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Sulfur Oxidation Increases the Rate of HIRE-Type [1.4]Thiazepinone Ring Expansion and Influences the Conformation of a Medium-Sized Heterocyclic Scaffold

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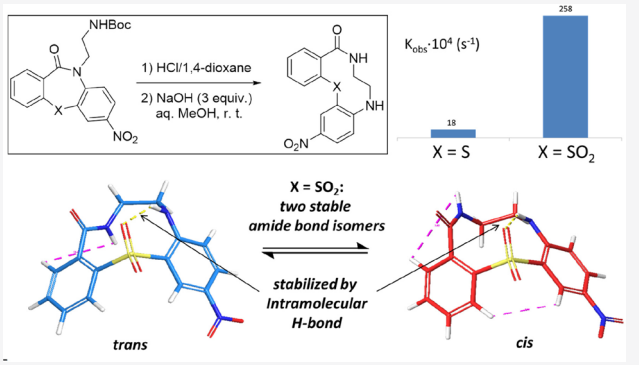
ABSTRACT: The hydrated imidazoline ring expansion (HIRE-type) reaction was investigated for a series of di(hetero)arene-fused [1.4]thiazepinones in comparison with their sulfone counterparts. The sulfones were found to undergo ring expansion at a much higher rate compared to the thioethers, much in line with the current mechanistic understanding of the process. Moreover, the amide bond *cis*- and *trans*-isomers of the ring-expanded products were found, in the case of sulfones, to be stabilized through an intramolecular hydrogen bond. The latter phenomenon was studied in detail by NMR experiments and corroborated by X-ray crystallographic information.



INTRODUCTION

Medium-sized (8- to 14-membered) rings have gained recognition as preferred scaffolds for lead generation in drug discovery.[1] A good balance of conformational rigidity and flexibility allows compounds based on such scaffolds to adopt a large number of energetically feasible conformations (compared to flat heterocyclic cores historically employed in lead generation libraries[2]) and still display a favorable absorption and membrane permeability profile (in contrast to overly flexible, linear scaffolds).[3] Being essentially "fuzzy shape" small molecule probes for protein binding sites, medium-sized rings may be particularly useful for interrogation of targets traditionally labeled undruggable (such as protein−protein interactions).[4] Unfortunately, medium-sized cyclic scaffolds are notoriously difficult to synthesize via ring closure due to unfavorable entropy associated with this process and transannular interactions present in such rings, which raises their enthalpy.[5] As a result, the current scarcity of medium-sized cyclic systems in current compound collections for drug discovery has driven the alternative synthetic methodology development which is based on expansion of smaller rings.[6]

In 2017, we described a ring expansion approach involving tetracyclic imidazoline-fused [1.4]oxazepines **1** (X = O, Figure 1). The compounds themselves proved rather resistant to hydrolysis. However, when activated by alkylation, the respective imidazolinium salts **2** underwent a rapid hydrolytic transformation into ring-expanded, 10-membered lactams **3** on treatment with 0.1% solution of K_2CO_3 in aqueous acetonitrile at room temperature.[7] The formation of **3** is thought to involve the formation of tetrahedral intermediate **4** which we viewed as a "hydrated imidazoline". Hence, the entire approach to ring expansion was dubbed the 'hydrated imidazoline ring expansion' or HIRE. In intermediate **4**, irreversible (due to the lower nucleophilicity of the anilinic nitrogen atom in **3**) breaking of the central C−N bond (highlighted red), presumably, leads to the formation of ring-expanded product **3**. However, the hydrated imidazoline **4** could be in equilibrium with 2-aminoethyl derivatives **5** which form through an alternative leaving group elimination and breaking of another C−N bond (highlighted blue). With this possibility in mind, we achieved ring expansion of purposefully synthesized seven-membered lactams **5** (X = O, S) via the formal 2-aminoethyl side chain insertion into the amide bond (or intramolecular N → N′ acyl migration).[8] At the same time, certain tetracyclic imidazolinium salts **2** (X = O,[9] NAlk[10]), when exposed to dilute aqueous basic solution, yielded only the product of side chain expulsion (**5**) but no ring-expanded product **3**. Applying forcing conditions to some of lactams **5** did help transform them into **3**, while for others the approach failed.[9] Aiming to understand the influence of electronic factors on the rate of transformation **5** → **3**, we established that electron-withdrawing substituents both in the carbonyl-bound

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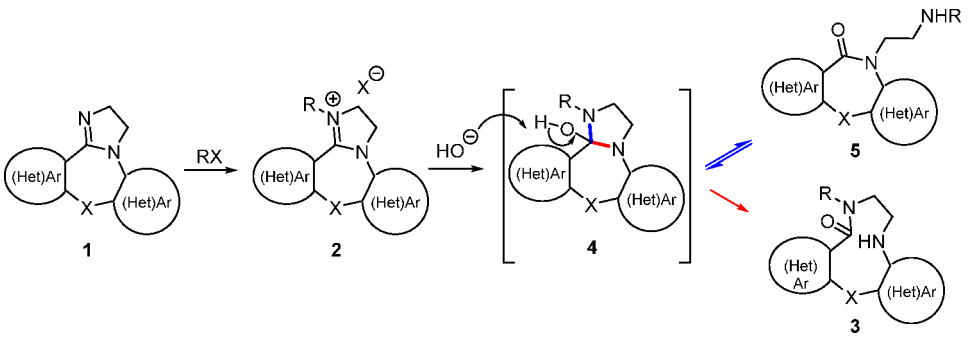
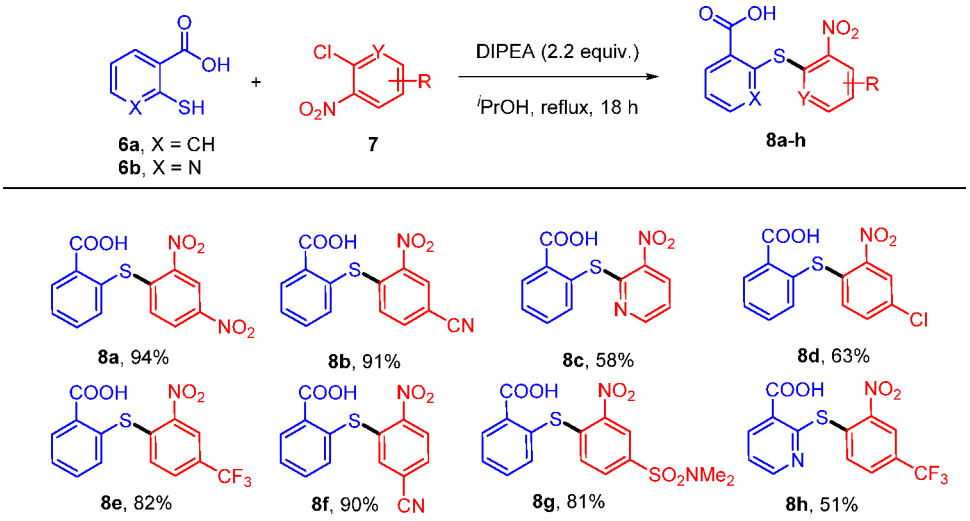


Figure 1. Hydrated imidazoline ring expansion (HIRE): a unified mechanistic view.

Scheme 1. Preparation of Carboxylic Acids 8a–h via S_NAr-Type Reaction



(hetero)aromatic ring and, to a much larger extent, in the nitrogen-bound (hetero)aromatic ring promote the reaction.[11] This prompted us to compare the rates of transformation **5** → **3** for [1,4]thiazepin-5-ones (X = S) and 1,4-thiazepin-5-one-1,1-dioxides (X = SO_2). In the latter, we reasoned the sulfone group would increase the electrophilicity of the lactam carbonyl carbon atom thus making the formation of **4** more energetically favorable. However, even more pronounced effects of the sulfone group were expected on the rate of subsequent aromatic amine departure from the tetrahedral carbon in **4** and the irreversible formation of **3** (Figure 1). Besides evaluating the effect of S → SO_2 oxidation on the rates of the HIRE-type ring expansion, we aimed to verify if such a perturbation of the electronic character of the [1,4]thiazepin-5-one core would facilitate the insertion of ω-aminoalkyl side chains longer than 2-aminoethyl (the process we designated as homo^x-HIRE[8]). Previously, insertion of 3-aminopropyl (homo-HIRE) and 4-aminobutyl (homo^2-HIRE) side chains led to the expansion of [1,4]thiazepin-5-one and [1,4]oxazepin-5-one core into 11- and 12-membered lactams (unfortunately, preparation of 13-membered lactams via homo^3-HIRE reaction failed).[8] Herein, we present the results obtained in the course of this investigation.

RESULTS AND DISCUSSION

To synthesize [1,4]thiazepin-5-ones for the present study, the following route was developed which represents a modification of the previously reported synthesis.[8] We found the new approach to offer significant advantage in the overall yield of the target compounds starting from thiosalicylic (**6a**) or 2-mercaptonicotinic (**6b**) acids. Thio compounds **6a–b** were reacted with *o*-nitro halo(hetero)arenes **7** in refluxing isopropyl alcohol in the presence of DIPEA to afford good to excellent yields of carboxylic acids **8a–h** (Scheme 1).

