S$ 402.1170, found 402.1160.

2-(*trans/cis*-1-Butyl-2-(3,4-dimethoxyphenyl)-4-oxoazetidin-3-yl)benzenesulfonic acid triethylammonium salt (*trans/cis*-20e). Eluent for chromatography EtOAc/MeOH/Et_3N (75 : 20 : 5); yield 133 mg (64%), *dr* 5:1; pale yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) of major *trans*-isomer δ 10.07 (br.s, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.31 (d, J = 6.3 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.84 (d, J = 8.1 Hz, 1H), 5.48 (s, 1H), 4.46 (s, 1H), 3.88 (s,

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3H), 3.87 (s, 3H), 3.66 – 3.55 (m, 1H), 2.98 (br.s, 6H), 2.91 – 2.82 (m, 1H), 1.59 – 1.50 (m, 2H), 1.44 – 1.34 (m, 2H), 1.21 (br.s, 9H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) of major *trans*-isomer δ 169.6, 149.0, 148.8, 144.2, 133.6, 130.6, 130.3, 127.8, 127.4, 127.2, 119.6, 111.1, 110.5, 64.9, 60.8, 56.1, 55.9, 46.2, 40.0, 30.0, 20.3, 13.6, 8.6. HRMS *m/z* $[M–H]^-$ calcd for $C_{21}H_{24}NO_6S$ 418.1330, found 418.1336.

2-(*trans/cis*-1-Benzyl-2-(2-methoxyphenyl)-4-oxoazetidin-3-yl)benzenesulfonic acid triethylammonium salt (*trans/cis*-20f). Eluent for chromatography EtOAc/MeOH/Et_3N (75 : 20 : 5); yield 137 mg (65%), *dr* 8.5:1; colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) of major *trans*-isomer δ 10.22 (br.s, 1H), 8.06 – 8.03 (m, 1H), 7.39 – 7.29 (m, 6H), 7.28 – 7.22 (m, 4H), 6.95 (t, J = 7.3 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 5.75 (d, J = 2.2 Hz, 8H), 4.88 (d, J = 15.0 Hz, 1H), 4.86 (d, J = 2.1 Hz, 1H), 3.87 (d, J = 15.0 Hz, 1H), 3.64 (s, 3H), 2.99 (qd, J = 7.3, 4.8 Hz, 6H), 1.21 (t, J = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) of major *trans*-isomer δ 170.1, 158.3, 144.3, 136.4, 133.9, 130.4, 129.2, 128.5, 128.0, 127.7, 127.5, 127.4, 126.8, 125.4, 120.6, 111.0, 59.7, 58.8, 55.6, 46.1, 44.7, 8.5. HRMS *m/z* $[M–H]^-$ calcd for $C_{23}H_{20}NO_5S$ 422.1068, found 422.1060.

2-(*trans/cis*-2-(4-Chlorophenyl)-4-oxo-1-propylazetidin-3-yl)benzenesulfonic acid triethylammonium salt (*trans/cis*-20g). Eluent for chromatography EtOAc/MeOH/Et_3N (80 : 15 : 5); yield 97 mg (50%), *dr* 10:1; colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) of major *trans*-isomer δ 10.10 (br.s, 1H), 8.05 (dd, J = 7.8, 1.3 Hz, 1H), 7.50 (dd, J = 7.7, 1.4 Hz, 1H), 7.44 (td, J = 7.5, 1.4 Hz, 1H), 7.38 – 7.29 (m, 5H), 5.45 (d, J = 1.6 Hz, 1H), 4.46 (d, J = 2.0 Hz, 1H), 3.55 (dt, J = 14.0, 7.7 Hz, 1H), 2.98 (qd, J = 7.3, 4.8 Hz, 6H), 2.80 (ddd, J = 14.1, 7.5, 5.8 Hz, 1H), 1.62 – 1.49 (m, 2H), 1.21 (t, J = 7.3 Hz, 9H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) of major *trans*-isomer δ 169.3, 144.0, 136.5, 133.7, 133.3, 130.7, 128.9, 128.6, 127.8, 127.4, 127.3, 64.2, 61.3, 46.1, 42.0, 21.2, 11.6, 8.5. HRMS *m/z* $[M–H]^-$ calcd for $C_{18}H_{17}ClNO_4S$ 378.0572, found 378.0581.

