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A rationalization for the structure–activity relationship of α-functionalized β-enamino γ-sultams

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ABSTRACT

Herein we describe the reaction of 2-methyl-2-(methylamino)propanenitrile and 1-(methylamino)cyclobutane-1-carbonitrile with α-functionalized sulfonyl chlorides and the reactivity of resulting α-functionalized β-enamino γ-sultams. The nature of the substituent or the functional group in the α-position has a decisive impact on the reactivity of β-enamino γ-sultams. In particular, α-unsubstituted β-enamino γ-sultams and those possessing either electron-donating substituents or phenyl group are prepared through the two-step procedure and are prone to acid-mediated hydrolysis. Contrary to that, a strong electron-withdrawing group in the α-position enables the synthesis of the corresponding β-enamino γ-sultams in a one-pot manner and makes them tolerate the acid-mediated hydrolysis. The analysis of the results of a complex study involving physical methods (NMR and IR spectroscopy, X-ray diffraction study) and DFT calculations (performed at PBE0 QZVP level of theory) allowed us to rationalize and formulate the rules of structure–activity relationship for the discussed sultams. It turned out, that the simplest way to predict the reactivity of α-functionalized β-enamino γ-sultams is the ^{1}H NMR spectroscopy: if the NH_2 group appears in the spectrum as a two-proton singlet the compound is highly likely can be further modified while the appearance of two separated one-proton singlets indicates a low reactivity of β-enamino γ-sultams.

1. Introduction

The discovery of *sulfa drugs* in the mid-1930s heralded a new era in medicine [1]. Since then, over 120 approved and marketed drugs have been used over the world along with more than 500 investigational and experimental drugs possessing SO_2—N fragment [2].

Cyclic sulfonamides (put simply, *sultams* – a portmanteau of the words *sul*fa lac*tams*) are of special interest [3–5] and great progress in their synthesis has been achieved in the last two decades [6–11]. With that, β-enamino γ-sultam scaffold has established itself as a key fragment in some compounds possessing antiviral activity. The inhibitors of HIV-1 reverse transcriptase may serve as an example (Fig. 1) [12]. In this regard, ATSAO-T [13,14] – the *aza*-analogue of TSAO-T [15,16] is of special interest.

Further studies on β-enamino γ-sultams are contributing to a better understanding of the structure–activity relationships thus facilitating their development as potential drug candidates.

Previously we have prepared a series of tetraminic acid sulfone analogues [17]. A little bit later, while studying their chemical properties and demonstrating their synthetic utility we prepared an array of derivatives. It was shown that both positions of the enamine fragment (*i.e.* C-5 atom and 4-amino group) were able to undergo electrophilic reactions [18]. This was also true for 6-membered counterparts [19]. Then we devised a one-pot method for the preparation of α-carbomethoxy β-enamino γ-sultams [20]. These compounds possessing two versatile functional handles – amino group and ester one, inspired our imagination. However, to great regret, they turned out quite resistant to the action of electrophiles and nucleophiles (Fig. 2).

The same tendency was observed within a series of β-enamino γ-sultones. Thus, α-unsubstituted β-enamino γ-sultones were readily

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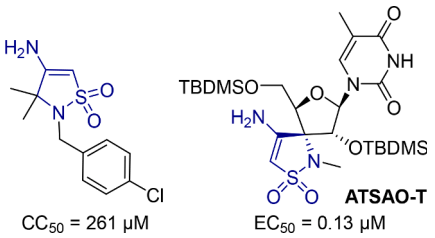


Fig. 1. β-Enamino γ-sultam-containing HIV-1(III_B)-specific reverse transcriptase inhibitors.

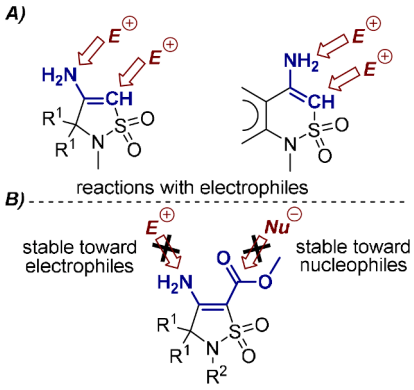


Fig. 2. Chemical behavior of enamino sultams.

reactive upon interaction both with electrophiles and nucleophiles [21]. With that, α-carbomethoxy β-enamino γ-sultones [22] as well as others possessing α-EWG β-enamino γ-sultones exhibited almost complete inactivity of the α-functional group and the β-amino one [23].

Such a drastic difference in the chemical behavior prompted us to conduct the present study with an aim to form and rationalize the structure–activity relationship within a series of α-functionalized β-enamino γ-sultams.

Following this goal we assigned two variation points in the structure of the β-enamino γ-sultam framework. On the one hand, it was the functional group in the C-5 position. On the other hand – alkyl substituent in the C-3 position. Hence, we focused on seven substituents/functional groups possessing varying degrees of inductive (*I*) and mesomeric (*M*) effects in the C-5 position and two variants of the substituents in the C-3 position (Fig. 3).

A series of 3,3-dimethyl substituted sultams are less sterically constrained and therefore implied to be the model compounds. At the same time, C-5 unsubstituted representative **1a** was chosen as a starting point in further comparative assessments.

The reasons for the introduction of spirocyclobutyl substituent are closely related to its structural features. Particularly, cyclobutane is the second most strained saturated carbocycle after cyclopropane (Fig. 4, A) [24,25]. The longer C—C bond (1.56 Å vs 1.54 Å in cyclohexane) is associated with the specific 1,3-C•••C non-bonded repulsions [26], that also drive cyclobutane to adopt the energetically most favorable puckered conformation with slightly reduced bond angle ∠CCC = 88° (Fig. 4, B and C) [27]. Another puzzling feature of this geometry is that the

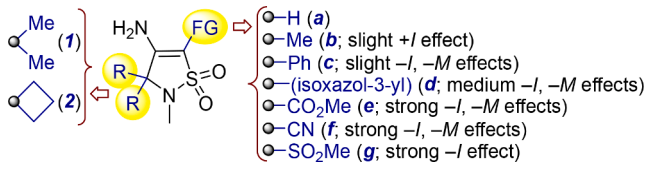


Fig. 3. Variation points in a series of studied α-functionalized β-enamino γ-sultams.

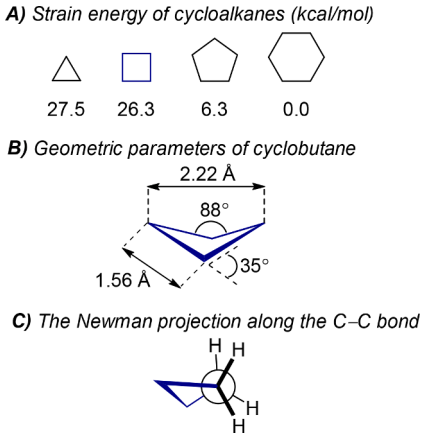


Fig. 4. Featured parameters of cyclobutane and other cycloalkanes.

methylene groups are rotated inwards, whereas rotation outwards might expect to reduce H•••H non-bonded interactions [28]. That is why introduced spirocyclobutyl substituent might have the biggest impact (*via* the transannular interaction) on the neighboring amino group of β-enamino γ-sultam core compared to other alkyl or unstrained spirocycloalkyl substituents.

Apart from that, the C—C bonds within the cyclobutane ring have slightly increased *p*-character, while the C—H bonds have more *s*-character [29]. With that, the reactivity of cyclobutanes [30] tends rather to those of conformationally flexible higher homologues than rigid cyclopropanes, which are sensitive to several reactions [31–37]. Collectively, among the sp^3-enriched frameworks the cyclobutane one is the smallest structural motif possessing both conformational restriction and stability.

Moreover, the cyclobutane framework takes on special significance for pharmaceutical and medicinal chemistry [38–40] as well as increasingly common in advanced building blocks [41–44].

2. Results and discussion

We initiated our study with the synthesis of the target compounds, which were the object of the present research. The level of theory for the DFT calculations was chosen after a comparative assessment of the provided geometries of the model β-enamino γ-sultam **1e** and the experimental values of the geometric parameters obtained by its single-crystal X-ray diffraction study. Since PBE0 QZVP provided the values closest to the experimental ones (Tables S1 and S2) it was used for the optimization of the molecular structure of all other β-enamino γ-sultams and further DFT calculations.

2.1. Synthesis of α-functionalized β-enamino γ-sultams

Based on our experience in the synthesis of sultam scaffold *via* the CSIC reaction [14,45–48] strategy, we have chosen the starting compounds for the present research. These were readily available amino nitriles, the Strecker adducts **3a,b** and the corresponding sulfonyl chlorides **4a–f** (Fig. 5).

There are two methods for the synthesis of target β-enamino γ-sultams **1** and **2** developed and optimized according to the chemical nature of the starting sulfonyl chlorides **4**. Specifically, the electron-withdrawing activity of the functional group or the substituent at the α-position of sulfonyl chlorides **4** played a pivotal role. The unsubstituted at the 5th position β-enamino γ-sultams or those possessing hydrocarbon substituent at the same position were prepared *via* the two-step procedure. In this way, amino nitriles **3a,b** were sulfonylated with **4a–c** at 0 °C in CH_2Cl_2 media and Et_3N as a base. The reaction mixture was left at rt overnight to ensure the completion of the sulfonylation process. Thereafter the crude sulfonamides **5a,c** and **6a–c** were involved

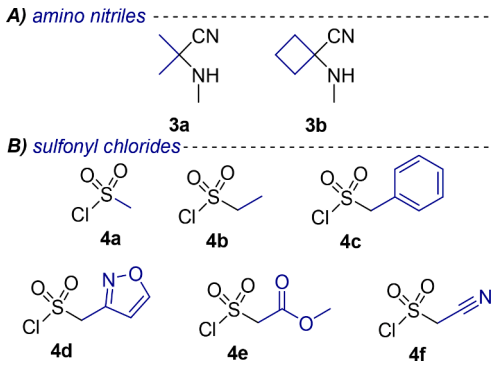


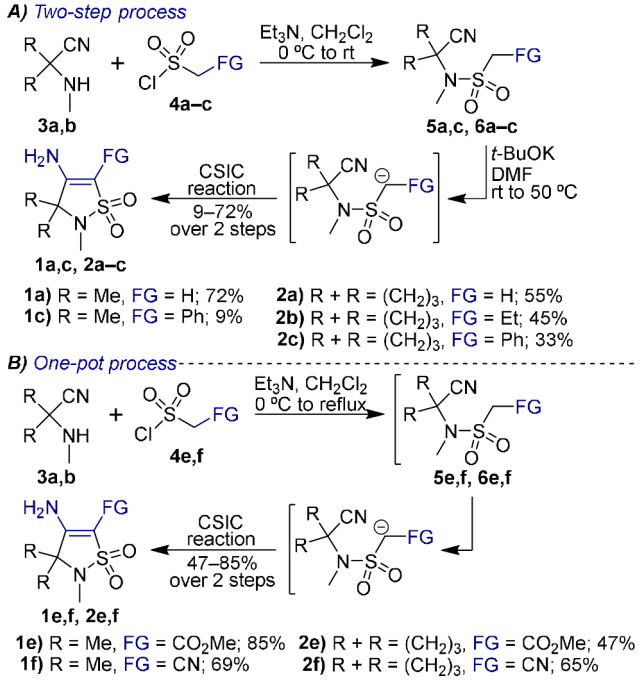
Fig. 5. Starting compounds for the synthesis of studied α-functionalized β-enamino γ-sultams.

in *t*-BuOK-mediated CSIC reaction thus affording the target β-enamino γ-sultams **1a,c** and **2a–c** (Scheme 1, A).