Starting from carboxylic acids **8a–h**, target [1,4]thiazepin-5-ones **9a–m** were synthesized using the following straightforward one-pot protocol. The carboxylic acid was activated with CDI, and the resulting imidazolide was treated with mono-Boc-protected ethylene diamine as well as α,ω-diaminoalkanes of various chain lengths (C_3–C_5). Once the amidation was complete, solid Cs_2CO_3 (3 equiv) was added to the reaction mixture, the temperature was raised to 60–80 °C, and at that temperature, the intramolecular S_NAr reaction was conducted over 18 h. As anticipated, it proceeded with an intermittent Smiles rearrangement[8] which defined the regiochemistry of products **9a–m** (Scheme 2).

In addition to the set of somewhat electronically biased [1,4]thiazepin-5-ones **9a–m** (all of which feature an electron-deficient nitrogen-bound (hetero)aromatic ring, we synthesized their electron-neutral analog **9n** which was prepared via alkylation of commercially available dibenzo[*b*,*f*][1,4]-thiazepin-11(10*H*)-one (**10**) (Scheme 3).

With a set of 14 Boc-protected [1,4]thiazepin-5-one starting materials **9a–n** for the HIRE-type ring expansion at hand, we converted all of them into their sulfone counterparts **11a–n** using a 3-fold excess of sodium periodate in the presence of a catalytic amount (5 mol %) of $RuCl_3$.[8] Reaction conducted in the CCl_4–MeCN–H_2O 1:1:2 mixture gave, after chromato-

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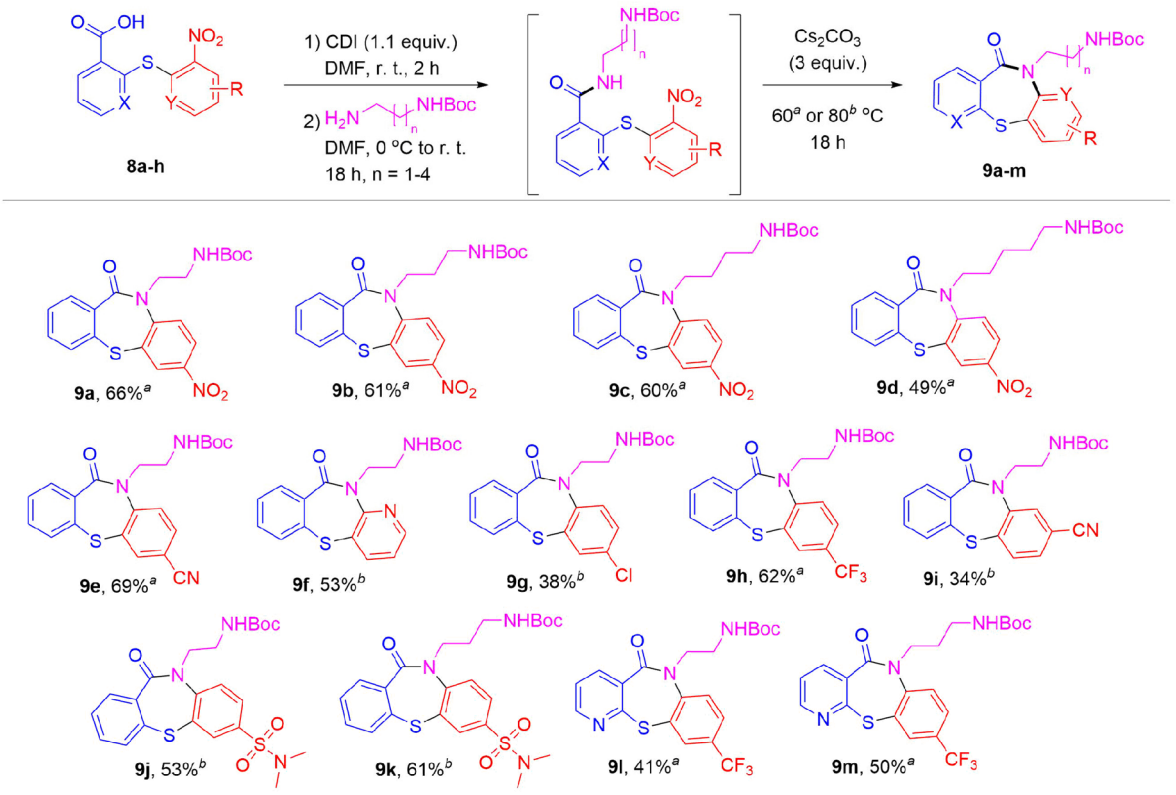
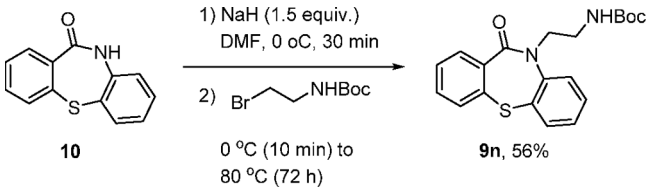
Scheme 2. Preparation of [1,4]Thiazepin-5-ones 9a−m



Scheme 3. Synthesis of Compound 9n from the Commercially Available Precursor



graphic purification or simple crystallization, generally good yields of sulfones **11a−n** throughout the set (Scheme 4).

At this point, we were set to involve [1,4]thiazepin-5-ones **9a−n** and their sulfone counterparts **11a−n** in the HIRE-type ring expansion reactions. To this end, the Boc protecting group was removed, and the resulting hydrochloride salt was dissolved in 50% aqueous methanol and treated with 3 equiv of 10% aqueous sodium hydroxide solution. For nearly all substrates, conversion of the starting material was complete in 18 h at room temperature leading to the isolated yields of ring-expanded thioethers **12** and sulfones **13** summarized in Scheme 5. Notable exceptions were presented by substrates **9g** and **9n** carrying an electron-neutral nitrogen-bound benzene ring. For these substrates, full conversion was only achieved at 60 °C over 7 and 30 days, respectively, leading to moderate yields of ring-expanded products **12g** and **12n**. This observation, as well as the fact that respective sulfones **11g** and **11n** gave excellent yields of the ring-expanded products **13g** and **13n** after 18 h at room temperature, is very much in line with the expected manifestation of the electronic effects on the HIRE rate[11] and our initial expectations (*vide supra*).

Besides the difference in HIRE rates (discussed below), sulfones generally gave ring-expanded lactams **13** in yields that are comparable or higher than those for ring-expanded thioethers **12**. One notable exception is sulfone lactam **13i** which was obtained in only 15% yield in contrast to its thioether analog **12i**. The major competing process in this case (as well as in other cases discussed below) was the hydrolysis of the lactam ring in **11i**. Competing lactam hydrolysis was also the predominant process observed for lactams **9c−d** and **11c−d** for which the desired homo[2/3]-HIRE[8] side chain insertion process was likely much slower for entropic reasons. In the case of lactams **9d** and **11c−d**, the respective lactam hydrolysis products **14a−c** were isolated in high yields and characterized by ^{1}H and ^{13}C NMR spectroscopy, high-resolution mass spectrometry, and single-crystal X-ray crystallography (**14b−c**) (Scheme 6).

In order to firmly establish that the rates of the HIRE (and homo^{x}-HIRE) process are generally higher for sulfones **11** as compared to thioethers **9**, we performed a spectrophotometric study of the reaction kinetics and calculated reaction rate constants (k_{obs}, s^{-1}) for the room-temperature reactions in which no competing substrate hydrolysis was observed, i.e. for all substrates **9** and **11** except for **9(11)c−d** and **9(11)i**. Substrates **9g** and **9n** were also excluded since they underwent an appreciable conversion only at 60 °C (see Supporting Information for details). These data are summarized in Table 1.

As it is evident from comparing the reaction rates presented in Table 1, sulfones **11** underwent the HIRE (homo-HIRE) process at substantially higher rates as compared to thioethers **9**. Homo-HIRE reactions (leading to 11-membered ring formation) were generally markedly slower compared to HIRE (*cf.* **9(11)a** and **9(11)b**, **9(11)j**, and **9(11)k**). However, introduction of a nitrogen atom into the carbonyl-bound aromatic ring seemed to make the difference in rates less