2-(*trans*-2-(4-Nitrophenyl)-4-oxo-1-propylazetidin-3-yl)benzenesulfonic acid triethylammonium salt (*trans*-20h). Eluent for chromatography EtOAc/MeOH/Et_3N (80 : 15 : 5); first was isolated *trans*-**20h**, yield 77 mg (39%); colorless solid, mp 176–178 °C (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (br.s, 1H), 8.22 (d, J = 8.7 Hz, 2H), 8.02 (dd, J = 7.8, 1.3 Hz, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.52 (dd, J = 7.7, 1.2 Hz, 1H), 7.46 (td, J = 7.5, 1.3 Hz, 1H), 7.34 (td, J = 7.6, 1.3 Hz, 1H), 5.47 (d, J = 1.8 Hz, 1H), 4.56 (d, J = 2.0 Hz, 1H), 3.60 (dt, J = 14.1, 7.7 Hz, 1H), 3.00 (qd, J = 7.3, 4.8 Hz, 6H), 2.88 – 2.77 (m, 1H), 1.64 – 1.47 (m, 2H), 1.21 (t, J = 7.3 Hz, 9H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 147.7, 145.7, 144.0, 133.0, 130.8, 128.4, 127.6, 127.6, 123.7, 64.0, 61.7, 46.1, 42.3, 21.2, 11.6, 8.5. HRMS *m/z* $[M–H]^-$ calcd for $C_{18}H_{17}N_2O_6S$ 389.0802, found 389.0785.

Next was isolated *trans/cis*-**20h** mixture (*dr* 1:8), yield 23 mg (12%); colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) of major *cis*-isomer δ 10.26 (br.s, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 8.7 Hz, 2H), 7.23 (dd, J = 7.6, 1.2 Hz, 1H), 7.15 (td, J = 7.6, 0.9 Hz, 1H), 7.07 (td, J = 7.5, 1.1 Hz, 1H), 6.07 (d, J = 5.4 Hz, 1H), 5.39 (d, J = 5.5 Hz, 1H), 3.71 (dt, J = 13.8, 7.7 Hz, 1H), 3.10 (qd, J = 7.3, 4.9 Hz, 6H), 2.97 (ddd, J = 13.6, 7.6, 5.8 Hz, 1H), 1.68 – 1.55 (m, 2H), 1.32 (t, J = 7.3 Hz, 9H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz,

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$CDCl_3$) of major *cis*-isomer δ 168.8, 147.1, 143.8, 143.7, 130.2, 130.1, 129.6, 129.0, 127.3, 126.9, 122.7, 60.5, 59.5, 46.2, 42.8, 21.0, 11.6, 8.6. HRMS *m/z* $[M–H]^-$ calcd for $C_{18}H_{17}N_2O_6S$ 389.0802, found 389.0794.

2-(*trans*-1-Isopropyl-2-(4-(methoxycarbonyl)phenyl)-4-oxoazetidin-3-yl)-benzenesulfonic acid triethylammonium salt (*trans*-20i). Eluent for chromatography EtOAc/MeOH/Et_3N (80 : 15 : 5); first was isolated *trans*-**20i**, yield 67 mg (26%); colorless solid, mp 157–159 °C (EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.47 – 7.39 (m, 2H), 7.34 – 7.24 (m, 1H), 5.43 (d, *J* = 2.0 Hz, 1H), 4.52 (d, *J* = 1.9 Hz, 1H), 3.90 (s, 3H), 3.89 – 3.77 (m, 1H), 2.93 (q, *J* = 7.3 Hz, 6H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.15 (t, *J* = 7.3 Hz, 9H), 1.04 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 166.9, 144.8, 144.2, 133.3, 130.6, 129.8, 129.7, 127.7, 127.5, 127.2, 127.2, 63.4, 60.3, 52.1, 46.0, 45.3, 21.4, 20.8, 8.5. HRMS *m/z* $[M–H]^-$ calcd for $C_{20}H_{20}NO_6S$ 402.1016, found 402.1025.