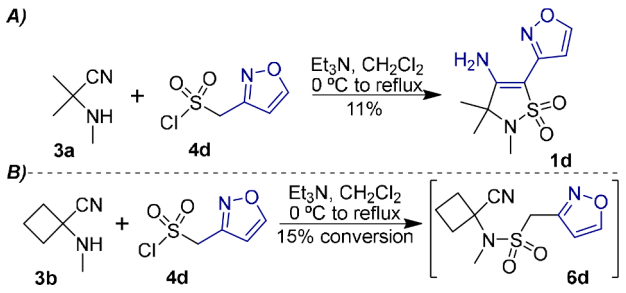
It should be noted, that sulfonylation of **3a** with **4b** was not fruitful. A variety of reaction conditions were attempted but none of them gave an acceptable yield of sulfonylated amino nitrile **5b**. Therefore, the corresponding β-enamino γ-sultam **1b** was not synthesized and studied.

In the case of sulfonyl chlorides possessing strong EWG (such as **4e** and **4f**), the two-step reaction can be performed in a one-pot manner. Thus, the sulfonylation step was carried out similarly to the aforementioned synthetic procedure with the only difference being that intermediate sulfonamides **5e,f** and **6e,f** were not isolated but involved in the cyclization step by refluxing the resulting reaction mixture. The active methylene moiety of **5e,f** and **6e,f** is acidic enough to be deprotonated by Et_3N thus enabling the CSIC reaction that provides the target β-enamino γ-sultams **1e,f** and **2e,f** (Scheme 1, B).

In these terms, the chemical behavior of isoxazole-derived sulfonyl chloride **4d** is quite interesting since it exhibits a dual nature. On the one hand, the reaction with **3a** proceeded through the one-pot method yielding the corresponding β-enamino γ-sultam **1d** (Scheme 2, A). On the other hand, the same reaction conditions (refluxing in CH_2Cl_2 and Et_3N) applied to cyclobutane-derived amino nitrile **3b** resulted in the



Scheme 1. Synthesis of α-functionalized β-enamino γ-sultams **1a,c,e,f** and **2a–c,e,f.**



Scheme 2. The reaction of aminonitriles **3a,b** with sulfonyl chloride **4d**

linear sulfonamide **6d** (Scheme 2, B). This can be attributed to the decisive impact of the cyclobutane framework on the reaction direction with the reagent possessing a functional group with a boundary electron-withdrawing effect.

Although the *t*-BuOK-mediated CSIC reaction protocol is usually efficient, this route failed when applied to **6d.** Therefore the corresponding β-enamino γ-sultam **2d** also was not prepared (not shown in Scheme).

Another fact of interest was the side reaction observed upon sulfonylation of aminonitriles with (het)aryl methane sulfonyl chlorides **4c** and **4d**. Thus, apart from desired products **1d** (for one-pot procedure) and **5c, 6c,d** (for two-step procedure) the unexpected by-products **7c, d** were formed in significant amounts (Scheme 3).

A rational explanation for this phenomenon was given by G. Opitz, who studied the formation of symmetrically 1,2-disubstituted ethylenes from primary sulfonyl chlorides upon base-mediated conditions (Scheme 4) [49–51].

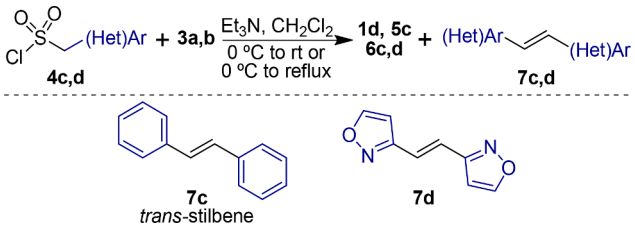
Finally, we reported the synthesis of α-mesyl β-enamino γ-sultam 1g, which fits into the concept of the current work. It was previously obtained upon mesylation of *N*-propyl substituted amino nitrile **3b** with mesyl chloride **4a** (Scheme 5) [52]. This reaction also looks odd at first glance but can be fully explained by another study by G. Opitz, devoted to the formation and reactivity of sulfenes [53–56].

To sum up, we had eleven (six 3,3-dimethyl substituted and five 3,3-spirocyclobutyl substituted) β-enamino γ-sultams (Fig. 6).

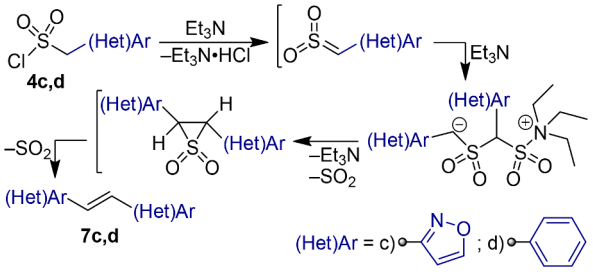
2.2. Acid mediated hydrolysis of α-functionalized β-enamino γ-sultams

With the set of α-functionalized β-enamino γ-sultams **1,2** in hands, we next performed the experiments on estimating their reactivity. In this regard, we focused on acid-mediated hydrolysis as the simplest chemical transformation involving the smallest reagents – the solvated proton and the molecule of water. This allows us to estimate the reactivity of the enamine functionality without taking into account steric factors caused by adjacent hydrocarbon substituents (γ-position) and another substituent or functional group (α-position).

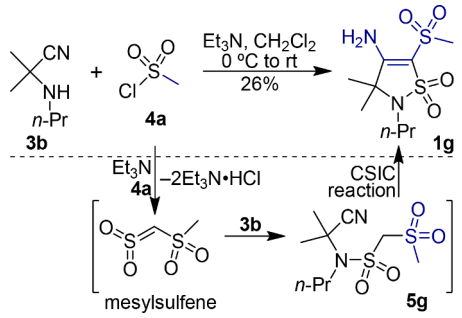
The acid-mediated hydrolysis of α-functionalized β-enamino γ-sultams **1,2** is expected to give the corresponding β-keto γ-sultams **8,9**. Toward this end, the pairs of appropriately substituted sultams possessing similar functional groups (or a substituent in the C-5 position) but different in the C-3 position (*i.e.* dimethyl and spirocyclobutyl



Scheme 3. The side reaction and by-products **7c,d** formed upon sulfonylation of amino nitriles **3a,b** with **4c,d.**



Scheme 4. A plausible mechanism for the formation of **7c,d** proposed by G. Opitz.



Scheme 5. Synthesis of α-mesyl β-enamino γ-sultam 1g.

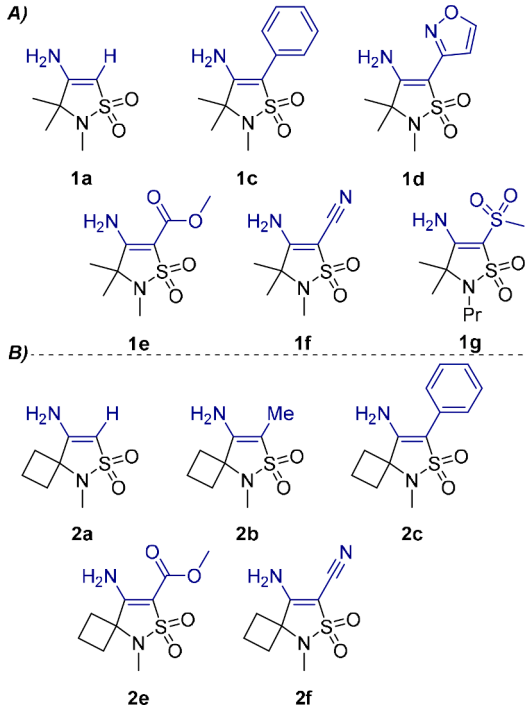
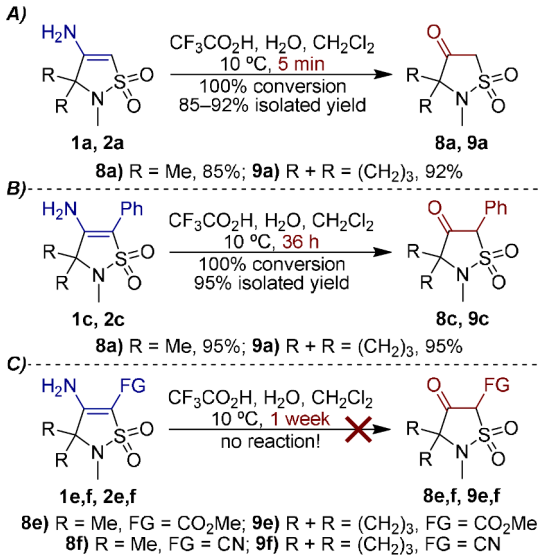


Fig. 6. α-Functionalized β-enamino γ-sultams discussed in this study.

substituents) were subjected to the action of the estimated quantity of CF_3CO_2H (3 eq.) and water (1.25 eq.) in CH_2Cl_2 media. These experiments allowed us to assess the impact of both the functional groups and the introduced spirocyclobutyl substituent.

It transpired that the nature of the functional group in the C-5 position had a decisive impact on the reactivity of β-enamino γ-sultams **1,2**, whereas the variation of the substituents in the C-3 position did not have a noticeable effect. Thus, C-5 unsubstituted β-enamino γ-sultams **1a** and **2a** completely hydrolyzed at 10 °C within 5 min (Scheme 6, A).



Scheme 6. Acid mediated hydrolysis of α-functionalized β-enamino γ-sultams.

The introduction of a phenyl substituent in the C-5 position significantly impeded the hydrolysis so that the complete conversion of β-enamino γ-sultams **1c** and **2c** into the corresponding β-keto γ-sultams **8c, 9c** took 36 h (Scheme 6, B). At the same time, the introduced functional groups with strong *–I* and *–M* effects (CO_2Me and CN) entirely precluded the possibility for hydrolysis and the corresponding β-enamino γ-sultams **1e,f** and **2e,f** remained fully intact even after a week of treatment with the above reaction media (Scheme 6, C).

2.3. NMR spectra analysis

Next, we analyzed and simulated the NMR spectra of the studied β-enamino γ-sultams. Since the ^1H and ^{13}C NMR chemical shift values were determined experimentally in DMSO-d_6, the calculated NMR chemical shift values were simulated in DMSO media with the PBE0 QZVP level of theory and showed good agreement with the experimental data. For a better understanding, further discussions will be centered around the atomic numbering scheme depicted in Fig. 7. The nomenclature adopted preserves a numeration common to all discussed products and tabulated values.