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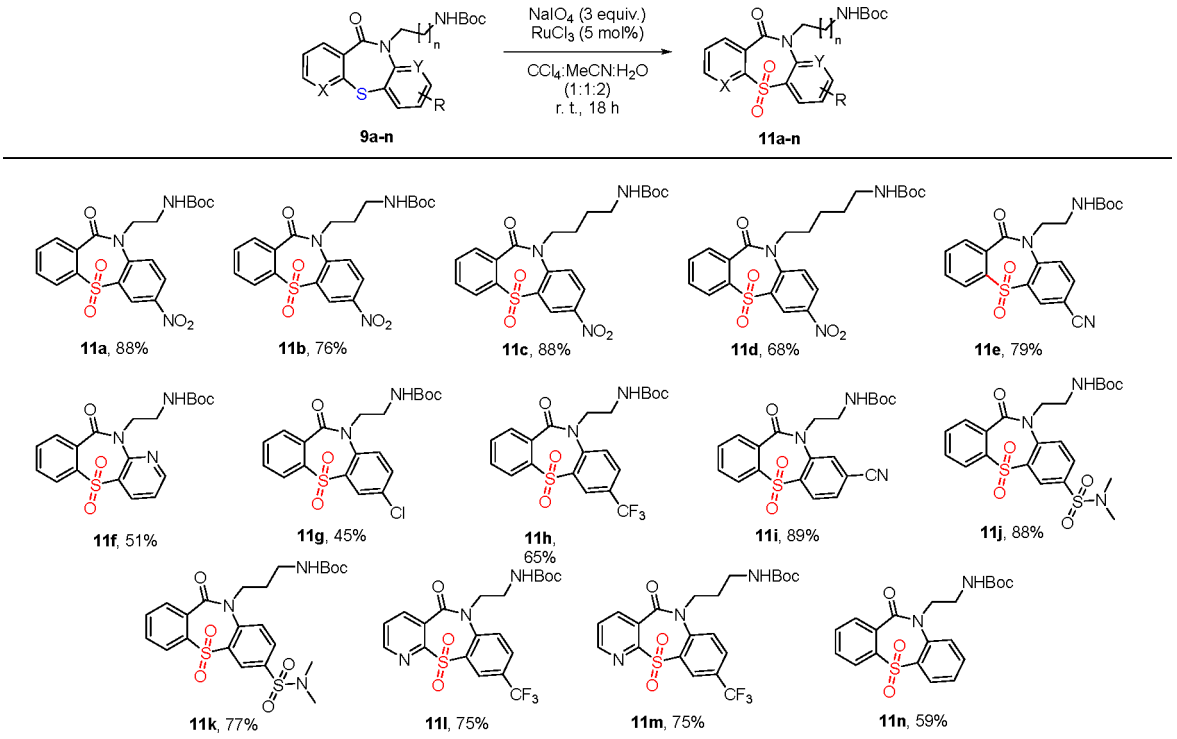
Scheme 4. S → SO_2 Oxidation of [1,4]Thiazepin-5-ones 9a−n



pronounced (*cf.* **9(11)l** and **9(11)m**). At the same time, pyrido compounds **9(11)l** reacted at the same rates as their phenyl analogs **9(11)f**, thereby confirming, again, that the substitution in the carbonyl-bound aromatic ring has a less pronounced effect on the rate of the ring expansion.[11]

A significant difference between ring-expanded thioethers **12** and sulfones **13** that we noted was in the ratio of what we presumed (and later confirmed) to be amide bond *cis*- and *trans*-isomers observed in the ^{1}H NMR spectra of these compounds. For instance, while compound **12a** displayed an ∼1:12 *cis*/*trans* ratio, for compound **13a** the proportion of the *cis*-isomer was markedly higher and thus the *cis*/*trans* ratio was 2:3 (Figure 2). We hypothesized that the apparent stabilization of the *cis*-isomer in **13a** could be due to the possible involvement of the sulfone oxygen atoms in intramolecular hydrogen bonding.[12]

We studied this phenomenon in detail for **13a** (Figure 3). Upon acquiring its EXSY spectrum in DMSO-d_6, exchange crosspeaks were observed (Figure 3A) suggesting the presence of two isomers in slow exchange. Interproton distances were deduced for each isomer based on NOE crosspeak intensities (t_{mix}: 500 ms at 400 MHz), using the *ortho* aromatic protons as the internal reference (2.44 Å). We observed 2.9 and 3.3 Å H^{11}−H^7 interatomic distances for the major and minor isomers, respectively. In addition, no H^{11}−H^{6a} NOE crosspeaks were observed for the major isomer, whereas strong H^{11}−H^{6a} crosspeaks, corresponding to 3.1 Å, were detected for the minor isomer. This suggested amide *cis*-*trans* isomerization to be the likely cause of the signal doubling, which corroborated the hypothesis by the large chemical shift differences of the amide carbon and nitrogen atoms of the isomers ($\Delta\delta_{CO}$ 1.9 ppm in ^{13}C and $\Delta\delta_{NH}$ 4.1 ppm in ^{15}N NMR; Figure 3B and C). Monte Carlo conformational searches using the OPLS3e force field with restrained C−CO−N−C dihedral angles, 0° for *cis* and 180° for *trans*, were performed to generate two ensembles, within a 42 kJ/mol energy interval from the global minimum. The Boltzmann weighted average H^{11}−H^7 distances differed 0.6 Å for the *cis* (3.8 Å) and *trans* (3.2 Å) isomers and 1.6 Å for H^{11}−H^{6a} (*cis* 3.2 Å, *trans* 4.8 Å). This reveals that the major set of signals of **13a** corresponds to the *trans* isomer.

The amide temperature coefficients $\Delta\delta/\Delta T_{NHcis}$ −0.1 ppb/K and $\Delta\delta/\Delta T_{NHtrans}$ −0.8 ppb/K (see Supporting Information) indicated that the amide proton of both isomers were solvent shielded, expectably by an intramolecular hydrogen bond to a sulfonyl oxygen, which rigidifies the macrocycle and thereby hinders amide bond isomerization.[13] The sharper line width of the ^{1}H NMR signals of **13a** as compared to **12a** (Figure 2) corroborates the formation of an intramolecular aniline to sulphonyl hydrogen bond in **13a**. The anilinic NH of **12a** lacks such stabilization and therefore is in a faster exchange (Figure 3E and F). The temperature dependence of the H^{11} and H^{16} chemical shifts of the *cis* and *trans* isomers of **13a** followed a classical slow exchange pattern (Figure 3D).[14] Hence, we observed signal broadening at 55−65 °C, compatible with intermediate exchange, whereas sharp signals and a decrease of the intensity of the minor signal set above 85 °C.[15] In agreement with the NMR observations an NH···O intramolecular hydrogen bond (d_{HO} 2.2 Å) was observed by X-ray diffraction for **13a**, which crystallized in its *cis* isomer (Figure 3F). It should be noted that the observation of a single solid state geometry despite the existence of an ensemble of conformers in solution is not unusual.[16,17]

■ CONCLUSIONS

In summary, we have investigated HIRE-type ring expansion in di(hetero)arene-fused [1.4]thiazepinones and in their S → SO_2 oxidized analogs. In accordance with the general mechanistic understanding and the previously undertaken mechanistic study of the electronic effects on the rate of the

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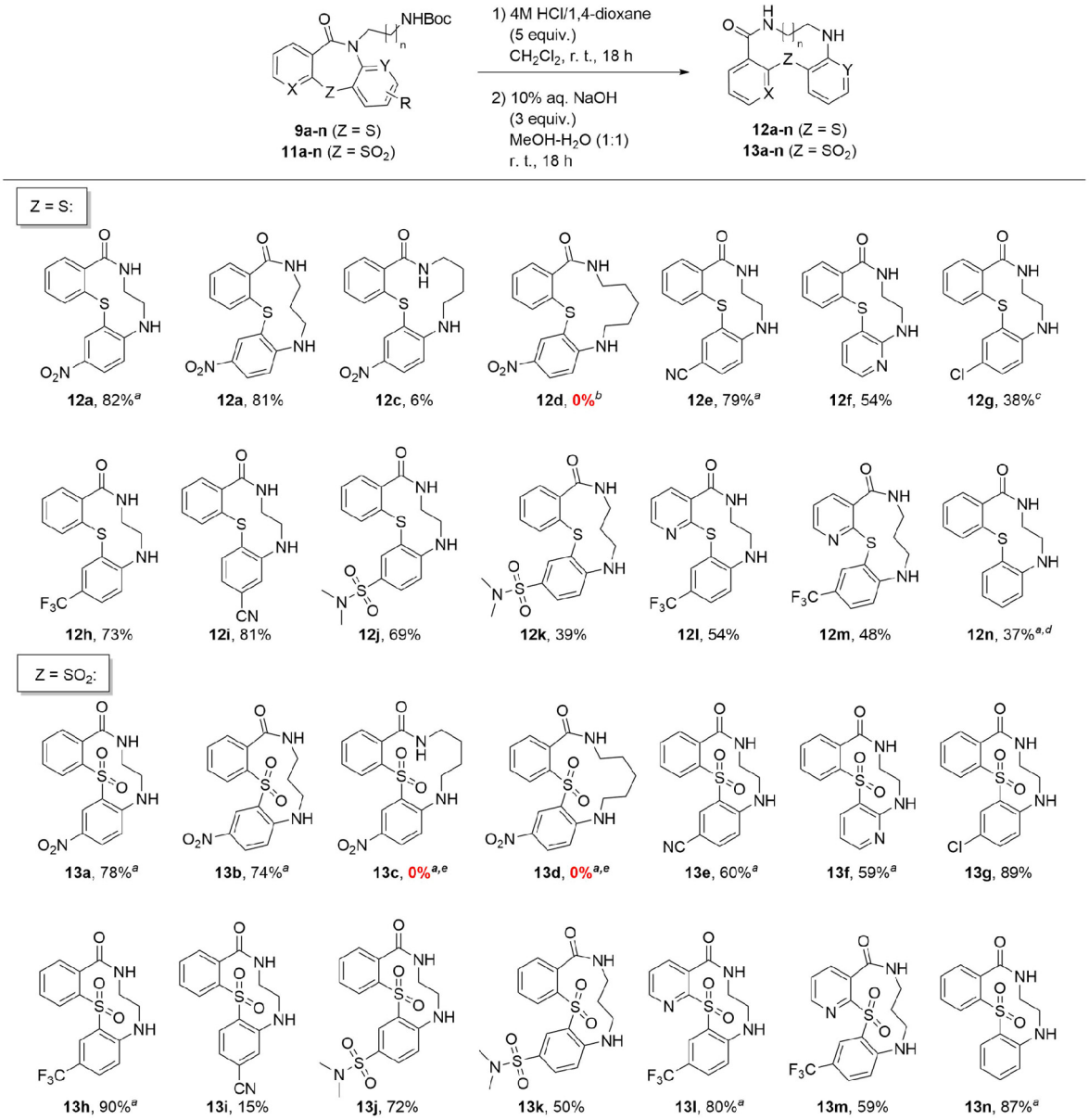
Scheme 5. HIRE Reaction of [1,4]Thiazepin-5-ones 9a−n and Their 1,1-Dioxide Counterparts 11a−n



[a]X-ray crystallographic structure obtained. [b]Lactam hydrolysis product isolated and characterized. [c]Reaction conducted over 7 days at 60 °C. [d]Reaction conducted over 30 days at 60 °C. [e]X-ray crystallographic structure of the lactam hydrolysis product obtained.