Next was isolated *trans/cis*-**20i** mixture (*dr* 1:1.1), yield 87 mg (34%); amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) of *cis*-isomer δ 10.17 (br.s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.73 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.30 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.15 (td, *J* = 7.5, 1.4 Hz, 1H), 7.04 (td, *J* = 7.6, 1.3 Hz, 1H), 5.94 (d, *J* = 5.9 Hz, 1H), 5.35 (d, *J* = 5.9 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.83 (s, 3H), 3.05 (qd, *J* = 7.3, 4.8 Hz, 6H), 1.42 (d, *J* = 6.7 Hz, 3H), 1.27 (t, *J* = 7.3 Hz, 9H), 1.17 (d, *J* = 6.7 Hz, 3H).

2-(*trans*-1-(2-Methoxy-2-oxoethyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-benzenesulfonic acid triethylammonium salt (*trans*-20j). Eluent for chromatography EtOAc/MeOH/Et_3N (75 : 20 : 5); yield 130 mg (66%); colorless solid, mp 151–153 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.00 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.77 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.46 (td, *J* = 7.6, 1.5 Hz, 1H), 7.30 – 7.22 (m, 3H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.64 (d, *J* = 2.2 Hz, 1H), 4.76 (d, *J* = 2.3 Hz, 1H), 4.46 (d, *J* = 18.1 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.45 (d, *J* = 18.1 Hz, 1H), 2.95 (qd, *J* = 7.3, 4.4 Hz, 6H), 1.16 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 168.9, 159.7, 144.4, 133.2, 130.6, 128.7, 128.6, 128.1, 127.5, 127.1, 114.1, 65.1, 61.5, 55.3, 52.4, 46.1, 41.0, 8.5. HRMS *m/z* $[M–H]^-$ calcd for $C_{19}H_{18}NO_7S$ 404.0809, found 404.0807.

2-(*trans*-1-Methyl-2-(3-nitrophenyl)-4-oxoazetidin-3-yl)benzene sulfonic acid triethylammonium salt (*trans*-20k). Eluent for chromatography EtOAc/MeOH/Et_3N (80 : 15 : 5); yield of *trans/cis*-isomers mixture 92 mg (50%), *dr* 4:1; yield of *trans*-**20k** after additional column chromatography 56 mg (30%); colorless amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (br.s, 1H), 8.20 – 8.17 (m, 1H), 8.12 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 7.96 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.70 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.40 (td, *J* = 7.5, 1.5 Hz, 1H), 7.28 (td, *J* = 7.5, 1.5 Hz, 1H), 5.45 (dd, *J* = 2.1, 1.0 Hz, 1H), 4.48 (d, *J* = 2.1 Hz, 1H), 2.96 (q, *J* = 7.3 Hz, 6H), 2.84 (d, *J* = 0.9 Hz, 3H), 1.15 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 148.3, 144.2, 140.1, 133.8, 132.8, 130.6, 129.6, 127.7, 127.5, 127.5, 123.1, 122.1, 65.6, 62.3, 46.2, 27.0, 8.5. HRMS *m/z* $[M–H]^-$ calcd for $C_{16}H_{13}N_2O_6S$ 361.0500, found 361.0499.