Interestingly, the NH_2 group appeared in the ^1H NMR spectrum as either one two-proton singlet or two separate one-proton singlets depending on the nature of the functional group or a substituent in the C-5 position. In particular, the amino group of β-enamino γ-sultams possessing electron-donating substituents (**1a** and **2a,b**) or slight electron-withdrawing substituents (**1c** and **2c**) in the C-5 position appeared in the spectrum as a two-proton singlet at 4.84–6.51 ppm. At the same time, the amino group of β-enamino γ-sultams **1e–g** and **2e,f** (possessing strong EWG in the C-5 position) appeared as two separate one-proton singlets and significantly downfield at 7.29–8.48 ppm and 7.56–8.73 ppm, respectively. These one-proton singlets can be separated from each

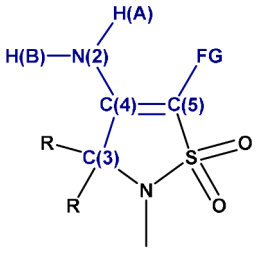


Fig. 7. The atomic numbering scheme for β-enamino γ-sultams **1**and **2**.

other by 0.66 ppm (1 g) (Fig. 8 and Tables 1 and 2).

The ^{1}H NMR spectra of **1e–g** and **2e,f** clearly showed that the N(2) atom bearing a high degree of positive charge significantly deshielded H (A) and H(B) protons (see Fig. 7) thereby shifting their signals downfield up to 8.73 ppm. Moreover, it causes increasing the multiplicity of the N (2)–C(4) bond and, as a consequence, prevents the rotation around it. That is the reason for the appearance of the NH_2 group as two separate one-proton singlets. And that is why the above β-enamino γ-sultams tolerated the acidic hydrolysis conditions by disabling the protonation of the amino group [57].

A similar tendency but to a less degree was observed in ^{13}C NMR spectra. While the C(4) atoms of **1a,c** and **2a–c** resonated at 152.1–160.6 ppm, C(4) atoms of their counterparts, **1e–g** and **2e,f**, appeared at 159.1–169.2 ppm. At the same time, the C(3) atoms of all the discussed β-enamino γ-sultams resonated at 60.9–65.2 ppm. The shifts of C(5) atoms are closely related to the nature of adjacent functional groups or substituents and are not indicative (Tables 1 and 2).

In this regard, the NMR spectra of isoxazole-derived β-enamino γ-sultam **1d** are of special interest. On the one hand, its ^{1}H NMR spectrum showed a very broad signal for the NH_2 group (stretched by 1.5 ppm) which had an intermediate shift value (as compared to **1a,c, 2a–c** and **1e–g, 2e,f**). On the other hand, its C(4) atom resonated at 159.1 ppm in the ^{13}C NMR spectrum which is also an intermediate shift value (Fig. 8 and Table 1). That is another example indicative of the boundary electron-withdrawing effect of the isoxazole core.

Collectively, these data fully correlate with the methods applied to the synthesis of β-enamino γ-sultams and their reactivity. Thus, **1a,c** and **2a–c** prepared through the two-step procedure (Scheme 1, A) and prone to acid-mediated hydrolysis (Scheme 6, A and *B*) possess NH_2 group appeared in the ^{1}H NMR spectrum as two-proton singlet at 4.84–6.51 ppm. Contrary to the above, β-enamino γ-sultams **1e–g** and **2e,f** prepared in a one-pot manner (Scheme 1, *B*) tolerate the acidic hydrolysis conditions (Scheme 6, *C*) and possess NH_2 group appeared in the ^{1}H NMR spectrum as two separate one-proton singlets at 7.29–8.48 ppm and 7.56–8.73 ppm, respectively.

It should be also emphasized, that spiroannelated cyclobutane substituent causes downfield shifting of NH_2 group signals in ^{1}H NMR spectra, which is fully correlated with the DFT calculations (Tables 1 and 2). Contrary to that, spiroannelated cyclopentane and cyclohexane substituents cause upfield shifting (Fig. 9) [17,20]. This is another evidence of stereoelectronic effects caused by cyclobutane scaffold (Fig. 10).

2.4. IR spectra analysis

Next, we analyzed and simulated the IR spectra of the studied β-enamino γ-sultams. The spectra were calculated using the PBE0 QZVP level of theory in a gas phase and showed good agreement with the experimental data. Besides, the computed vibrational frequencies were scaled using the scale factor of 0.9942 to omit the anharmonicity effects [58].

The IR spectrum showed the presence of a strong band from H—N—H stretching vibrations at 3446–3358 cm^{-1} (asymmetric) and 3354–3204 cm^{-1} (symmetric) as well as a strong band from C═C stretching vibration at 1684–1647 cm^{-1}. Apart from that, β-enamino γ-sultams revealed a strong band at 1641–1599 cm^{-1} resulting from the H—N—H bending vibration.

The atypical frequency of CO_2Me group stretching vibration of β-enamino γ-sultams **1e** and **2e** (ν(C═O) = 1557 and 1555 cm^{-1}, respectively) indicates a significant level of conjugation and the contribution of amide-like structure in the enamine framework (Tables 3 and 4). This is another evidence of the presence of a positive charge at the N(2) atom, previously deduced from the NMR spectra analysis (Section 2.3).

2.5. X-Ray analysis

Previously we described the molecular structure of β-enamino γ-sultams **1e** [20] and 1g [52] based on the results of the X-ray diffraction study. Within the framework of the present work, we had obtained the single crystals of other two β-enamino γ-sultams, namely **1c** and **1d**. These experimental values of the geometric parameters were analyzed and compared with geometries for all the discussed β-enamino γ-sultams optimized using PBE0 QZVP level of theory (Tables 5 and 6) that allowed us to formulate a rule of thumb for structure–activity relationship.

On the whole, there was good agreement between calculated and experimental data except for the α-phenyl β-enamino γ-sultams **1c** and, apparently, **2c**. Nevertheless, there is a clear correlation between the N (2)–C(4) bond length and reactivity of discussed β-enamino γ-sultams.

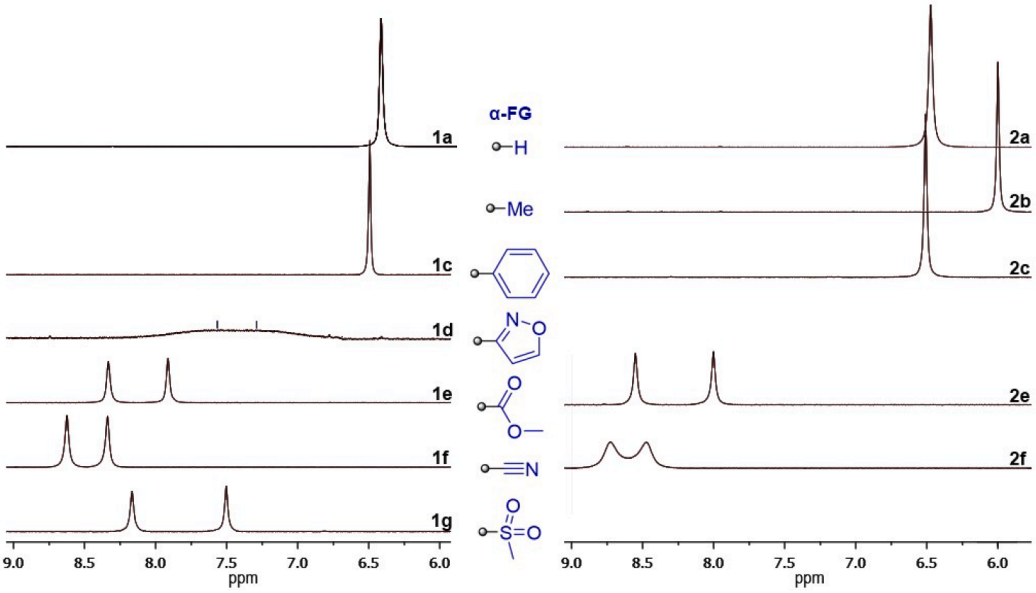


Fig. 8. Location and shape of the amino group signals of α-functionalized β-enamino γ-sultams in ^{1}H NMR spectra (the signals of the (het)aryl cores were deleted programmably).

Table 1
Experimental and calculated ^{1}H and ^{13}C NMR chemical shift values (ppm) of α-functionalized β-enamino fragment of sultams **1a,c–g**.

Atom	1a		1c		1d		1e		1f		1g	
	Exp.	DFT	Exp.	DFT	Exp.	DFT	Exp.	DFT	Exp.	DFT	Exp.	DFT
H(A)[a]	6.41	4.84[d]	6.49	5.13[d]	7.56	7.56	8.33	8.27	8.62	6.12	8.16	10.21
H(B)[a]					7.29	5.99	7.91	6.08	8.34	6.11	7.50	9.29
C(3)[b]	62.3	69.40	60.9	67.4	61.6	68.2	61.1	67.8	62.7	70.0	62.6	72.9
C(4)[b]	160.6	171.3	154.6	165.9	159.1	170.5	168.6	180.6	169.2	182.1	165.1	190.0
C(5)[b]	86.0	91.5	98.3	106.5	89.6	97.7	92.3	100.6	74.0	80.6	97.1	160.3
FG[c]	5.11[a]	5.25[a]	129.2[b]	141.1[b]	152.8[b]	164.8[b]	162.4[b]	174.9[b]	111.7[b]	124.7[b]	–	–

[a] ^{1}H NMR chemical shift value.
[b] ^{13}C NMR chemical shift value.
[c] An atom of a functional group attached to C-5 of sultam core; therefore either ^{1}H or ^{13}C NMR chemical shift value is provided.
[d] An average ^{1}H NMR chemical shift of equivalent protons.

Table 2
Experimental and calculated ^{1}H and ^{13}C NMR chemical shift values (ppm) of α-functionalized β-enamino fragment of sultams **2a–c,e,f**.

Atom	2a		2b		2c		2e		2f	
	Exp.	DFT	Exp.	DFT	Exp.	DFT	Exp.	DFT	Exp.	DFT
H(A)[a]	6.47	5.05[d]	6.00	4.72[d]	6.51	5.29[d]	8.55	8.55	8.73	6.56
H(B)[a]							8.00	6.58	8.48	6.25
C(3)[b]	65.1	70.9	64.1	69.7	64.1	69.2	63.9	69.5	65.2	72.4
C(4)[b]	159.2	171.3	152.1	164.1	152.9	165.5	167.2	180.5	167.9	185.0
C(5)[b]	86.6	92.7	92.8	101.6	99.0	107.9	92.4	100.2	74.0	79.5
FG[c]	5.14[a]	5.29[a]	5.1[b]	6.5[b]	128.9[b]	140.4[b]	162.3[b]	174.8[b]	111.7[b]	125.5[b]

[a] ^{1}H NMR chemical shift value.
[b] ^{13}C NMR chemical shift value.
[c] An atom of a functional group attached to C-5 of sultam core; therefore either ^{1}H or ^{13}C NMR chemical shift value is provided.
[d] An average ^{1}H NMR chemical shift of equivalent protons.