HIRE reaction, sulfones underwent the ring expansion at a markedly faster rate compared to thioethers. Besides the effect on the HIRE reaction rate, oxidation to sulfones was shown to have a profound influence on the conformational behavior of the ring-expanded products. Specifically, in contrast to thioethers, sulfones were shown to exist as an equilibrium mixture of amide-bond *cis*- and *trans*-isomers. The energy barrier between these isomeric forms is heightened due to the existence of an intramolecular hydrogen bond involving the sulfone oxygen atom. These findings significantly expand our knowledge base concerning the preparation as well as conformational rigidity/flexibility of medium-sized rings as scaffolds for drug discovery.

EXPERIMENTAL SECTION

General. NMR spectroscopic data were recorded with a 400 spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for $^{13}C\{^{1}H\}$) and a 500 spectrometer (500.03 for ^{1}H and 125 MHz for $^{13}C\{^{1}H\}$) in DMSO-d_6 and in $CDCl_3$ and were referenced to residual solvent proton signals (δ_H = 2.50 and 7.26 ppm, respectively) and solvent carbon signals (δ_C = 39.5 and 77.0 ppm, respectively). Mass spectra were recorded with an HRMS-ESI-qTOF spectrometer (electrospray ionization mode, positive ion detection). Single crystal X-ray data were obtained using Agilent Technologies SuperNova Atlas and an Agilent Technologies Xcalibur Eos diffractometers at a temperature of 100 K. Spectrophotometric measurements were performed on a UV-1800 Shimadzu double beam spectrophotometer (Japan) using 10.00 mm quartz cells. Flash column chromatography on silica was performed with a Biotage Isolera Prime instrument using Biotage SNAP KP-Sil 25g cartridges. TLC was performed with Macherey-Nagel ≪Alugram Sil G/UV254≫ plates. Melting points were determined with a Stuart SMP50 instrument in open capillary tubes and are uncorrected. All reactions were performed in air, unless otherwise noted. Toluene was distilled from sodium and stored over MS 4 Å. Ethyl acetate and DMSO were dried over MS 4 Å.

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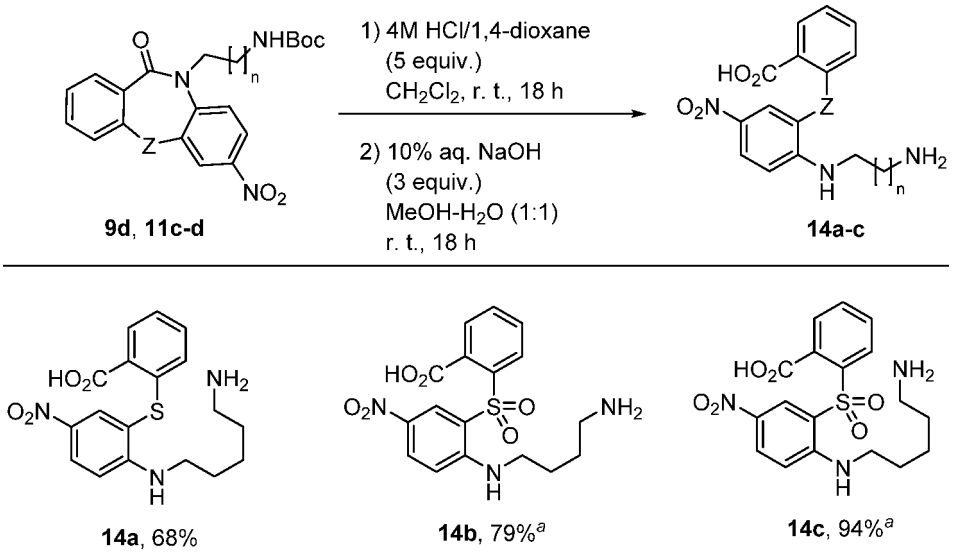
Scheme 6. Predominant Hydrolysis Observed in Attempted Homo$^{2/3}$-HIRE Transformation of Lactams 9d and 10c−d



[a]Structure confirmed by X-ray crystallography.

Table 1. Experimentally Determined Rate Constants (k_{obs}·10^4 s^{-1}) for the HIRE Reaction of Substrates 9 and 11

	a	b	e	f	g	h	j	k	l	m	n
9	18	4.2	9	2.6	–	2.5	5	0.7	2.5	1.3	–
11	258	107	86	37	12	39	63	14	39	32	5

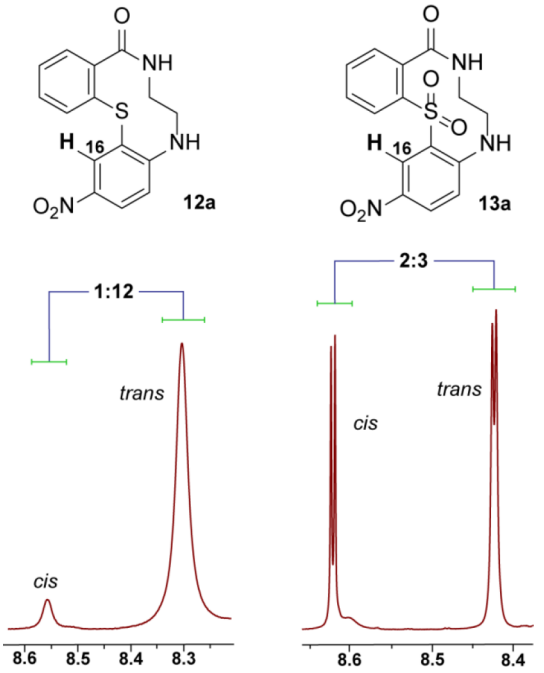


Figure 2. ^{1}H NMR spectra of compounds **12a** and **13a** show two sets of signals with 1:12 and 2:3 ratios, respectively. This signal doubling is shown to originate from the *cis* and *trans* amide isomers.

General Procedure for the Preparation of Carboxylic Acids 8a−h. To a solution of acid **6a,b** (10.0 mmol) and *o*-nitro halo(hetero)arenes **7** (10.0 mmol) in 50 mL of propan-2-ol DIPEA (3.82 mL, 22.0 mmol) was added. The resulting mixture was heated in an oil bath at reflux overnight. Then the solvent was evaporated. The residue was diluted with H_2O (100 mL) and acidified with AcOH (5 mL). The precipitated product was filtered through a glass filter and washed with water. The solid residue was dried at 60 °C overnight.

*2-((2,4-Dinitrophenyl)thio)benzoic Acid (**8a**).* Yield 3.01 g, 94%; yellow solid; mp 179−181 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.65−13.14 (br s, 1H), 8.90 (d, J = 2.5 Hz, 1H), 8.35 (dd, J = 9.0, 2.6 Hz, 1H), 8.08−7.91 (m, 1H), 7.79−7.64 (m, 3H), 7.13 (d, J = 9.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.7, 145.8, 145.3, 144.9, 137.2, 137.0, 133.4, 131.4, 131.3, 131.2, 129.6, 128.0, 121.5 ppm. HRMS (ESI), m/z calcd for $C_{13}H_7N_2O_6S^-$ [M−H]$^-$ 319.0019, found 319.0028.

*2-((4-Cyano-2-nitrophenyl)thio)benzoic Acid (**8b**).* Yield 2.73 g, 91%; yellow solid; mp 184−186 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.57−13.11 (br s, 1H), 8.74 (d, J = 1.8 Hz, 1H), 8.02−7.91 (m, 2H), 7.71−7.60 (m, 3H), 7.06 (d, J = 8.5 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.8, 146.1, 143.5, 136.9 (2C), 136.7, 133.3, 131.3, 131.2, 131.0, 130.2, 129.9, 117.4, 109.1 ppm. HRMS (ESI), m/z calcd for $C_{14}H_7N_2O_4S^-$ [M−H]$^-$ 299.0121, found 299.0133.