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2-(*trans*-2-(3-(Benzyloxy)phenyl)-1-(furan-2-ylmethyl)-4-oxoazetidin-3-yl)-benzenesulfonic acid triethylammonium salt (*trans*-20l). Eluent for chromatography EtOAc/MeOH/Et_3N (80 : 15 : 5); yield 189 mg (64%); colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (br.s, 1H), 8.2 – 8.0 (m, 1H), 7.5 – 7.4 (m, 2H), 7.4 – 7.4 (m, 5H), 7.4 – 7.3 (m, 1H), 7.3 – 7.2 (m, 2H), 7.0 – 6.9 (m, 2H), 6.9 – 6.8 (m, 1H), 6.3 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.1 (d, *J* = 3.2 Hz, 1H), 5.6 (d, *J* = 2.3 Hz, 1H), 5.1 (s, 2H), 4.9 (d, *J* = 15.8 Hz, 1H), 4.4 (d, *J* = 2.1 Hz, 1H), 3.9 (d, *J* = 15.7 Hz, 1H), 2.9 (q, *J* = 7.3 Hz, 6H), 1.2 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 158.9, 149.3, 144.3, 142.6, 139.2, 137.0, 133.3, 130.5, 129.6, 128.6, 127.9, 127.8, 127.6, 127.4, 127.1, 119.9, 114.8, 113.5, 110.5, 108.5, 70.0, 64.7, 61.0, 46.0, 37.1, 8.4. HRMS *m/z* [M–H]$^-$ calcd for $C_{27}H_{24}NO_6S$ 488.1173, found 488.1159.

2-(*trans*-1-Cyclopropyl-2-oxo-4-(thiophen-2-yl)azetidin-3-yl)benzenesulfonic acid triethylammonium salt (*trans*-20m). Eluent for chromatography EtOAc/MeOH/Et_3N (80 : 15 : 5); yield 133 mg (59%); colorless solid, mp 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (br.s, 1H), 8.09 – 7.92 (m, 1H), 7.37 (td, *J* = 7.5, 1.4 Hz, 1H), 7.31 – 7.21 (m, 3H), 7.17 (dd, *J* = 3.6, 1.1 Hz, 1H), 6.95 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.56 (d, *J* = 2.1 Hz, 1H), 4.69 (d, *J* = 2.1 Hz, 1H), 2.96 (qd, *J* = 7.3, 4.7 Hz, 6H), 1.15 (t, *J* = 7.3 Hz, 9H), 1.02 – 0.92 (m, 1H), 0.81 – 0.70 (m, 3H), 0.70 – 0.60 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 144.4, 141.9, 132.9, 130.5, 127.8, 127.3, 127.1, 127.0, 126.8, 125.3, 61.1, 60.5, 46.2, 23.1, 8.6, 5.7, 5.0. HRMS *m/z* [M–H]$^-$ calcd for $C_{16}H_{14}NO_4S_2$ 348.0370, found 348.0369.

2-(*trans*-1-(4-Methoxybenzyl)-2-(5-nitrofuran-2-yl)-4-oxoazetidin-3-yl)-benzenesulfonic acid triethylammonium salt (*trans*-20n). Eluent for chromatography EtOAc/MeOH/Et_3N (75 : 20 : 5); yield 58 mg (21%); colorless solid, mp 167–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (br.s, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.33 – 7.29 (m, 1H), 7.20 – 7.09 (m, 3H), 6.85 – 6.76 (m, 2H), 6.62 (d, *J* = 3.7 Hz, 1H), 5.80 (d, *J* = 2.3 Hz, 1H), 4.66 (d, *J* = 14.9 Hz, 1H), 4.38 (d, *J* = 2.3 Hz, 1H), 4.20 (d, *J* = 14.7 Hz, 1H), 3.77 (s, 3H), 3.04 (q, *J* = 7.3 Hz, 6H), 1.24 (t, *J* = 7.4 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 159.3, 155.3, 151.7, 144.2, 132.0, 131.1, 130.7, 129.9, 128.6, 127.7, 127.5, 127.0, 114.1, 113.7, 113.1, 112.8, 58.4, 56.8, 55.3, 46.2, 44.9, 8.5. HRMS *m/z* [M–H]$^-$ calcd for $C_{21}H_{17}N_2O_8S$ 457.0711, found 457.0729.