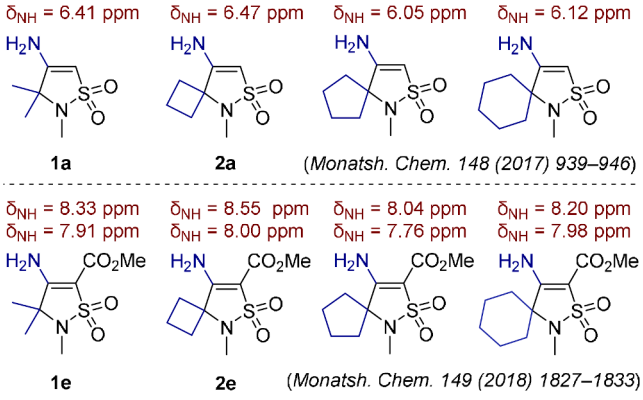


Fig. 9. ^{1}H NMR chemical shifts values (ppm) of NH_2 group in a homologous series of β-enamino γ-sultams.

Specifically, those representatives prepared through the two-step procedure (Scheme 1, A) and prone to acid-mediated hydrolysis (Scheme 6, A and B) possess N(2)–C(4) bond lengths equal to or longer than 1.34 Å. On the other hand, N(2)–C(4) bond length less than 1.33 Å is characteristic of β-enamino γ-sultams prepared in a one-pot manner (Scheme 1, B) and tolerated the acidic hydrolysis (Scheme 6, C). With that, N(2)–C(4) bond length in isoxazole-derived β-enamino γ-sultam **1d** had an intermediate value of 1.334 Å (Tables 5 and 6).

2.6. Thermodynamic analysis

The standard thermodynamic functions, based on vibrational analyses and statistical thermodynamics were obtained at 298 K using PBE0 QZVP level of theory in a gas phase. The Gibbs free energy for the reaction of formation of β-enamino γ-sultams **1** and **2** was calculated following Scheme 7, A.

The data obtained (Table 7) allowed us to suggest, that the Gibbs free energy values also correlated with the reactivity of discussed compounds. Within a series of β-enamino γ-sultams the ΔG value for the reaction of formation of representatives **1a,c** and **2a–c**, *i.e.* those, prepared through the two-step procedure (Scheme 1, A) and prone to acid-mediated hydrolysis (Scheme 6, A and *B*) was up to 7 times less than ΔG value for the formation of **1e,f** and **2e,f** prepared in a one-pot manner (Scheme 1, B) and tolerated the acidic hydrolysis (Scheme 6, C).

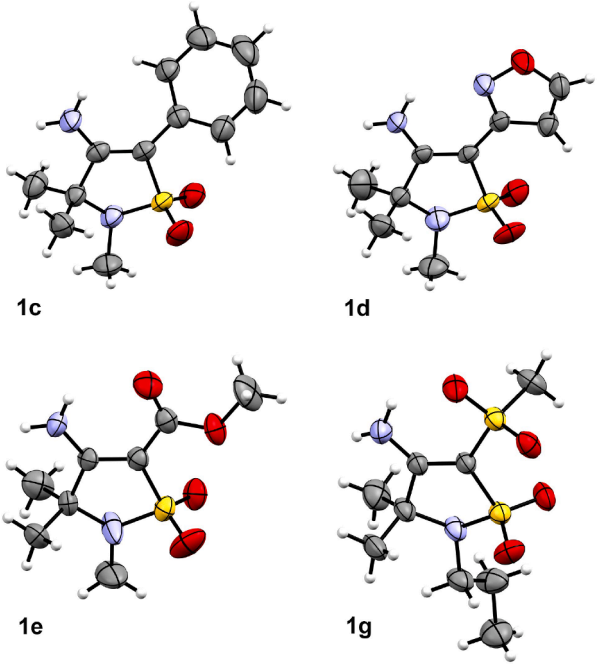


Fig. 10. Molecular structure of compounds **1c,d,e,g** according to results of X-ray diffraction study.

Table 3
Experimental and calculated frequencies (cm^{-1}) and assignments for vibrations of α-functionalized β-enamino sultams **1a,c–f**.

Vibrational assignments	1a			1c			1d			1e			1f		
	Exp.	DFT scaled	DFT unscaled	Exp.	DFT scaled	DFT unscaled	Exp.	DFT scaled	DFT unscaled	Exp.	DFT scaled	DFT unscaled	Exp.	DFT scaled	DFT unscaled
ν(as) NH_2	3402	3700	3722	3437	3680	3702	3415	3709	3731	3402	3713	3735	3358	3728	3750
ν(s) NH_2	3226	3596	3617	3354	3569	3590	3332	3503	3523	3235	3494	3514	3204	3599	3620
ν C═C	1654	1705	1715	1654	1711	1721	1652	1699	1709	1684	1734	1744	1671	1691	1701
δ NH_2	1601	1632	1642	1619	1657	1667	1603	1611	1620	1641	1674	1684	1599	1624	1634
ν(as) SO_2	1250	1351	1359	1255	1347	1355	1255	1348	1356	1303	1349	1357	1263	1374	1382
ν(s) SO_2	1099	1165	1172	1138	1262	1269	1121	1220	1227	1112	1228	1235	1143	1226	1233
ν FG[a]	–	–	–	1599[b]	1630[b]	1640[b]	1557[c]	1609[c]	1618[c]	1557[d]	1571[d]	1580[d]	2224[e]	2326[e]	2340[e]

[a] Characteristic vibration of an α-functional group or α-substituent.
[b] pH stretching vibration (ν C═C).
[c] 3-Isoxazolyl stretching vibration (ν C═C).
[d] CO_2Me stretching vibration (ν C═O).
[e] C≡N stretching vibration (ν C≡N).

Table 4
Experimental and calculated frequencies (cm^{-1}) and assignments for vibrations of α-functionalized β-enamino sultams **2a–c,e,f**.

Vibrational assignments	2a			2b			2c			1e			1f		
	Exp.	DFT scaled	DFT unscaled	Exp.	DFT scaled	DFT unscaled	Exp.	DFT scaled	DFT unscaled	Exp.	DFT scaled	DFT unscaled	Exp.	DFT scaled	DFT unscaled
ν(as) NH_2	3433	3708	3730	3437	3690	3712	3446	3675	3696	3398	3709	3731	3367	3720	3742
ν(s) NH_2	3354	3602	3623	3354	3589	3610	3354	3565	3586	3235	3491	3511	3209	3592	3613
ν C═C	1654	1700	1710	1667	1742	1752	1647	1707	1717	1680	1732	1742	1669	1680	1690
δ NH_2	1599	1637	1647	1636	1641	1651	1619	1656	1666	1641	1670	1680	1599	1616	1625
ν(as) SO_2	1237	1354	1362	1237	1345	1353	1257	1349	1357	1314	1354	1362	1279	1406	1414
ν(s) SO_2	1093	1173	1180	1104	1223	1230	1147	1244	1251	1161	1173	1180	1154	1223	1230
ν FG[a]	–	–	–	3240[b]	3129[b]	3147[b]	1602[c]	1630[c]	1640[c]	1555[d]	1569[d]	1578[d]	2220[e]	2320[e]	2334[e]

[a] Characteristic vibration of an α-functional group or α-substituent;.
[b] CH_3 stretching vibration (ν C–H);.
[c] pH stretching vibration (ν C═C);.
[d] CO_2Me stretching vibration (ν C═O);.
[e] C≡N stretching vibration (ν C≡N);.

Table 5
Calculated and experimental atomic distances in the structures of β-enamino γ-sultams **1a,c–g**.

Molecule	Bond length, Å			
	N(2)–C(4)	C(4)–C(5)	C(3)–C(4)	C(5)–FG
1a	1.362[a]	1.336[a]	1.519[a]	1.078[a,c]
1c	1.363[a]	1.344[a]	1.516[a]	1.465[a]
	1.343(3)[b]	1.356(3)[b]	1.530(3)[b]	1.474(3)[b]
1d	1.338[a]	1.353[a]	1.516[a]	1.439[a]
	1.334(4)[b]	1.354(4)[b]	1.520(5)[b]	1.445(5)[b]
1e	1.330[a]	1.360[a]	1.514[a]	1.445[a]
	1.328(9)[b]	1.352(9)[b]	1.539(8)[b]	1.436(9)[b]
1f	1.337[a]	1.354[a]	1.515[a]	1.402[a]
1g	1.330[a]	1.358[a]	1.534[a]	1.733[a,d]
	1.328(8)[b]	1.359(7)[b]	1.519(7)[b]	1.726(4)[b]

[a] Calculated value.
[b] Experimental value obtained from X-ray diffraction study.
[c] C—H bond distance.
[d] C—S bond distance.

Again, the ΔG for the reaction of formation of isoxazole-derived β-enamino γ-sultam **1d** had an intermediate value (Table 7).

Apart from that, we calculated the shift of the Gibbs free energy for the hypothetic isodesmic reaction (Scheme 7, B) at the same level of the theory (PBE0 QZVP). The values obtained (ΔG ≤ 2.5 kcal/mol) showed that the tension caused by spirocyclobutane substituent would not affect the chemical behavior of β-enamino γ-sultams **2** being compared to their unstrained counterparts **1** (Table 7). Indeed, this was confirmed by the experiments on acid-mediated hydrolysis (Section 2.2, Scheme 6).

Table 6
Calculated atomic distances in the structure of β-enamino γ-sultams **2a–c,e,f**.

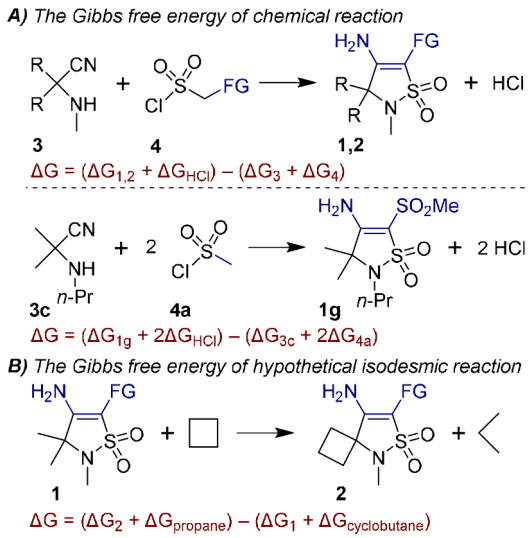
Molecule	Bond length, Å			
	N(2)–C(4)	C(4)–C(5)	C(3)–C(4)	C(5)–FG
2a	1.361	1.337	1.509	1.078[a]
2b	1.370	1.338	1.508	1.486
2c	1.365	1.345	1.506	1.465
2e	1.330	1.362	1.505	1.445
2f	1.336	1.358	1.519	1.400

[a] C–H bond distance.