*2-((3-Nitropyridin-2-yl)thio)benzoic Acid (**8c**).* Yield 1.60 g, 58%; light orange solid; mp 156−158 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39−12.81 (br s, 1H), 8.57 (dd, J = 4.6, 1.6 Hz, 1H), 7.89 (dd, J = 6.6, 2.5 Hz, 1H), 7.73−7.51 (m, 4H), 7.43 (dd, J = 8.3, 4.6 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 167.9, 154.1, 142.3, 137.4, 136.6, 134.6, 133.7, 132.2, 130.8, 130.0, 126.5, 121.3 ppm. HRMS (ESI), m/z calcd for $C_{12}H_7N_2O_4S^-$ [M−H]$^-$ 275.0121, found 275.0117.

*2-((4-Chloro-2-nitrophenyl)thio)benzoic Acid (**8d**).* Yield 1.95 g, 63%; yellow solid; mp 164−166 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.70−13.13 (br s, 1H), 8.28 (d, J = 2.3 Hz, 1H), 8.03 (dd, J = 7.8, 1.7 Hz, 1H), 7.92 (dd, J = 7.6, 1.7 Hz, 1H), 7.73 (dd, J = 8.6, 2.4 Hz, 1H), 7.61−7.54 (m, 2H), 7.22 (d, J = 8.7 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.9, 149.3, 139.4, 134.6, 134.2, 133.9, 133.8, 133.1, 132.5, 131.2, 129.1, 126.4, 125.3 ppm. HRMS (ESI), m/z calcd for $C_{13}H_7ClNO_4S^-$ [M−H]$^-$ 307.9790, found 307.9794.

*2-((2-Nitro-4-(trifluoromethyl)phenyl)thio)benzoic Acid (**8e**).* Yield 2.81 g, 82%; yellow solid; mp 179−181 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43−13.30 (br s, 1H), 8.51 (d, J = 2.0 Hz, 1H),

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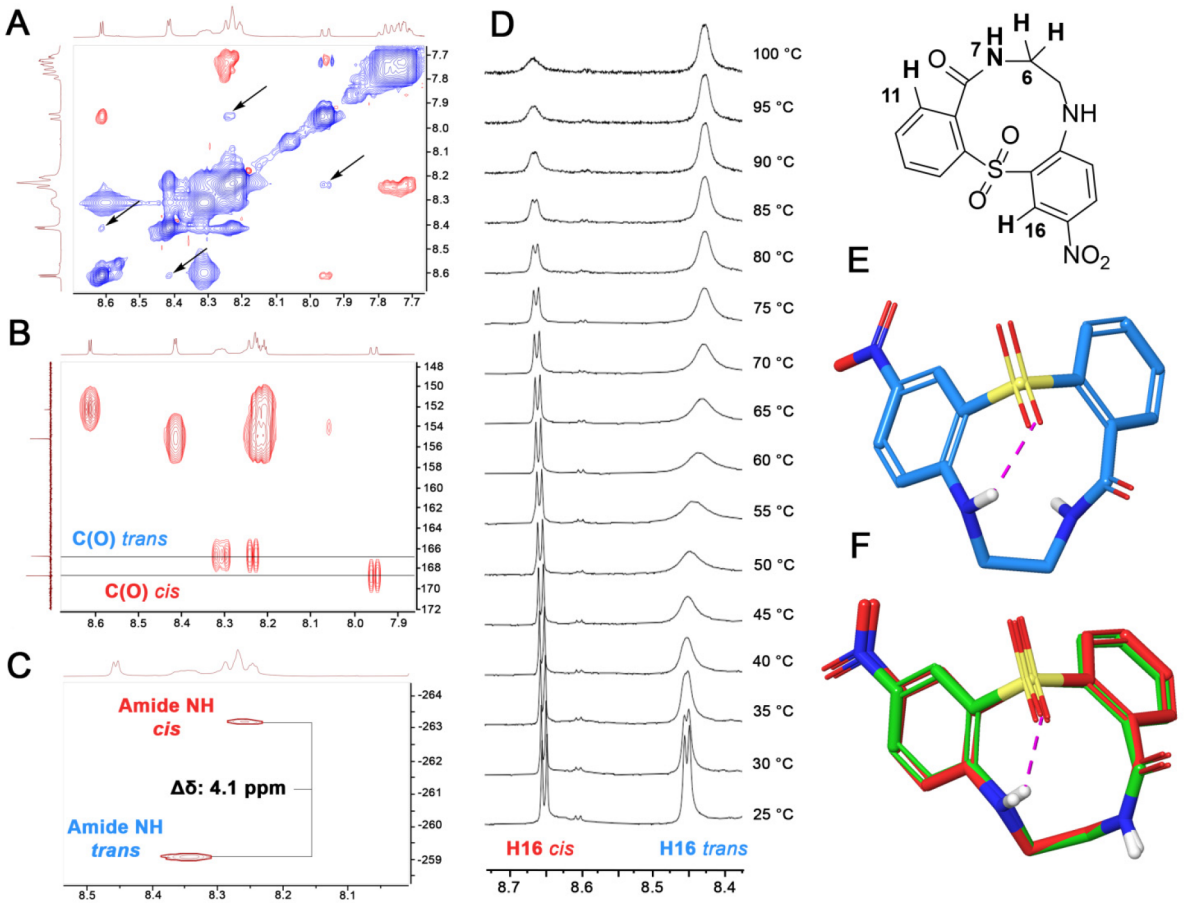

Figure 3. (A) EXSY spectrum of **13a** showing exchange cross peaks (arrows) indicating both sets of signals originating from the same molecule. (B) HMBC spectrum showing chemical shift difference of the carbonyl carbon of the cis and trans isomer. (C) ^{15}N HSQC spectrum showing chemical shift difference of the amide nitrogen of the cis and trans isomer. (D) Variable temperature NMR recorded in DMSO-d_6 for **13a** showing peaks of the cis isomer decreasing with temperature and peak shape alternation of the trans peaks of H^{11}. (E) Lowest energy transisomer as calculated by a Monte Carlo conformational search. Intramolecular hydrogen bond indicated by a dashed line. (F) The overlaid geometries of cis-**13a** observed by X-ray crystallography (green) in the solid state and by NMR in DMSO-d_6 solution (red), with the isomer-stabilizing intramolecular hydrogen bond being highlighted with a dashed line.

7.98−7.91 (m, 2H), 7.68−7.59 (m, 3H), 7.18 (d, J = 8.5 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.9, 146.5, 141.9, 136.5(2C), 133.2, 132.0, 131.2, 130.7(2C), 130.4 (q, J = 5.2 Hz), 127.1 (q, J = 33.8 Hz), 123.5 (q, J = 272.4 Hz), 123.1 (q, J = 4.4 Hz) ppm. HRMS (ESI), m/z calcd for $C_{14}H_7F_3NO_4S^-$ [M−H]$^-$ 342.0053, found 342.0059.

*2-((5-Cyano-2-nitrophenyl)thio)benzoic Acid (**8f**).* Yield 2.69 g, 90%; yellow solid; mp 179−181 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.51−13.33 (br s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.04 (dd, J = 8.4, 1.8 Hz, 1H), 7.95 (dd, J = 7.6, 1.8 Hz, 1H), 7.70 (d, J = 1.8 Hz, 1H), 7.63−7.53 (m, 2H), 7.34 (dd, J = 7.6, 1.6 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.9, 151.4, 137.1, 134.6, 133.7, 133.6, 133.5, 133.3, 132.3, 131.3, 129.3, 126.6, 117.3, 116.7 ppm. HRMS (ESI), m/z calcd for $C_{14}H_7N_2O_4S^-$ [M−H]$^-$ 299.0132, found 299.0130.

*2-((4-(N,N-Dimethylsulfamoyl)-2-nitrophenyl)thio)benzoic Acid (**8g**).* Yield 3.10 g, 81%; yellow solid; mp 171−173 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40−13.28 (br s, 1H), 8.40 (d, J = 2.0 Hz, 1H), 7.98−7.93 (m, 1H), 7.89 (dd, J = 8.6, 2.1 Hz, 1H), 7.70−7.63 (m, 3H), 7.17 (d, J = 8.6 Hz, 1H), 2.67 (s, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.8, 146.1, 142.7, 136.8, 136.7, 133.3, 133.2, 132.1, 131.6, 131.3, 130.9, 130.4, 125.0, 38.0(2C) ppm. HRMS (ESI), m/z calcd for $C_{15}H_{14}N_2O_6S_2$[M + H]$^+$ 383.0366, found 383.0369.

*2-((2-Nitro-4-(trifluoromethyl)phenyl)thio)nicotinic Acid (**8h**).* Yield 1.76 g, 51%; dark yellow solid; mp 166−168 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.22−13.63 (br s, 1H), 8.55−8.50 (m, 1H), 8.47 (d, J = 1.8 Hz, 1H), 8.42 (dd, J = 4.7, 1.8 Hz, 1H), 8.31 (dd, J = 7.8, 1.8 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 7.8, 4.7 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 166.8, 158.0, 152.6, 144.3, 139.9, 139.5, 139.0, 131.9, 130.5 (q, J = 33.6 Hz), 129.7 (q, J = 3.9 Hz), 129.3 (q, J = 3.7 Hz), 123.3 (q, J = 272.7 Hz), 115.5 ppm. HRMS (ESI), m/z calcd for $C_{13}H_7F_3N_2O_4SNa$ [M + Na]$^+$ 366.9971, found 366.9970.