2-(*trans*-2-Oxo-1-(pyridin-3-ylmethyl)-4-(thiophen-3-yl)azetidin-3-yl)-benzenesulfonic acid triethylammonium salt (*trans*-20o). Eluent for chromatography EtOAc/MeOH/Et_3N (75 : 20 : 5); yield 72 mg (29%); colorless amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6+$CDCl_3$) δ 10.42 (br.s, 1H), 8.61 – 8.30 (m, 2H), 7.93 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.43 (s, 1H), 7.36 – 7.26 (m, 2H), 7.26 – 7.15 (m, 3H), 7.01 (dd, *J* = 4.9, 1.4 Hz, 1H), 5.68 (d, *J* = 2.2 Hz, 1H), 4.69 (d, *J* = 15.4 Hz, 1H), 4.49 (d, *J* = 2.3 Hz, 1H), 4.01 (d, *J* = 15.4 Hz, 1H), 2.98 (qd, *J* = 7.3, 4.7 Hz, 6H), 1.21 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (101 MHz, DMSO-d_6+$CDCl_3$) δ 173.9, 153.0, 152.5, 152.4, 152.3, 144.1, 142.7, 138.3, 138.3, 134.3, 132.2, 132.1, 131.8, 131.7, 129.5, 129.3, 65.6, 64.0, 50.8, 47.0, 13.8. HRMS *m/z* [M–H]$^-$ calcd for $C_{19}H_{15}N_2O_4S_2$ 399.0479, found 399.0476.

2-(*trans*-2-Oxo-1-propyl-4-(pyridin-3-yl)azetidin-3-yl)benzenesulfonic acid triethylammonium salt (*trans*-20p). Eluent for chromatography EtOAc/MeOH/Et_3N (75 : 20 :

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5); yield of *trans/cis*-**20p** mixture 109 mg (61%), *dr* 2.8:1; after additional column chromatography: yield of *trans*-**20p** 50 mg (28%); colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (br.s, 1H), 8.58 (d, *J* = 2.2 Hz, 1H), 8.53 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.01 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.51 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.44 (td, *J* = 7.5, 1.4 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.29 (d, *J* = 6.1 Hz, 1H), 5.51 (d, *J* = 1.9 Hz, 1H), 4.47 (d, *J* = 2.0 Hz, 1H), 3.56 (dt, *J* = 14.0, 7.7 Hz, 1H), 2.97 (q, *J* = 7.3 Hz, 6H), 2.80 (dt, *J* = 13.6, 6.3 Hz, 1H), 1.64 – 1.44 (m, 2H), 1.19 (t, *J* = 7.3 Hz, 9H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 149.0, 149.0, 144.2, 135.3, 134.0, 133.2, 130.6, 127.6, 127.5, 127.4, 123.7, 62.7, 61.1, 46.0, 42.1, 21.2, 11.6, 8.5. HRMS *m/z* $[M–H]^-$ calcd for $C_{17}H_{17}N_2O_4S$ 345.0915, found 345.0916.

2-(*cis*-2-Oxo-1-propyl-4-(pyridin-3-yl)azetidin-3-yl)benzenesulfonic acid triethylammonium salt (*cis*-20p). Isolated after additional column chromatography: yield 18 mg (10%); colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (br.s, 1H), 8.48 (d, *J* = 2.1 Hz, 1H), 8.26 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.74 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.64 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.29 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.18 (td, *J* = 7.5, 1.4 Hz, 1H), 7.06 (td, *J* = 7.6, 1.3 Hz, 1H), 7.00 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.02 (d, *J* = 5.6 Hz, 1H), 5.30 (d, *J* = 5.6 Hz, 1H), 3.65 (dt, *J* = 13.9, 7.8 Hz, 1H), 3.09 (q, *J* = 7.3 Hz, 6H), 2.94 (ddd, *J* = 13.7, 7.7, 5.8 Hz, 1H), 1.67 – 1.51 (m, 2H), 1.30 (t, *J* = 7.3 Hz, 9H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 149.0, 148.2, 143.9, 136.5, 131.6, 130.4, 130.2, 129.7, 127.1, 126.9, 122.7, 59.2, 59.0, 46.2, 42.6, 21.0, 11.6, 8.6. HRMS *m/z* $[M–H]^-$ calcd for $C_{17}H_{17}N_2O_4S$ 345.0915, found 345.0903.