2.7. Frontier molecular orbitals analysis

The frontier molecular orbitals (FMOs) are other important characteristics of compounds since the stability and reactivity of compounds are closely related to the values of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). The HOMO demonstrates the donor orbitals involved in reactions with electrophiles and the LUMO demonstrates acceptor orbitals binding the nucleophiles. Apart from that, the molecules with a high chemical reactivity are generally accomplice with a small energy gap between frontier orbitals ($\Delta E = E_{LUMO} - E_{HOMO}$).

The computed energy data of HOMO and LUMO and the corresponding energy gaps ΔE in the gas phase are shown in Tables 8 and 9 and depicted in Figs. 11 and 12.



Scheme 7. Calculation of the Gibbs free energy for the chemical (*A*) and hypothetical isodesmic (*B*) reactions.

Table 7
Calculated values of the Gibbs free energy for the chemical reaction of β-enamino γ-sultam formation and hypothetical isodesmic reaction.

Substituent or functional group in the 5th position	ΔG of chemical reaction (kcal/mol)		ΔG of isodesmic reaction (kcal/mol)
	Sultam **1** (3,3-Me_2)	Sultam **2** (3,3-$(CH_2)_3$)	
H (**a**)	−8.71	−4.49	−2.22
Me (**b**)	–	−7.02	–
Ph (**c**)	−13.2	−8.99	−2.25
isoxazol-3-yl (**d**)	−20.9	–	–
CO_2Me (**e**)	−32.3	−28.3	−2.38
CN (**f**)	−21.3	−15.3	−0.42
SO_2Me (**g**)	−8.06	–	–

The HOMO electron density of β-enamino γ-sultams is mainly centered on the N(2), C(4), and C(5) atoms. The reactivity towards electrophiles, namely H_3O^+ under acidic hydrolysis may be assessed from the HOMO energy: the higher E_{HOMO} of the substrates means a higher reactivity towards electrophiles. Indeed, the calculated HOMO energy for **1a** (−6.815 eV) and **2a** (−6.772 eV), prone to hydrolysis, was higher than calculated HOMO energy for **1e** (−6.918 eV), **1f** (−7.228 eV), **2e** (−6.916 eV), and **2f** (−7.180 eV), which tolerated the acidic media. The discrepancy between the calculated HOMO energy for α-phenyl β-enamino γ-sultams **1c** (−6.354 eV) and **2c** (−6.363 eV) and their reactivity (Scheme 6, *B*) as compared to **1a** and **2a** may be again attributed to inaccuracy of the DFT calculations at the chosen level of theory, which we previously faced when analyzing the results of X-ray diffraction study (Section 2.5 and Table 5).

Intriguingly, at the same time, the rate of hydrolysis of the studied compounds fully correlates with the calculated energy levels of LUMO: β-enamino γ-sultams with greater reactivity have a higher level of their LUMO (Tables 8 and 9 and Figs. 11 and 12).

The calculated energy gap values for all discussed compounds (ΔE = 5.461–6.674 eV) indicated that β-enamino γ-sultams are stable and low-reactive compounds.

3. Conclusion

To sum up, we prepared two series of β-enamino γ-sultams possessing either a common substituent (including hydrogen atom) or functional group in the C-5 position and decorated with dimethyl or spirocyclobutyl substituent in the C-3 position (Fig. 6). It turned out that the nature of the substituent or the functional group in the C-5 position had a decisive impact on the reactivity of β-enamino γ-sultams. With an aim to rationalize and formulate the rules of the structure−activity relationship, we resorted to a number of physical methods (NMR and IR spectroscopy, X-ray diffraction study) and DFT calculations performed at a rather advanced level of theory (PBE0 QZVP).

Thus, β-enamino γ-sultams of *type 1* (**1a,c** and **2a–c**) (Fig. 13) can be prepared through the two-step procedure (Scheme 1, A) and are prone to acid-mediated hydrolysis (Scheme 6, A and B). Their NH_2 group appears in the ^{1}H NMR spectrum as a two-proton singlet at 4.84–6.51 ppm and their N(2)–C(4) bond length is equal to or longer than 1.34 Å. The calculated Gibbs free energy for the reaction of their formation is equal to or greater than –13.2 kcal/mol while the calculated energy of their HOMO is equal to or higher than –6.8 eV.

Contrary to that, β-enamino γ-sultams of *type 2* (**1e–g** and **2e,f**) (Fig. 13) are prepared in one-pot manner (Scheme 1, B) and tolerate the acid-mediated hydrolysis (Scheme 6, C). Their NH_2 group is shown in the ^{1}H NMR spectrum as two separate one-proton singlets at 7.29–8.48 ppm and 7.56–8.73 ppm, respectively and their N(2)–C(4) bond length is equal to or shorter than 1.33 Å. The calculated Gibbs free energy for the reaction of their formation is equal to or less than −15.3 kcal/mol, while the calculated energy of their HOMO is equal to or less than −6.9 eV.

At the same time, some substituents or functional groups such as isoxazole ring possess specific stereoelectronic characteristics that cause intermediate chemical behavior and physical characteristics.

The DFT calculations confirmed and supplemented the experimental data. With that, the observed discrepancies between the calculated and experimental data may be both attributed to different aggregate states (*i.e.* the experimental data correspond to the structures in the solid phase or a solution, while the DFT calculations associated to the gaseous phase) and inaccuracy of the chosen level of theory.

Collectively, the simplest way to predict the reactivity of α-functionalized β-enamino γ-sultams is the ^{1}H NMR spectroscopy: if the NH_2 group appears in the spectrum as a two-proton singlet the compound is highly likely can be further modified.

We hope that the present work will stimulate further studies in sultam chemistry and will facilitate the efforts of the chemists involved in organic and lead-oriented synthesis [59–61].

4. Experimental section

The experiments were conducted at 10 °C since it was an ambient temperature in our laboratory (Taras Shevchenko National University of Kyiv) in winter 2022–2023. The solvents were purified according to the standard procedures [62]. All the starting materials were obtained from Enamine Ltd. and UORSY. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. ^{1}H and ^{13}C{^{1}H} spectra were recorded on a Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR and 151 MHz for ^{13}C NMR), a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H and 126 MHz for ^{13}C), or a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H and 101 MHz for ^{13}C). Chemical shifts are reported in ppm downfield from TMS as an internal standard. IR spectra were recorded on a Perkin Elmer BX II spectrometer in KBr pellets and are reported in cm^{-1}. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI). Elemental analyses were performed on a CHNOS elementary Vario MICRO Cube analyzer. DFT calculations were performed using ORCA 5.0.3 software package [63–66] and Avogadro1.2.0 software [67] for visualization. X-Ray diffraction studies of compounds **1c** and **1d** were performed on an automatic "Bruker APEX II" diffractometer (graphite monochromated MoKα radiation, CCD-detector, φ- and ω-scanning). The structures were solved by direct method using SHELXTL package [68].

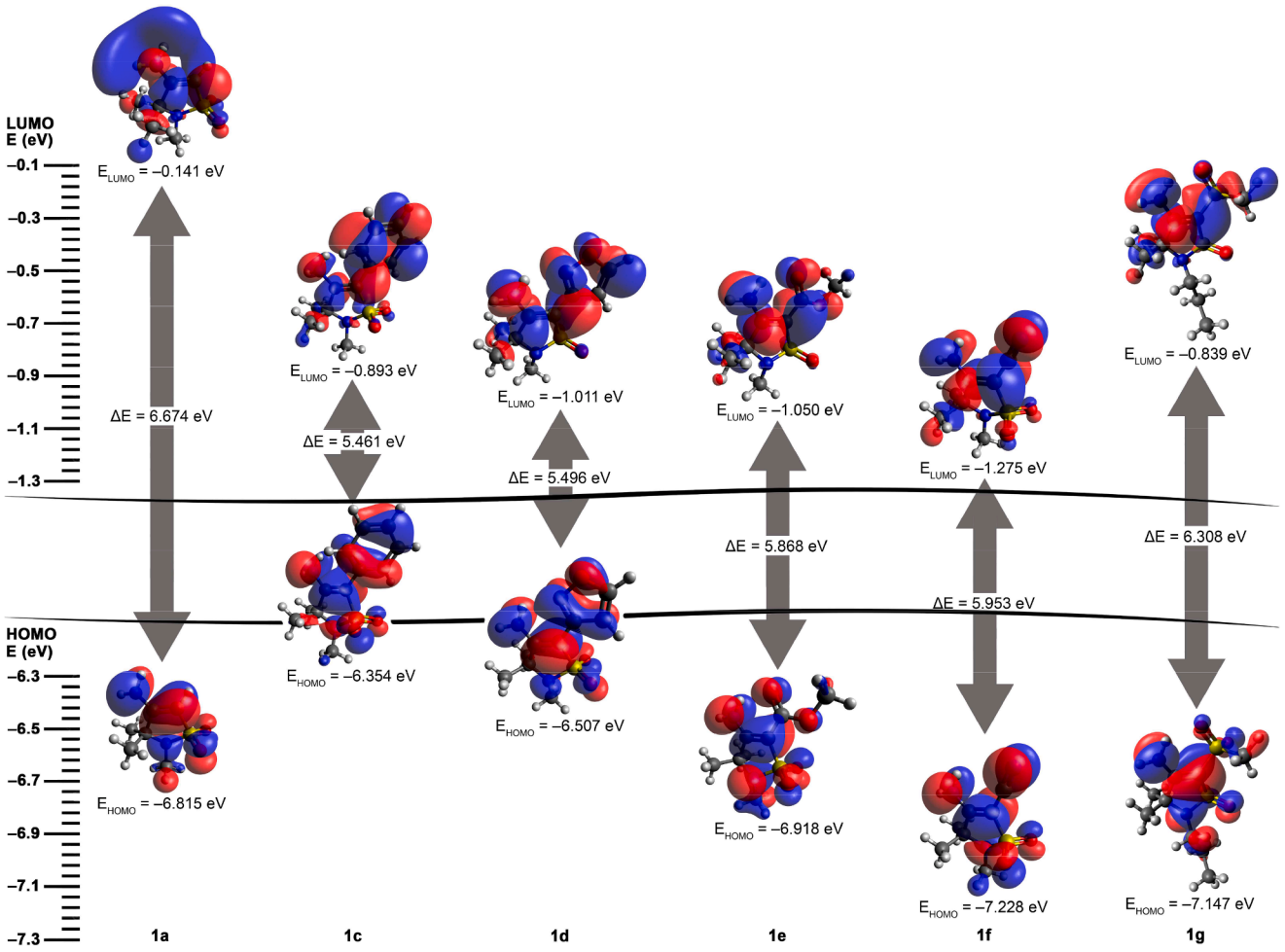


Fig. 11. The graphical representation for the calculated frontier molecular orbitals and HOMO–LUMO energy gap for β-enamino γ-sultams **1a,c–g**.