General Procedure the Preparation of [1,4]Thiazepin-5-ones 9a−m. To a solution of acid **8a−h** (2.00 mmol) in 20 mL of DMF CDI (360 mg, 2.20 mmol) was added. The mixture was stirred at room temperature for 1.5−2 h. Afterward, the mixture was cooled to 0 °C and *mono-Boc*-protected diaminoalkane (2.00 mmol) was added. The resulting mixture was stirred at the same temperature for 1 h and then was stirred overnight at room temperature. Then Cs_2CO_3 (1950 mg, 6.00 mmol) was added, and the mixture was stirred at the corresponding temperature (60 °C for **9a−e**, **9h**, **9l−m**; 80 °C for **9f−g**, **9i−k**) in an oil bath for 24 h. The reaction progress was monitored by TLC analysis (toluene/acetone/hexane = 3/5/5). Then the solvent was evaporated. The residue was diluted with water (50 mL) and extracted with CH_2Cl_2 (60 mL). The organic layer was separated, washed with 1% NaOH aqueous solution (3 × 30 mL) and water (2 × 20 mL), and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The resulting compounds were purified by column chromatography at CH_2Cl_2/EtOAc = 20/1.

*tert-Butyl (2-(7-Nitro-11-oxodibenzo[b,f][1,4]thiazepin-10(11H)-yl)ethyl)carbamate (**9a**).* Yield 548 mg, 66%; beige solid; R_f = 0.17

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(CH_2Cl_2/EtOAc = 20/1); mp 120−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 2.7 Hz, 1H), 8.20 (dd, J = 8.9, 2.7 Hz, 1H), 7.75−7.68 (m, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.53−7.46 (m, 1H), 7.44−7.33 (m, 2H), 5.05−4.92 (br s, 1H), 4.66 (dt, J = 13.5, 5.1 Hz, 1H), 3.99 (dt, J = 13.5, 6.8 Hz, 1H), 3.58−3.38 (m, 2H), 1.32 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.3, 155.7, 149.7, 144.7, 137.5, 137.2, 131.6(2C), 131.3, 129.4(2C), 128.2, 126.4, 125.0, 79.5, 51.5, 39.2, 28.3(3C) ppm. HRMS (ESI), m/z calcd for $C_{20}H_{21}N_3O_5SNa$ [M + Na]$^+$ 438.1094, found 438.1081.

*tert-Butyl (3-(7-Nitro-11-oxodibenzo[b,f][1,4]thiazepin-10(11H)-yl)propyl)carbamate (**9b**).* Yield 524 mg, 61%; light beige solid; R_f = 0.25 (CH_2Cl_2/EtOAc = 20/1); mp 110−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 2.7 Hz, 1H), 8.19 (dd, J = 8.9, 2.6 Hz, 1H), 7.72−7.67 (m, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.52−7.46 (m, 1H), 7.42−7.33 (m, 2H), 5.06−4.95 (br s, 1H), 4.90−4.78 (m, 1H), 3.80−3.67 (m, 1H), 3.44−3.29 (m, 1H), 3.26−3.13 (m, 1H), 1.99−1.86 (m, 1H), 1.79−1.69 (m, 1H), 1.43 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.5, 156.0, 149.0, 144.8, 137.9, 137.6, 137.4, 131.5, 131.4, 131.2, 129.3, 128.5, 126.2, 124.8, 79.2, 48.7, 37.5, 28.6, 28.4(3C) ppm. HRMS (ESI), m/z calcd for $C_{21}H_{23}N_3O_5SNa$ [M + Na]$^+$ 452.1251, found 452.1262.

*tert-Butyl (4-(7-Nitro-11-oxodibenzo[b,f][1,4]thiazepin-10(11H)-yl)butyl)carbamate (**9c**).* Yield 53 mg, 60%; brown oil; R_f = 0.22 (CH_2Cl_2/EtOAc = 20/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 2.6 Hz, 1H), 8.19 (dd, J = 8.9, 2.6 Hz, 1H), 7.75−7.67 (m, 1H), 7.52 (d, J = 8.9 Hz, 1H), 7.50−7.44 (m, 1H), 7.40−7.33 (m, 2H), 4.82−4.68 (m, 1H), 4.65−4.47 (br s, 1H), 3.77−3.64 (m, 1H), 3.13 (q, J = 6.6 Hz, 2H), 1.80−1.66 (m, 2H), 1.64−1.53 (m, 2H), 1.43 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.1, 156.0, 149.3, 144.6, 137.7, 137.6, 137.4, 131.6, 131.4, 131.1, 129.2, 128.4, 126.1, 124.7, 79.2, 51.0, 39.9, 28.4(3C), 27.5, 25.5 ppm. HRMS (ESI), m/z calcd for $C_{22}H_{25}N_3O_5SNa$ [M + Na]$^+$ 466.1407, found 466.1390.

*tert-Butyl (5-(7-Nitro-11-oxodibenzo[b,f][1,4]thiazepin-10(11H)-yl)pentyl)carbamate (**9d**).* Yield 448 mg, 49%; brown oil; R_f = 0.22 (CH_2Cl_2/EtOAc = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 2.6 Hz, 1H), 8.19 (dd, J = 8.9, 2.7 Hz, 1H), 7.75−7.67 (m, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.50−7.44 (m, 1H), 7.42−7.32 (m, 2H), 4.82−4.68 (m, 1H, CH), 4.63−4.46 (br s, 1H), 3.74−3.61 (m, 1H), 3.10 (q, J = 6.5 Hz, 2H), 1.81−1.60 (m, 2H), 1.57−1.35 (m, 13H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.1, 156.0, 155.9, 149.3, 144.6, 137.7, 137.4, 131.7, 131.4, 131.1, 129.2, 128.5, 126.1, 124.7, 51.1, 40.3, 29.6, 28.4(3C), 27.8, 23.9, 22.5 ppm. HRMS (ESI), m/z calcd for $C_{23}H_{27}N_3O_5SNa$ [M + Na]$^+$ 480.1564, found 480.1558.

*tert-Butyl (2-(7-Cyano-11-oxodibenzo[b,f][1,4]thiazepin-10-(11H)-yl)ethyl)carbamate (**9e**).* Yield546 mg, 69%; white solid; R_f = 0.21 (CH_2Cl_2/EtOAc = 20/1); mp 146−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 1.9 Hz, 1H), 7.74−7.68 (m, 1H), 7.63 (dd, J = 8.5, 2.0 Hz, 1H), 7.53−7.45 (m, 2H), 7.43−7.34 (m, 2H), 5.04−4.94 (br s, 1H), 4.69−4.59 (m, 1H), 4.01−3.88 (m, 1H), 3.61−3.38 (m, 2H), 1.34 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.4, 155.7, 148.2, 137.5, 137.3, 137.2, 136.7, 133.4, 131.6, 131.5, 131.2, 129.3, 126.7, 117.2, 110.2, 79.5, 51.4, 39.2, 28.3(3C) ppm. HRMS (ESI), m/z calcd for $C_{21}H_{21}N_3O_3SNa$ [M + Na]$^+$ 418.1196, found 418.1194.

*tert-Butyl (2-(10-Oxobenzo[f]pyrido[3,2-b][1,4]thiazepin-11-(10H)-yl)ethyl)carbamate (**9f**).* Yield 394 mg, 53%; beige solid; R_f = 0.16 (CH_2Cl_2/EtOAc = 10/1); mp 93−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, J = 4.7, 1.9 Hz, 1H), 7.93 (dd, J = 7.7, 1.8 Hz, 1H), 7.74−7.68 (m, 1H), 7.50−7.43 (m, 1H), 7.40−7.32 (m, 2H), 7.10 (dd, J = 7.7, 4.7 Hz, 1H), 5.53−5.41 (br s, 1H), 4.58−4.47 (m, 1H), 4.47−4.35 (m, 1H), 3.62−3.42 (m, 2H), 1.39 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.7, 155.9, 148.8, 141.8, 138.1, 137.1, 131.8(2C), 131.2, 130.7, 130.1, 129.0, 121.4, 78.9, 48.6, 39.6, 28.4(3C) ppm. HRMS (ESI), m/z calcd for $C_{19}H_{21}N_3O_3SNa$ [M + Na]$^+$ 394.1196, found 394.1199.

*tert-Butyl (2-(7-Chloro-11-oxodibenzo[b,f][1,4]thiazepin-10-(11H)-yl)ethyl)carbamate (**9g**).* Yield 308 mg, 38%; white solid; R_f = 0.18 (CH_2Cl_2/EtOAc = 20/1); mp 118−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, J = 7.1, 2.1 Hz, 1H), 7.62 (t, J = 1.3 Hz, 1H), 7.47 (dd, J = 7.2, 1.8 Hz, 1H), 7.40−7.29 (m, 4H), 5.06 (t, J = 5.9 Hz, 1H), 4.73−4.62 (m, 1H), 3.90−3.77 (m, 1H), 3.58−3.33 (m, 2H), 1.35 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.7, 155.8, 142.6, 138.1, 137.8, 137.6, 132.7, 131.6, 131.4, 131.2, 131.1, 130.1, 129.0, 127.1, 79.3, 51.1, 39.2, 28.3(3C) ppm. HRMS (ESI), m/z calcd for $C_{20}H_{21}ClN_2O_3S$ [M + H]$^+$ 405.1034, found 405.1026.