2-(*trans/cis*-1-Cyclohexyl-2-ethyl-4-oxoazetidin-3-yl)benzenesulfonic acid triethylammonium salt (*trans/cis*-20q). Eluent for chromatography EtOAc/MeOH/Et_3N (85 : 10 : 5); yield of *trans/cis*-**20q** mixture 24 mg (11%), *dr* 8:1; colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) of major *trans*-isomer δ 8.02 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.34 (td, *J* = 7.3, 1.3 Hz, 1H), 7.28 (d, *J* = 7.1 Hz, 1H), 7.21 (td, *J* = 7.6, 1.4 Hz, 1H), 6.41 (br.s, 1H), 5.24 (d, *J* = 2.1 Hz, 1H), 3.58 (ddd, *J* = 6.8, 3.8, 2.1 Hz, 1H), 3.49 (tt, *J* = 11.5, 3.7 Hz, 1H), 2.87 (q, *J* = 7.3 Hz, 6H), 2.09 – 1.91 (m, 2H), 1.89 – 1.61 (m, 5H), 1.60 – 1.45 (m, 2H), 1.38 – 1.20 (m, 3H), 1.17 (t, *J* = 7.3 Hz, 9H), 1.03 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) of major *trans*-isomer δ 169.0, 144.6, 134.4, 130.2, 127.7, 127.2, 126.6, 63.1, 54.6, 52.2, 46.2, 32.1, 31.1, 26.1, 25.4, 25.4, 25.3, 9.6, 8.9. HRMS *m/z* $[M–H]^-$ calcd for $C_{17}H_{22}NO_4S$ 336.1275, found 336.1285.

2-(*cis*-1-Cyclohexyl-2-ethyl-4-oxoazetidin-3-yl)benzenesulfonic acid triethylammonium salt (*cis*-20q). Next was isolated *cis*-**20q;** yield 115 mg (53%); colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (br.s, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 4.2 Hz, 2H), 7.32 – 7.21 (m, 1H), 5.58 (d, *J* = 5.4 Hz, 1H), 4.06 – 3.91 (m, 1H), 3.48 (tt, *J* = 11.8, 3.8 Hz, 1H), 3.13 – 2.98 (m, 6H), 2.01 – 1.88 (m, 2H), 1.86 – 1.71 (m, 3H), 1.71 – 1.62 (m, 1H), 1.62 – 1.49 (m, 1H), 1.49 – 1.35 (m, 2H), 1.34 – 1.11 (m, 12H), 0.70 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 144.7, 132.0, 130.4, 129.7, 127.4, 126.9, 58.9, 54.6, 52.7, 46.3, 32.2, 30.8, 25.5, 25.4, 25.4, 24.1, 10.8, 8.7. HRMS *m/z* $[M–H]^-$ calcd for $C_{17}H_{22}NO_4S$ 336.1275, found 336.1272.

2-(*trans/cis*-1-Butyl-2-isopropyl-4-oxoazetidin-3-yl)benzenesulfonic acid triethylammonium salt (*trans/cis*-20r). Eluent for chromatography EtOAc/MeOH/Et_3N (85 : 10 : 5); yield 103 mg (48%), *dr* 1:1.1; colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) signals of *cis*-isomer δ

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9.84 (br.s, 1H), 8.00 – 7.98 (m, 1H), 7.40 – 7.31 (m, 2H), 7.27 – 7.23 (m, 1H), 5.62 (d, *J* = 5.6 Hz, 1H), 3.79 (dd, *J* = 7.7, 5.6 Hz, 1H), 3.70 – 3.54 (m, 1H), 3.09 – 2.99 (m, 7H), 1.77 (dq, *J* = 13.8, 6.9 Hz, 1H), 1.70 – 1.51 (m, 2H), 1.47 – 1.29 (m, 2H), 1.22 (t, *J* = 7.3 Hz, 9H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.93 (t, *J* = 6.6 Hz, 3H), 0.59 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) signals of *cis*-isomer δ 170.1, 144.9, 131.8, 130.6, 129.5, 127.4, 127.0, 63.7, 54.8, 46.3, 42.1, 30.2, 29.1, 20.3, 20.2, 19.8, 13.69, 8.6.