Positions of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with $U_{iso} = nU_{eq}$ of the carrier atom ($n = 1.5$ for methyl groups and $n = 1.2$ for other hydrogen atoms). The crystallographic data and experimental parameters are listed in Table S3. Final atomic coordinates, geometrical parameters and crystallographic data have been deposited with the Cambridge Crystallographic Data center, 11 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk). CCDC deposition numbers for structures **1c, 1d, 1e** and 1g are 2284597, 2284598, 1543634 and 1918144, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data center *via* www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the preparation of β-enamino γ-sultams 1a and 2a (Two-step method). The solution of sulfonyl chloride **4a** (5 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred ice-cold solution of cyanohydrin **3a and b** (5 mmol) and Et_3N (1.01 g, 1.39 ml, 10 mmol) in CH_2Cl_2 (15 ml). The reaction mixture was allowed to equilibrate to 10 °C and stirred at this temperature overnight thereafter it was evaporated to dryness at reduced pressure and diluted with water (5 ml). Thus formed crude **5a, 6a** was filtered, washed with water (2 ml), and air dried. Then it was dissolved in DMF (5 mL) and added dropwise to the stirred solution of *t*-BuOK (842 mg, 7.5 mmol) in DMF (8 mL). The reaction mixture was stirred at 10 °C for 30 min thereafter it was heated to 50 °C (internal temperature) and stirred at this temperature for 2 h. After the scheduled time, the mixture was evaporated to dryness at reduced pressure, triturated with water (5 ml), filtered, and washed with water (2 ml) to give the crude β-enamino γ-sultam **1a, 2a** which was recrystallized from *i*-PrOH.

4-Amino-2,3,3-trimethyl-2,3-dihydroisothiazole 1,1-dioxide (1a). Was obtained from **3a** (491 mg) and **4a** (573 mg). Yield 634 mg (3.6 mmol, 72 %); white solid, mp 241–242 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.41 (s, 2H, NH_2), 5.11 (s, 1H, CH), 2.47 (s, 3H, NCH_3), 1.25 (s, 6H, 2 × CH_3) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.6 (C-4), 86.0 (C-5), 62.3 (C-3), 22.8 (NCH_3), 22.6 (2 × CH_3) ppm; IR (KBr) n 3402 (ν_{as} NH_2), 3226 (ν_s NH_2), 1654 (ν C═C), 1601 (δ NH_2), 1250 (ν_{as} SO_2), 1099 (ν_s SO_2) cm^{-1}; LCMS (CI), *m/z*: 177 $[M + H]^+$; Anal. calcd. for $C_6H_{12}N_2O_2S$: C 40.89; H 6.86; N 15.90; S 18.19. Found: C 40.81; H 7.00; N 15.52; S 18.52. Physical properties and spectra data were found to be identical with the ones described previously [18].

8-Amino-5-methyl-6-thia-5-azaspiro [3.4] oct-7-ene 6,6-dioxide (2a). Was obtained from **3b** (551 mg) and **4a** (573 mg). Yield 518 mg (2.75 mmol, 55 %); white powder, mp 231–232 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.47 (s, 2H, NH_2), 5.14 (s, 1H, CH), 2.68 (s, 3H, NCH_3), 2.51–2.43 (m, 2H, CH_2'-2,4 cyclobutyl), 2.31 (td, J = 10.3, 5.8 Hz, 2H, CH_2'-2,4 cyclobutyl), 2.00–1.88 (m, 1H, CH_2'-3 cyclobutyl), 1.84 (dt, J = 12.8, 5.8 Hz, 1H, CH_2'-3 cyclobutyl) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.2 (C-4), 86.6 (C-5), 65.1 (C-3), 28.4 (NCH_3), 23.6 (2 × CH_2, C′-2,4 cyclobutyl), 13.2 (CH_2, C′-3 cyclobutyl) ppm; IR (KBr) n 3433 (ν_{as} NH_2), 3354 (ν_s NH_2), 1654 (ν C═C), 1599 (δ NH_2), 1237 (ν_{as} SO_2), 1093 (ν_s SO_2) cm^{-1}; LCMS (CI), *m/z*: 187 $[M–H]^-$; Anal. calcd. for $C_7H_{12}N_2O_2S$: C, 44.66; H, 6.43; N, 14.88; S, 17.03. Found: C, 44.27; H, 6.76; N, 14.51; S, 17.30.

8-Amino-5,7-dimethyl-6-thia-5-azaspiro [3.4] oct-7-ene 6,6-dioxide (2b) (Two-step method). The solution of sulfonyl chloride **4b** (643 mg, 5 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred ice-cold solution of cyanohydrin **3b** (551 mg, 5 mmol) and Et_3N (1.01 g,

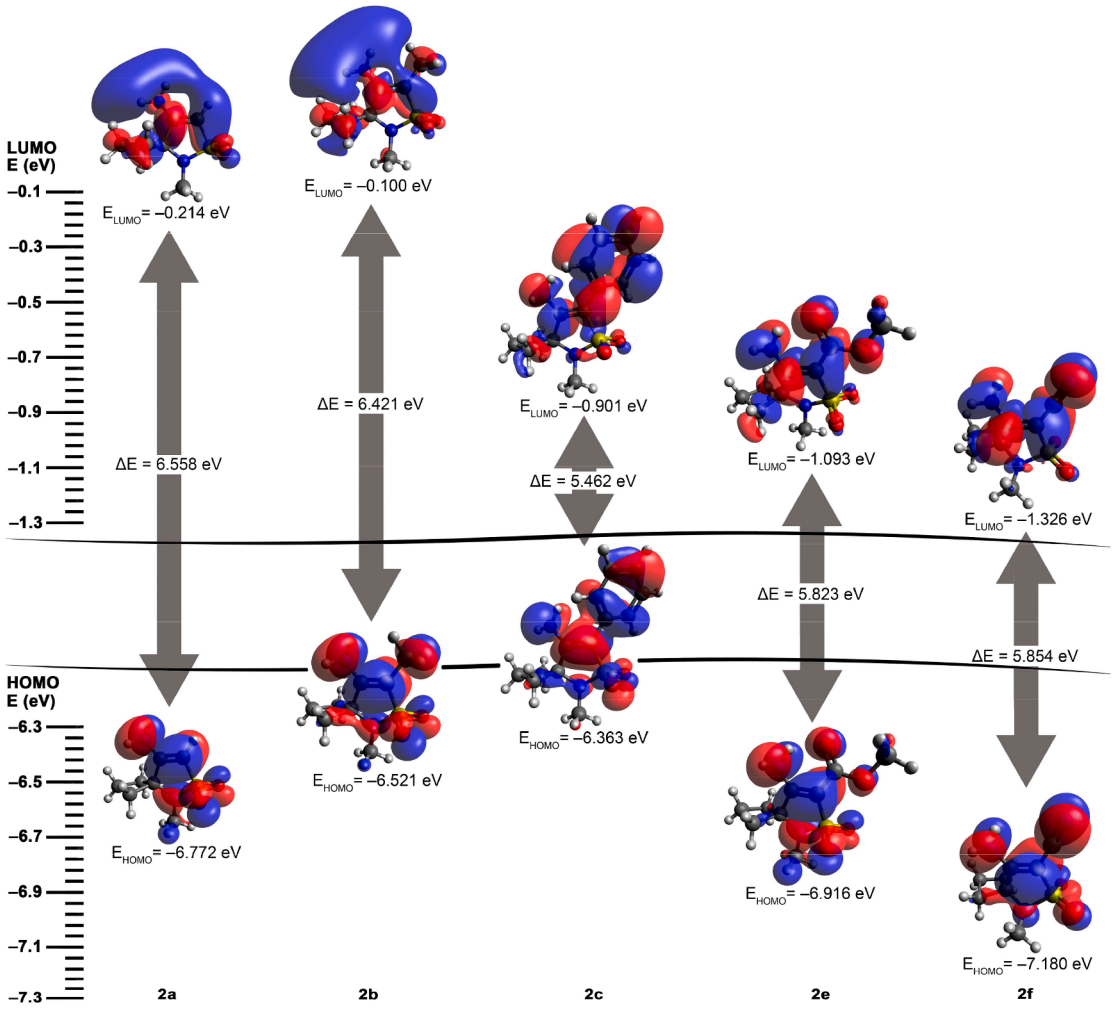


Fig. 12. The graphical representation for the calculated frontier molecular orbitals and HOMO–LUMO energy gap for β-enamino γ-sultams **2a–c,e,f**.

Table 8
The tabular representation for the calculated frontier molecular orbitals and HOMO–LUMO energy gap for β-enamino γ-sultams **1a,c–g**.

Orbital	Energy (eV)					
	1a	1c	1d	1e	1f	1g
LUMO	−0.141	−0.893	−1.011	−1.050	−1.275	−0.839
HOMO	−6.815	−6.354	−6.507	−6.918	−7.228	−7.147
ΔE	6.674	5.461	5.496	5.868	5.953	6.308

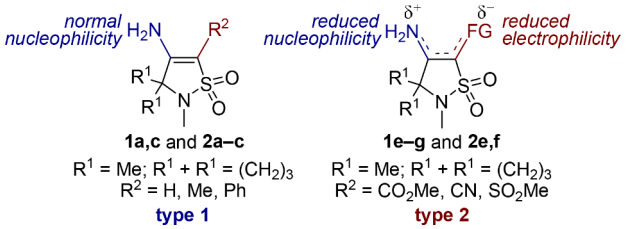


Fig. 13. Two types of discussed β-enamino γ-sultams.

Table 9
The tabular representation for the calculated frontier molecular orbitals and HOMO–LUMO energy gap for β-enamino γ-sultams **2a–c,e,f**.

Orbital	Energy (eV)				
	2a	2b	2c	2e	2f
LUMO	−0.214	−0.100	−0.901	−1.093	−1.326
HOMO	−6.772	−6.521	−6.363	−6.916	−7.180
ΔE	6.558	6.421	5.462	5.823	5.854

1.39 ml, 10 mmol) in CH_2Cl_2 (15 ml). The reaction mixture was allowed to equilibrate to 10 °C and stirred at this temperature overnight thereafter it was evaporated to dryness at reduced pressure, diluted with water (5 ml), and extracted with EtOAc (2 × 5 mL). The organic layer was dried (Na_2SO_4) and evaporated at reduced pressure. Thus obtained crude **6b** was dissolved in DMF (5 mL) and added dropwise to the stirred solution of *t*-BuOK (842 mg, 7.5 mmol) in DMF (8 mL). The reaction mixture was stirred at 10 °C for 30 min thereafter it was heated to 50 °C (internal temperature) and stirred at this temperature for 2 h. After the scheduled time, the mixture was evaporated to dryness at reduced pressure, triturated with water (5 ml), filtered, and washed with water (2 ml) to give the crude β-enamino γ-sultam **2b** which was recrystallized from *i*-PrOH. Yield 455 mg (2.25 mmol, 45 %); white powder, mp 207–208 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.00 (s, 2H, NH_2), 2.71 (s, 3H, NCH_3), 2.48–2.39 (m, 2H, CH_2'-2,4 cyclobutyl), 2.31 (dt, J = 13.5, 7.7 Hz, 2H, CH_2'-2,4 cyclobutyl), 1.94 (h, J = 9.5, 8.3 Hz, 1H, CH_2'-3 cyclobutyl), 1.87–1.77 (m, 1H, CH_2'-3 cyclobutyl), 1.70 (s, 3H, CH_3) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.1 (C-4), 92.8 (C-5), 64.1 (C-3), 28.4 (NCH_3), 23.8 (2 × CH_2, C′-2,4 cyclobutyl), 13.3 (CH_2, C′-3 cyclobutyl), 5.1 (CH_3) ppm; IR (KBr) n 3437 (ν_{as} NH_2), 3354 (ν_s NH_2), 3240 (ν C–H), 1667 (ν C═C), 1636 (δ NH_2), 1237 (ν_{as} SO_2), 1104 (ν_s

SO_2) cm^{-1}; LCMS (CI), *m/z*: 203 $[M + H]^+$; Anal. calcd. for $C_8H_{14}N_2O_2S$: C, 47.50; H, 6.98; N, 13.85; S, 15.85. Found: C, 47.66; H, 7.32; N, 13.62; S, 15.57.