*tert-Butyl (2-(11-Oxo-7-(trifluoromethyl)dibenzo[b,f][1,4]-thiazepin-10(11H)-yl)ethyl)carbamate (**9h**).* Yield 544 mg, 62%; white solid; R_f = 0.26 (CH_2Cl_2/EtOAc = 20/1); mp 143−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 2.1 Hz, 1H), 7.75−7.70 (m, 1H), 7.60 (dd, J = 8.5, 2.1 Hz, 1H), 7.53−7.46 (m, 2H), 7.41−7.32 (m, 2H), 5.04 (t, J = 6.2 Hz, 1H), 4.74−4.64 (m, 1H), 4.00−3.88 (m, 1H), 3.61−3.35 (m, 2H), 1.31 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.6, 155.7, 147.3, 137.9, 137.6, 136.7, 131.5, 131.3, 131.2, 130.2 (q, J = 3.6 Hz), 129.1, 128.5 (q, J = 32.5 Hz), 126.9 (q, J = 3.1 Hz), 126.4, 123.2 (q, J = 272.7 Hz), 79.3, 51.4, 39.3, 28.2(3C) ppm. HRMS (ESI), m/z calcd for $C_{21}H_{21}F_3N_2O_3SNa$ [M + Na]$^+$ 461.1117, found 461.1104.

*tert-Butyl (2-(8-Cyano-11-oxodibenzo[b,f][1,4]thiazepin-10-(11H)-yl)ethyl)carbamate (**9i**).* Yield 269 mg, 34%; white solid; R_f = 0.19 (CH_2Cl_2/EtOAc = 20/1); mp 203−205 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.71 (m, 2H), 7.69−7.64 (m, 1H), 7.47 (dd, J = 7.5, 1.6 Hz, 1H), 7.44−7.32 (m, 3H), 5.09−4.92 (br s, 1H), 4.71 (dt, J = 13.6, 5.3 Hz, 1H), 3.84 (dt, J = 13.7, 6.0 Hz, 1H), 3.58−3.34 (m, 2H), 1.35 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.4, 155.7, 144.9, 142.0, 137.4, 137.3, 134.0, 131.6, 131.4, 131.3, 129.6, 129.5, 129.3, 117.2, 113.9, 79.5, 51.6, 39.1, 28.3(3C) ppm. HRMS (ESI), m/z calcd for $C_{21}H_{21}N_3O_3SNa$ [M + Na]$^+$ 418.1196, found 418.1211.

*tert-Butyl (2-(7-(N,N-Dimethylsulfamoyl)-11-oxodibenzo[b,f]-[1,4]thiazepin-10(11H)-yl)ethyl)carbamate (**9j**).* Yield 506 mg, 53%; beige solid; R_f = 0.15 (CH_2Cl_2/EtOAc = 20/1); mp 165−167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 2.1 Hz, 1H), 7.76−7.69 (m, 2H), 7.54 (d, J = 8.5 Hz, 1H), 7.52−7.45 (m, 1H), 7.42−7.33 (m, 2H), 5.09−5.01 (br s, 1H), 4.71−4.59 (m, 1H), 3.99−3.89 (m, 1H), 3.62−3.50 (m, 1H), 3.50−3.38 (m, 1H), 2.77 (s, 6H), 1.37 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.6, 155.8, 147.8, 137.7, 137.5, 137.0, 134.1, 132.3, 131.6, 131.4, 131.3, 129.2, 129.1, 126.3, 79.5, 51.6, 39.1, 37.8(2C), 28.3(3C) ppm. HRMS (ESI), m/z calcd for $C_{22}H_{27}N_3O_5S_2Na$ [M + Na]$^+$ 500.1284, found 500.1280.

*tert-Butyl(3-(7-(N,N-Dimethylsulfamoyl)-11-oxodibenzo[b,f]-[1,4]thiazepin-10(11H)-yl)propyl)carbamate (**9k**).* Yield 600 mg, 61%; yellow solid; R_f = 0.16 (CH_2Cl_2/EtOAc = 20/1); mp 169−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 2.1 Hz, 1H), 7.76−7.68 (m, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.47 (dd, J = 6.7, 2.2 Hz, 1H), 7.41−7.32 (m, 2H), 5.15−4.93 (br s, 1H), 4.88−4.75 (m, 1H), 3.78−3.65 (m, 1H), 3.43−3.29 (m, 1H), 3.26−3.13 (m, 1H), 2.77 (s, 6H), 1.98−1.82 (m, 1H), 1.80−1.66 (m, 1H), 1.45 (s, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.8, 156.0, 147.0, 137.8, 137.7(2C), 133.9, 132.5, 131.4, 131.3, 131.2, 129.1, 128.9, 126.2, 79.2, 48.6, 41.0, 37.9(2C), 28.6, 28.4(3C) ppm. HRMS (ESI), m/z calcd for $C_{23}H_{29}N_3O_5S_2Na$ [M + Na]$^+$ 514.1441, found 514.1443.

*tert-Butyl (2-(5-Oxo-9-(trifluoromethyl)benzo[b]pyrido[3,2-f]-[1,4]thiazepin-6(5H)-yl)ethyl)carbamate (**9l**).* Yield 360 mg, 41%; light beige solid; R_f = 0.11 (CH_2Cl_2/EtOAc = 20/1); mp 151−153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, J = 4.8, 1.9 Hz, 1H), 8.05−7.99 (m, 2H), 7.65 (dd, J = 8.5, 2.1 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.34 (dd, J = 7.8, 4.8 Hz, 1H), 5.03−4.89 (br s, 1H), 4.74−4.62 (m, 1H), 4.06−3.94 (m, 1H), 3.56−3.38 (m, 2H), 1.31 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.9, 157.7, 155.7, 151.1, 146.3, 140.0, 134.0, 133.8, 131.3 (q, J = 4.8 Hz), 129.0 (q, J = 33.4 Hz), 127.3 (q, J = 3.5 Hz), 126.3, 124.0, 123.0 (q, J = 272.6 Hz), 79.5, 51.2, 39.3, 28.8(3C) ppm. HRMS (ESI), m/z calcd for $C_{20}H_{20}F_3N_3O_3SNa$ [M + Na]$^+$ 462.1070, found 462.1071.

*tert-Butyl (3-(5-Oxo-9-(trifluoromethyl)benzo[b]pyrido[3,2-f]-[1,4]thiazepin-6(5H)-yl)propyl)carbamate (**9m**).* Yield 453 mg, 50%; beige solid; R_f = 0.15 (CH_2Cl_2/EtOAc = 20/1); mp 156−158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52−8.47 (m, 1H), 8.01 (dd, J = 7.7, 1.9 Hz, 2H), 7.64 (dd, J = 8.6, 2.2 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.33 (dd, J = 7.8, 4.7 Hz, 1H), 5.03−4.89 (br s, 1H), 4.90−4.74

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(m, 1H), 3.79−3.63 (m, 1H), 3.42−3.27 (m, 1H), 3.25−3.09 (m, 1H), 1.98−1.82 (m, 1H), 1.80−1.67 (m, 1H), 1.44 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.1, 157.8, 156.0, 151.1, 145.4, 139.9, 134.8, 133.9, 131.5 (q, J = 3.7 Hz), 129.0 (q, J = 33.6 Hz), 127.1 (q, J = 3.4 Hz), 126.1, 123.9, 123.0 (q, J = 272.7 Hz), 79.3, 48.4, 37.6, 29.7, 28.4(3C) ppm. HRMS (ESI), m/z calcd for $C_{21}H_{22}F_3N_3O_3SNa$ $[M + Na]^+$ 476.1226, found 476.1217.

Preparation of *tert*-Butyl (2-(11-oxodibenzo[*b*,*f*][1,4]-thiazepin-10(11*H*)-yl)ethyl)carbamate (9n). Sodium hydride (60% suspension in mineral oil, 0.451 g, 7.5 mmol) was added slowly to a solution of dibenzo[b,f][1,4]thioazepin-11(10H)-one (**10**) (1.136 g, 5.0 mmol) in DMF (8 mL) at 0 °C. The mixture was stirred at the same temperature for 30 min. Then *tert*-butyl (2-bromoethyl)carbamate (1.233 g, 5.5 mmol) was added. The resulting mixture was stirred at 0 °C for 10 min. Then the mixture was stirred at 80 °C in an oil bath for 72 h. The resulting mixture was cooled to room temperature. Then the solvent was evaporated. The residue was suspended in EtOAc and filtered. Then the filtrate was evaporated. The product was crystallized from diethyl ether and filtered. The resulting product was purified by column chromatography in CH_2Cl_2/EtOAc = 20/1 (R_f = 0.17). The yield 1.037 g; white solid; mp 107−109 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 7.2, 2.0 Hz, 1H), 7.64−7.59 (m, 1H), 7.47 (dd, J = 7.3, 1.7 Hz, 1H), 7.38−7.29 (m, 4H), 7.17−7.11 (m, 1H), 5.24−5.06 (br s, 1H), 4.77−4.66 (m, 1H), 3.91−3.78 (m, 1H), 3.61−3.47 (m, 1H), 3.44−3.29 (m, 1H), 1.34 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.0, 155.8, 143.9, 139.0, 138.0, 136.2, 133.1, 131.4, 131.0, 130.9, 129.9, 128.7, 126.6, 126.1, 79.2, 51.2, 39.2, 28.3(3C) ppm. HRMS (ESI), m/z calcd for $C_{20}H_{22}N_2O_3SNa$ $[M + Na]^+$ 393.1243, found 393.1242.