^{1}H NMR (400 MHz, $CDCl_3$) signals of *trans*-isomer δ 9.84 (br.s, 1H), 8.03 – 8.00 (m, 1H), 7.35 – 7.32 (m, 1H), 7.26 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 5.36 (s, 1H), 3.70 – 3.54 (m, 1H), 3.50 (dd, *J* = 4.6, 2.2 Hz, 1H), 3.09 – 2.99 (m, 7H), 2.24 – 2.10 (m, 1H), 1.70 – 1.51 (m, 2H), 1.47 – 1.29 (m, 2H), 1.22 (t, *J* = 7.3 Hz, 9H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.97 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) signals of *trans*-isomer δ 169.7, 144.5, 134.0, 130.3, 127.8, 127.5, 126.7, 67.7, 53.0, 46.3, 40.9, 29.8, 29.7, 20.4, 18.1, 18.0, 13.68, 8.6. The stereoisomers signals assignment is based on HMBC and HSQC spectra.

HRMS *m/z* $[M–H]^-$ calcd for $C_{16}H_{22}NO_4S$ 324.1275, found 324.1269.

General procedure for the preparation of sulfonamides 24a-b from compound *trans*-20b

To a stirred ice-cooled suspension of compound *trans*-**20b** (323 mg, 0.6 mmol) in dry DMF (3 mL) thionyl chloride (300 mg, 2.5 mmol) was added. The mixture was stirred for 20 min under cooling and then at ambient temperature for 16 hours. The resulting mixture was concentrated *in vacuo* at 35 °C, triturated with ice water (10 mL) and extracted with EtOAc (2×20 mL). Organic phases were dried over $MgSO_4$ and evaporated to dryness to give 300 mg of crude sulfonyl chloride **23** which was used for preparation of sulfonamides without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.74 (td, *J* = 7.7, 1.4 Hz, 1H), 7.55 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.52 (ddd, *J* = 8.0, 7.5, 1.3 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.32 (d, *J* = 2.4 Hz, 1H), 4.92 (d, *J* = 14.8 Hz, 1H), 4.23 (d, *J* = 2.2 Hz, 1H), 3.82 (s, 3H), 3.73 (d, *J* = 14.7 Hz, 1H), 2.40 (s, 3H). HRMS *m/z* $[M+H]^+$ calcd for $C_{24}H_{22}ClNO_4S$ 456.1031, found 456.1052.

2-(*trans*-1-(4-Methoxybenzyl)-2-oxo-4-(*p*-tolyl)azetidin-3-yl)benzenesulfon-amide (24a). The crude sulfonyl chloride **23** from previous step (100 mg) was dissolved in THF (3 mL) and under stirring and ice-cooling gaseous ammonia was passed through the solution for 2 hours. The mixture was stirred at ambient temperature for 2 hours, then evaporated and subjected to column chromatography on silica gel (eluent – $CHCl_3$); yield 65 mg (75% for 2 steps); pale beige solid, mp 195–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.56 (td, *J* = 7.6, 1.3 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.27 – 7.20 (m, 4H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.85 (s, 2H), 5.53 (d, *J* = 2.3 Hz, 1H), 4.83 (d, *J* = 2.6 Hz, 1H), 4.80 (d, *J* = 15.0 Hz, 1H), 3.83 (s, 3H), 3.83 (d, *J* = 14.8 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 159.3, 141.4, 139.1 133.0, 132.8, 132.0, 129.9, 129.8, 129.2, 128.2, 128.1, 127.1, 126.9, 114.3, 61.1, 58.7, 55.3, 44.2, 21.2. HRMS *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}N_2O_4S$ 437.1530, found 437.1520.