General procedure for the preparation of α-phenyl β-enamino γ-sultams 1c and 2c (Two-step method). The pre-cold solution (0 °C) of sulfonyl chloride **4c** (953 mg, 5 mmol) in CH_2Cl_2 (15 ml) was added dropwise to a stirred ice-cold solution of cyanohydrin **3a and b** (5 mmol) in CH_2Cl_2 (15 ml). The reaction mixture was left at 0 °C for 2 h whereupon the solution of Et_3N (1.01 g, 1.39 ml, 10 mmol) in CH_2Cl_2 (5 ml) was added dropwise. Then it was allowed to equilibrate to 10 °C and stirred at this temperature overnight thereafter it was evaporated to dryness at reduced pressure and diluted with water (5 ml). Thus formed crude **5c, 6c** was filtered, successively washed with water (2 ml) and hexane (3 × 3 mL), and air dried. Then it was dissolved in DMF (5 mL) and added dropwise to the stirred solution of *t*-BuOK (842 mg, 7.5 mmol) in DMF (8 mL). The reaction mixture was stirred at 10 °C for 30 min thereafter it was heated to 50 °C (internal temperature) and stirred at this temperature for 2 h. After the scheduled time, the mixture was evaporated to dryness at reduced pressure, triturated with water (5 ml), filtered, and washed with water (2 ml) to give the crude α-phenyl β-enamino γ-sultam **1c, 2c** which was recrystallized from *i*-PrOH.

4-Amino-2,3,3-trimethyl-5-phenyl-2,3-dihydroisothiazole 1,1-dioxide (1c). Was obtained from **3a** (491 mg). Yield 114 mg (0.45 mmol, 9 %); brownish crystals, mp 177–178 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.49 (d, $J = 7.4$ Hz, 2H, CH′-2,6 Ph), 7.42 (t, $J = 7.4$ Hz, 2H, CH′-3,5 Ph), 7.28 (t, $J = 7.4$ Hz, 1H, CH′-4 Ph), 6.49 (s, 2H, NH_2), 2.59 (s, 3H, NCH_3), 1.37 (s, 6H, 2 × CH_3) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.6 (C-4), 129.2 (C″-1 Ph), 128.8 (2 × CH, C″-2,6 Ph), 127.5 (2 × CH, C″-3,5 Ph), 126.6 (CH, C″-4 Ph), 98.3 (C-5), 60.9 (C-3), 23.0 (NCH_3), 22.7 (2 × CH_3) ppm; IR (KBr) n 3437 (ν_{as} NH_2), 3354 (ν_s NH_2), 1654 (ν C═C), 1619 (δ NH_2), 1599 (ν C═C), 1255 (ν_{as} SO_2), 1138 (ν_s SO_2) cm^{-1}; LCMS (CI), *m/z*: 253 $[M + H]^+$; Anal. calcd. for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10; S, 12.71. Found: C, 56.90; H, 6.49; N, 11.03; S, 12.55.

8-Amino-5-methyl-7-phenyl-6-thia-5-azaspiro [3.4] oct-7-ene 6,6-dioxide (2c). Was obtained from **3b** (551 mg). Yield 436 mg (1.65 mmol, 33 %); off-white powder, mp 156–157 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.48 (d, $J = 8.1$ Hz, 2H, CH″-2,6 Ph), 7.43 (t, $J = 8.1$ Hz, 2H, CH″-3,5 Ph), 7.28 (t, $J = 8.1$ Hz, 1H, CH″-4 Ph), 6.51 (s, 2H, NH_2), 2.82 (s, 3H, NCH_3), 2.59–2.49 (m, 4H, 2 × CH_2′-2,4 cyclobutyl), 2.02 (q, $J =$ 9.4 Hz, 1H, CH_2′-3 cyclobutyl), 1.92 (q, $J = 9.4$ Hz, 1H, CH_2′-3 cyclobutyl) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.9 (C-4), 128.9 (C″-1 Ph), 128.8 (2 × CH, C″-2,6 Ph), 127.6 (2 × CH, C″-3,5 Ph), 126.8 (CH, C″-4 Ph), 99.0 (C-5), 64.1 (C-3), 28.5 (NCH_3), 23.8 (2 × CH_2, C′-2,4 cyclobutyl), 13.5 (CH_2, C′-3 cyclobutyl) ppm; IR (KBr) n 3446 (ν_{as} NH_2), 3354 (ν_s NH_2), 1647 (ν C═C), 1619 (δ NH_2), 1602 (ν C═C), 1257 (ν_{as} SO_2), 1147 (ν_s SO_2) cm^{-1}; LCMS (CI), *m/z*: 265 $[M + H]^+$; Anal. calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 59.38; H, 5.81; N, 10.53; S, 12.24.

The synthesis of β-enamino γ-sultam 1d and alkene 7d (One-pot method). The solution of sulfonyl chloride **4d** (908 mg, 5 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred ice-cold solution of cyanohydrin **3a** (491 mg, 5 mmol) and Et_3N (1.01 g, 1.39 ml, 10 mmol) in CH_2Cl_2 (15 ml). The reaction mixture was allowed to equilibrate to 10 °C and stirred at this temperature overnight thereafter it was refluxed for 4 h. Then it was evaporated to dryness at reduced pressure and triturated with water (5 ml). Thus formed precipitate was filtered and washed with water (2 × 2 ml) affording the title compound **7d.** The filtrate was left at 10 °C overnight whereupon the formed crystals were filtered to give the target β-enamino γ-sultam **1d.**

4-Amino-5-(isoxazol-3-yl)−2,3,3-trimethyl-2,3-dihydroisothiazole 1,1-dioxide (1d). Yield 134 mg (0.55 mmol, 11 %); yellowish crystals, mp 188–189 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (s, 1H, CH′-5 isoxazolyl), 7.56 (br. s, 1H, NH_2), 7.29 (br. s, 1H, NH_2), 6.59 (s, 1H, CH′-4 isoxazolyl), 2.61 (s, 3H, NCH_3), 1.40 (s, 6H, 2 × CH_3) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.4 (C′-5, isoxazolyl), 159.1 (C-4), 152.8 (C′-3, isoxazolyl), 100.9 (C′-4, isoxazolyl), 89.6 (C-5), 61.6 (C-3), 22.7 (2 × CH_3 and NCH_3) ppm; IR (KBr) n 3415 (ν_{as} NH_2), 3332 (ν_s NH_2), 1652 (ν C═C), 1603 (δ NH_2), 1557 (ν C═C), 1255 (ν_{as} SO_2), 1121 (ν_s SO_2) cm^{-1}; LCMS (CI), *m/z*: 242 $[M–H]^-$; Anal. calcd. for $C_9H_{13}N_3O_3S$: C, 44.43; H, 5.39; N, 17.27; S, 13.18. Found: C, 44.37; H, 5.17; N, 16.91; S, 13.39.

(*E*)-1,2-Di(isoxazol-3-yl)ethane (7d). Yield 158 mg (0.98 mmol, 39 %); white powder, mp 183–185 °C (dec.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (s, 2H, 2 × CH-5, isoxazolyl), 7.54 (s, 2H, –CH═CH–), 7.19 (s, 2H, 2 × CH-4, isoxazolyl) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.3 (C-5, isoxazolyl), 160.0 (C-4, isoxazolyl), 123.7 (CH), 102.4 (C-4, isoxazolyl) ppm; LCMS (CI), *m/z*: 163 $[M + H]^+$; Anal. calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 58.88; H, 3.97; N, 17.34.

A *ca.* 1:1.3 mixture of *N*-(1-Cyanocyclobutyl)-1-(isoxazol-3-yl)-*N*-methylmethanesulfonamide (6d) and (*E*)-1,2-Di(isoxazol-3-yl) ethane (7d). The solution of sulfonyl chloride **4d** (908 mg, 5 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred ice-cold solution of cyanohydrin **3b** (551 mg, 5 mmol) and Et_3N (1.01 g, 1.39 ml, 10 mmol) in CH_2Cl_2 (15 ml). The reaction mixture was allowed to equilibrate to 10 °C and stirred at this temperature overnight thereafter it was refluxed for 4 h. Then it was evaporated to dryness at reduced pressure, triturated with water (5 ml), filtered, and washed with water (2 × 2 ml) affording the title mixture. Yield 349 mg.

***N*-(1-Cyanocyclobutyl)-1-(isoxazol-3-yl)-*N*-methylmethanesulfonamide (6d, *spectra data*).** ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.00 (s, 1H, CH′-5 isoxazolyl), 6.70 (s, 1H, CH′-4 isoxazolyl), 4.83 (s, 2H, CH_2SO_2), 2.73 (s, 3H, NCH_3), 2.45 (t, $J = 9.4$ Hz, 2H, CH_2′-2,4 cyclobutyl), 2.37 (q, $J = 10.6$ Hz, 2H, CH_2′-2,4 cyclobutyl), 1.94 (h, $J = 10.6$ Hz, 1H, CH_2′-3 cyclobutyl), 1.79 (q, $J = 9.4$ Hz, 1H, CH_2′-3 cyclobutyl) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.0 (C-5, isoxazolyl), 153.1 (C-4, isoxazolyl), 120.8 (C≡N), 106.2 (C-4, isoxazolyl), 54.8 (C), 48.5 (CH_2SO_2), 33.6 (2 × CH_2, C′-2,4 cyclobutyl), 31.8 (NCH_3), 14.1 (CH_2, C′-3 cyclobutyl) ppm; LCMS (CI), *m/z*: 163 $[M + H]^+$.