***N*-(3,4-Dimethoxyphenethyl)-2-(*trans*-1-(4-methoxybenzyl)-2-oxo-4-(*p*-tolyl)-azetidin-3-yl)benzenesulfonamide (24b).** The solution of crude sulfonyl chloride **23** (100 mg) in dry DCM (2 mL) was added to the stirred solution of 2-(3,4-dimethoxyphenyl)ethanamine (36 mg, 0.2

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mmol) and pyridine (20 mg, 0.25 mmol) in dry DCM (2 mL). The mixture was stirred for 3 hours at ambient temperature, then it was washed with water (3 mL), evaporated and subjected to column chromatography on silica gel (eluent – $CHCl_3$); yield 68 mg (57% for 2 steps); pale yellow solid, mp 171–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.53 (td, *J* = 7.6, 1.2 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.38 (td, *J* = 7.8, 1.0 Hz, 1H), 7.18 (s, 4H),7.06 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.66 – 6.61 (m, 2H), 5.96 (t, *J* = 6.1 Hz, 1H), 5.45 (d, *J* = 2.3 Hz, 1H), 4.77 (d, *J* = 14.8 Hz, 1H), 4.64 (d, *J* = 2.6 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.78 (d, *J* = 14.7 Hz, 1H), 3.15 – 3.03 (m, 1H), 3.00 – 2.90 (m, 1H), 2.76 – 2.58 (m, 2H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 159.3, 148.9, 147.7, 139.0, 138.5, 133.0, 132.9, 132.6, 130.8, 130.3, 129.9, 129.8, 128.6, 127.6, 127.2, 126.9, 120.7, 114.2, 112.1, 111.3, 60.9, 59.8, 55.9, 55.8, 55.2, 44.8, 44.0, 35.6, 21.2. HRMS *m/z* $[M+Na]^+$ calcd for $C_{34}H_{36}N_2NaO_6S$ 623.2186, found 623.2194.

***trans*-3-(2-((3,4-Dihydroisoquinolin-2(1*H*)-yl)sulfonyl)phenyl)-1-(4-methoxy-benzyl)-4-(*p*-tolyl)azetidin-2-one (24c).** The solution of crude sulfonyl chloride **23** (100 mg) in dry DCM (2 mL) was added to the stirred solution of 1,2,3,4-tetrahydroisoquinoline (27 mg, 0.2 mmol) and pyridine (20 mg, 0.25 mmol) in dry DCM (2 mL). The mixture was stirred for 3 hours at ambient temperature, then it was washed with water (3 mL), evaporated and subjected to column chromatography on silica gel (eluent – $CHCl_3$); yield 68 mg (62% for 2 steps); pale beige amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.60 (td, *J* = 7.7, 1.4 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.17 (s, 4H), 7.16 – 7.11 (m, 4H), 7.07 – 7.01 (m, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.87 – 6.83 (m, 1H), 5.38 (d, *J* = 1.9 Hz, 1H), 4.90 (d, *J* = 14.8 Hz, 1H), 4.22 (d, *J* = 2.1 Hz, 1H), 4.10 (d, *J* = 15.4 Hz, 1H), 4.01 (d, *J* = 15.4 Hz, 1H), 3.83 (s, 3H), 3.68 (d, *J* = 14.7 Hz, 1H), 3.20 (ddd, *J* = 12.1, 6.8, 5.2 Hz, 1H), 3.15 – 3.09 (m, 1H), 2.82 – 2.65 (m, 2H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 159.2, 138.6, 136.2, 135.4, 133.7, 133.5, 133.1, 131.5, 130.7, 129.9, 129.6, 129.1, 128.8, 127.79, 127.78, 127.1, 126.6, 126.3, 126.2, 114.2, 64.1, 60.2, 55.3, 46.3, 43.7, 42.8, 28.5, 21.3. HRMS *m/z* $[M+Na]^+$ calcd for $C_{33}H_{32}N_2NaO_4S$ 575.1975, found 575.1982.

Supporting Information

Electronic supplementary information (ESI) available: Figures of ^{1}H, ^{13}C NMR spectra for compounds **14, 20a-r, 24a-c** and X-ray data for compound *trans*-**20h** (CCDC 1548177). For ESI and crystallographic data in CIF or other electronic format see DOI: .

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