General procedure for the preparation of α-functionalized β-enamino γ-sultams 1e,f and 2e,f (One-pot method). The solution of sulfonyl chloride **4e and f** (5 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred ice-cold solution of cyanohydrin **3a,b** (5 mmol) and Et_3N (1.01 g, 1.39 ml, 10 mmol) in CH_2Cl_2 (15 ml). The reaction mixture was allowed to equilibrate to 10 °C and stirred at this temperature overnight thereafter it was refluxed for 4 h. Then it was evaporated to dryness at reduced pressure and triturated with water (5 ml). Thus formed precipitate was filtered and washed with water (2 × 2 ml) affording the target β-enamino γ-sultams **1e,f** and **2e,f**. If necessary, the product can be recrystallized from *i*-PrOH (**1e,f**) and *n*-BuOH (**2e,f**).

Methyl 4-amino-2,3,3-trimethyl-2,3-dihydroisothiazole-5-carboxylate 1,1-dioxide (1e). Was obtained from **3a** (491 mg) and **4e** (863 mg). Yield 996 mg (4.25 mmol, 85 %); white powder, mp 250–251 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.33 (s, 1H, NH_2), 7.91 (s, 1H, NH_2), 3.72 (s, 3H, OCH_3), 2.53 (s, 3H, NCH_3), 1.35 (s, 6H, 2 × CH_3) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.6 (C-4), 162.4 (C═O), 92.3 (C-5), 61.1 (C-3), 51.0 (OCH_3), 22.4 (2 × CH_3 and NCH_3) ppm; IR (KBr) n 3402 (ν_{as} NH_2), 3235 (ν_s NH_2), 1684 (ν C═C), 1641 (δ NH_2), 1557 (ν C═O), 1303 (ν_{as} SO_2), 1112 (ν_s SO_2) cm^{-1}; LCMS (CI), *m/z*: 233 $[M–H]^-$; Anal. calcd. for $C_8H_{14}N_2O_4S$: C, 41.02; H, 6.02; N, 11.96; S, 13.69. Found: C, 41.24; H, 6.05; N, 11.74; S, 13.80. Physical properties and spectra data were found to be identical with the ones described previously [20].

4-Amino-2,3,3-trimethyl-2,3-dihydroisothiazole-5-carbonitrile 1,1-dioxide (1f). Was obtained from **3a** (491 mg) and **4f** (698 mg). Yield 694 mg (3.45 mmol, 69 %); off-white powder, mp 268–269 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H, NH_2), 8.34 (s, 1H, NH_2), 2.56 (s, 3H, NCH_3), 1.35 (s, 6H, 2 × CH_3) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2 (C-4), 111.7 (C≡N), 74.0 (C-5), 62.7 (C-3), 23.1 (NCH_3), 22.4 (2 × CH_3) ppm; IR (KBr) n 3358 (ν_{as} NH_2), 3204 (ν_s NH_2), 2224 (ν C≡N), 1671 (ν C═C), 1599 (δ NH_2), 1263 (ν_{as} SO_2), 1143 (ν_s SO_2) cm^{-1}; LCMS (CI), *m/z*: 200 $[M–H]^-$; Anal. calcd. for $C_7H_{11}N_3O_2S$: C, 41.78; H, 5.51; N, 20.88; S, 15.93. Found: C, 41.87; H, 5.24; N, 21.04; S,

16.29.

Methyl 8-amino-5-methyl-6-thia-5-azaspiro [3.4] oct-7-ene-7-carboxylate 6,6-dioxide (2e). Was obtained from **3b** (551 mg) and **4e** (863 mg). Yield 579 mg (2.35 mmol, 47 %); white powder, mp 223–224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H, NH_2), 8.00 (s, 1H, NH_2), 3.71 (s, 3H, OCH_3), 2.74 (s, 3H, NCH_3), 2.59–2.51 (m, 2H, CH_2'-2,4 cyclobutyl), 2.45–2.36 (m, 2H, CH_2'-2,4 cyclobutyl), 2.07–1.97 (m, 1H, CH_2'-3 cyclobutyl), 1.96–1.84 (m, 1H, CH_2'-3 cyclobutyl) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.2 (C-4), 162.3 (C═O), 92.4 (C-5), 63.9 (C-3), 51.0 (OCH_3), 28.5 (NCH_3), 23.3 (2 × CH_2, C′-2,4 cyclobutyl), 13.3 (CH_2, C′-3 cyclobutyl) ppm; IR (KBr) n 3398 (ν_{as} NH_2), 3235 (ν_s NH_2), 1680 (ν C═C), 1641 (δ NH_2), 1555 (ν C═O), 1314 (ν_{as} SO_2), 1161 (ν_s SO_2) cm^{-1}; LCMS (CI), *m/z*: 245 [M–H]$^-$; Anal. calcd. for $C_9H_{14}N_2O_4S$: C, 43.89; H, 5.73; N, 11.37; S, 13.02. Found: C, 43.85; H, 5.77; N, 11.21; S, 12.82.

8-Amino-5-methyl-6-thia-5-azaspiro [3.4] oct-7-ene-7-carbonitrile 6,6-dioxide (2f). Was obtained from **3b** (551 mg) and **4f** (698 mg). Yield 693 mg (3.25 mmol, 65 %); off-white powder, mp 254–255 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H, NH_2), 8.48 (s, 1H, NH_2), 2.77 (s, 3H, NCH_3), 2.61–2.52 (m, 2H, CH_2'-2,4 cyclobutyl), 2.38 (dq, J = 14.3, 7.0 Hz, 2H, CH_2'-2,4 cyclobutyl), 2.06–1.95 (m, 1H, CH_2'-3 cyclobutyl), 1.95–1.83 (m, 1H, CH_2'-3 cyclobutyl) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.9 (C-4), 111.7 (C≡N), 74.0 (C-5), 65.2 (C-3), 28.6 (NCH_3), 24.1 (2 × CH_2, C′-2,4 cyclobutyl), 13.1 (CH_2, C′-3 cyclobutyl) ppm; IR (KBr) n 3367 (ν_{as} NH_2), 3209 (ν_s NH_2), 2220 (ν C≡N), 1669 (ν C═C), 1599 (δ NH_2), 1279 (ν_{as} SO_2), 1154 (ν_s SO_2) cm^{-1}; LCMS (CI), *m/z*: 212 [M–H]$^-$; Anal. calcd. for $C_8H_{11}N_3O_2S$: C, 45.06; H, 5.20; N, 19.70; S, 15.03. Found: C, 44.74; H, 4.85; N, 19.92; S, 15.35.

4-Amino-3,3-dimethyl-5-(methylsulfonyl)-2-propyl-2,3-dihydroisothiazole 1,1-dioxide (1g, ***spectra data*****).** Was prepared following the literature method [52]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H, NH_2), 7.50 (s, 1H, NH_2), 3.11 (s, 3H, SO_2CH_3), 2.97 (t, J = 7.2 Hz, 2H, NCH_2), 1.62 (h, J = 7.2 Hz, 2H, NCH_2CH_2), 1.37 (s, 6H, 2 × CH_3), 0.90 (t, J = 7.2 Hz, 3H, CH_2CH_3) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.1 (C-4), 97.1 (C-5), 62.6 (C-3), 44.4 (SO_2CH_3), 40.9 (NCH_2), 23.2 (2 × CH_3), 22.5 (NCH_2CH_2), 11.2 (CH_2CH_3) ppm; LCMS (CI), *m/z*: 283 [M + H]$^+$.

General procedure for the TFA-mediated hydrolysis of β-enamino γ-sultams 1a,c and 2a,c. β-Enamino γ-sultam **1a,c, 2a,c** (0.4 mmol) was dissolved in CH_2Cl_2 (5 mL) followed by the addition of a mixture of CF_3CO_2H (137 mg, 92 μL, 1.2 mmol) and water (9 mg, 9 μL, 0.5 mmol). Thus obtained reaction mixture had been stirred at 10 °C until TLC showed full conversion of the starting material. Then it was evaporated to dryness at reduced pressure, triturated with water (1 ml), and extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was dried (Na_2SO_4) and evaporated at reduced pressure to give pure β-keto γ-sultam **8a,c, 9a,c**.

2,3,3-Trimethylisothiazolidin-4-one 1,1-dioxide (8a). Was obtained from **1a** (70 mg); reaction time 5 min. Yield 60 mg (0.34 mmol, 85 %). Physical properties and spectra data were found to be identical to the ones described previously [69,70].

5-Methyl-6-thia-5-azaspiro [3.4] octan-8-one 6,6-dioxide (9a). Was obtained from **2a** (75 mg); reaction time 5 min. Yield 70 mg (0.37 mmol, 92 %). Physical properties and spectra data were found to be identical to the ones described previously [71].

2,3,3-Trimethyl-5-phenylisothiazolidin-4-one 1,1-dioxide (8c). Was obtained from **1c** (101 mg); reaction time 36 h. Yield 96 mg (0.38 mmol, 95 %). Physical properties and spectra data were found to be identical to the ones described previously [70].

5-Methyl-7-phenyl-6-thia-5-azaspiro [3.4] octan-8-one 6,6-dioxide (9c). Was obtained from **2c** (106 mg); reaction time 36 h. Yield 101 mg (0.38 mmol, 95 %); white powder, mp 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.38 (m, 3H, CH″-3,4,5 Ph), 7.28–7.23 (m, 2H, CH″-2,6 Ph), 4.83 (s, 1H, CH), 3.00 (s, 3H, NCH_3), 2.64–2.41 (m, 4H, 2 × CH_2'-2,4 cyclobutyl), 2.14 (dp, J = 11.6, 9.0 Hz, 1H, CH_2'-3 cyclobutyl), 1.99–1.84 (m, 1H, CH_2'-3 cyclobutyl) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.8 (CO), 130.7 (2 × CH, C″-2,6 Ph), 129.8 (C″-1 Ph), 129.2 (2 × CH, C″-3,5 Ph), 126.9 (CH, C″−4 Ph), 70.7 (C), 69.1 (CH), 29.1 (CH_2, C′-2 cyclobutyl), 28.9 (CH_2, C′-4 cyclobutyl), 24.2 (NCH_3), 14.3 (CH_2, C′-3 cyclobutyl) ppm; IR (KBr) n 2905 (ν CH), 1756 (ν C═O), 1454 (ν C═C), 1320 (ν_{as} SO_2), 1147 (ν_s SO_2) cm^{-1}; LCMS (CI), *m/z*: 264 [M–H]$^-$; Anal. calcd. for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28; S, 12.08. Found: C, 58.59; H, 5.63; N, 4.96; S, 12.42 (Tables 3 and 4).

Supplementary material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

CRediT authorship contribution statement

Alexey V. Dobrydnev: Conceptualization, Supervision, Project administration, Methodology, Writing – original draft, Writing – review & editing. **Maria V. Popova:** Investigation, Visualization. **Andrii V. Yatsymyrskyi:** Software. **Svitlana V. Shishkina:** Investigation. **Yaroslav O. Chuchvera:** Investigation. **Yulian M. Volovenko:** Resources, Funding acquisition.

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

No data was used for the research described in the article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2023.136745.

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