General Procedure the Preparation of [1,4]Thiazepin 5,5-Dioxides 11a−n. Sodium periodate (257 mg, 1.20 mmol, 3 equiv) was added to a stirred solution of [1,4]thiazepin-5-ones **9a−n** (0.40, 1 equiv) in a mixture of CCl_4 (10 mL) and water (20 mL). Once all of the $NaIO_4$ had dissolved, a catalytic amount of $RuCl_3$ (4.2 mg, 0.02 mmol) was added and the reaction mixture was stirred vigorously at room temperature overnight. It was extracted with CH_2Cl_2 (50 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The products **11a**, **11e−j**, **11l**, and **11n** were purified by crystallization from methanol, and the products **11b−d**, **11k**, **11** were purified by column chromatography in CH_2Cl_2/EtOAc = 20/1.

*tert-Butyl (2-(7-Nitro-5,5-dioxido-11-oxodibenzo[b,f][1,4]-thiazepin-10(11H)-yl)ethyl)carbamate (**11a**).* Yield 157 mg, 88%; white solid; mp 154−156 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 2.7 Hz, 1H), 8.42 (dd, J = 9.0, 2.7 Hz, 1H), 7.99 (dd, J = 7.7, 1.3 Hz, 1H), 7.90 (dd, J = 7.7, 1.3 Hz, 1H), 7.79−7.65 (m, 3H), 5.21 (t, J = 6.3 Hz, 1H), 4.78 (dt, J = 13.7, 3.7 Hz, 1H), 4.21 (dt, J = 13.7, 6.9 Hz, 1H), 3.54 (td, J = 6.6, 3.7 Hz, 2H), 1.24 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.0, 155.8, 145.5, 144.6, 140.4, 137.8, 134.8, 132.1, 131.9, 131.2, 129.0, 127.6, 124.2, 122.7, 79.3, 51.9, 39.7, 28.2(3C) ppm. HRMS (ESI), m/z calcd for $C_{20}H_{21}N_3O_7SNa$ $[M + Na]^+$ 470.0992, found 470.1000.

*tert-Butyl (3-(7-Nitro-5,5-dioxido-11-oxodibenzo[b,f][1,4]-thiazepin-10(11H)-yl)propyl)carbamate (**11b**).* Yield 140 mg, 76%; white solid; R_f = 0.26 (CH_2Cl_2/EtOAc = 20/1); mp 181−183 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 2.7 Hz, 1H), 8.43 (dd, J = 8.9, 2.7 Hz, 1H), 7.97 (dd, J = 7.7, 1.4 Hz, 1H), 7.89 (dd, J = 7.6, 1.4 Hz, 1H), 7.77−7.62 (m, 3H), 4.95−4.84 (br s, 1H), 4.84−4.72 (m, 1H), 3.99−3.86 (m, 1H), 3.35−3.14 (m, 2H), 2.05−1.94 (m, 2H), 1.44 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.3, 156.1, 144.7, 144.6, 140.6, 138.8, 134.6, 132.2, 131.9, 131.2, 128.9, 127.0, 124.1, 123.0, 79.3, 49.5, 38.0, 28.4(3C), 28.1 ppm. HRMS (ESI), m/z calcd for $C_{21}H_{23}N_3O_7SNa$ $[M + Na]^+$ 484.1149, found 484.1165.

*tert-Butyl (4-(7-Nitro-5,5-dioxido-11-oxodibenzo[b,f][1,4]-thiazepin-10(11H)-yl)butyl)carbamate (**11c**).* Yield 167 mg, 88%; yellow oil; R_f = 0.20 (CH_2Cl_2/EtOAc = 20/1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 2.6 Hz, 1H), 8.43 (dd, J = 9.0, 2.7 Hz, 1H), 7.96 (dd, J = 7.8, 1.3 Hz, 1H), 7.89 (dd, J = 7.6, 1.2 Hz, 1H), 7.76−7.61 (m, 3H), 4.75−4.58 (m, 2H), 3.99−3.84 (m, 1H), 3.23−3.08 (m, 2H), 1.94−1.73 (m, 2H), 1.65−1.52 (m, 2H), 1.43 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 156.1, 144.8, 144.5, 140.5, 138.7, 134.6, 132.2, 131.8, 131.3, 128.8, 127.1, 124.0, 122.9, 79.2, 51.5, 39.7, 28.4(3C), 27.6, 24.5 ppm. HRMS (ESI), m/z calcd for $C_{22}H_{25}N_3O_7SNa$ $[M + Na]^+$ 498.1305, found 498.1303.

*tert-Butyl (5-(7-Nitro-5,5-dioxido-11-oxodibenzo[b,f][1,4]-thiazepin-10(11H)-yl)pentyl)carbamate (**11d**).* Yield 133 mg, 68%; beige oil; R_f = 0.29 (CH_2Cl_2/EtOAc = 20/1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 2.7 Hz, 1H), 8.43 (dd, J = 9.0, 2.7 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.75−7.62 (m, 3H), 4.70−4.53 (m, 2H), 3.96−3.82 (m, 1H), 3.11 (q, J = 7.1 Hz, 2H), 1.97−1.72 (m, 2H), 1.64−1.34 (m, 13H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.0, 156.0, 144.9, 144.5, 140.5, 138.7, 134.5, 132.2, 131.8, 131.4, 128.8, 126.9, 124.0, 122.9, 79.1, 51.9, 40.1, 29.6, 28.4(3C), 27.0, 24.0 ppm. HRMS (ESI), m/z calcd for $C_{23}H_{27}N_3O_7SNa$ $[M + Na]^+$ 512.1462, found 512.1463.

*tert-Butyl (2-(7-Cyano-5,5-dioxido-11-oxodibenzo[b,f][1,4]-thiazepin-10(11H)-yl)ethyl)carbamate (**11e**).* Yield 137 mg, 79%; white solid; mp 179−181 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 2.0 Hz, 1H), 7.97 (dd, J = 7.7, 1.3 Hz, 1H), 7.90 (dd, J = 7.6, 1.3 Hz, 1H), 7.86 (dd, J = 8.5, 2.1 Hz, 1H), 7.74 (td, J = 7.6, 1.4 Hz, 1H), 7.69 (dd, J = 7.7, 1.4 Hz, 1H), 7.67−7.61 (m, 1H), 5.22 (t, J = 6.1 Hz, 1H), 4.75 (dt, J = 13.6, 3.6 Hz, 1H), 4.17 (dt, J = 13.8, 6.9 Hz, 1H), 3.53 (td, J = 6.6, 3.7 Hz, 2H), 1.28 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.0, 155.8, 144.0, 140.5, 137.9, 137.5, 134.7, 132.1, 131.8, 131.2, 130.9, 127.5, 124.1, 116.3, 110.3, 79.2, 51.8, 39.7, 28.2(3C) ppm. HRMS (ESI), m/z calcd for $C_{21}H_{21}N_3O_5SK$ $[M + K]^+$ 466.0833, found 466.0839.

*tert-Butyl (2-(5,5-Dioxido-10-oxobenzo[f]pyrido[3,2-b][1,4]-thiazepin-11(10H)-yl)ethyl)carbamate (**11f**).* Yield 82 mg, 51%; white solid; mp 132−134 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, J = 4.7, 1.9 Hz, 1H), 8.36 (dd, J = 7.8, 1.9 Hz, 1H), 7.94 (ddd, J = 7.7, 6.2, 1.3 Hz, 2H), 7.73 (td, J = 7.6, 1.4 Hz, 1H), 7.66 (td, J = 7.6, 1.3 Hz, 1H), 7.33 (dd, J = 7.9, 4.7 Hz, 1H), 5.34 (t, J = 6.1 Hz, 1H), 4.88−4.74 (m, 1H), 4.64−4.49 (m, 1H), 3.59−3.49 (m, 2H), 1.29 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 155.8, 153.2, 151.8, 140.5, 135.9, 134.4, 132.4, 131.8, 131.7, 131.5, 123.6, 121.0, 78.8, 49.0, 39.7, 28.3(3C) ppm. HRMS (ESI), m/z calcd for $C_{19}H_{21}N_3O_5SNa$ $[M + Na]^+$ 426.1094, found 426.1093.

*tert-Butyl (2-(7-Chloro-5,5-dioxido-11-oxodibenzo[b,f][1,4]-thiazepin-10(11H)-yl)ethyl)carbamate (**11g**).* Yield 79 mg, 45%; white solid; mp 130−133 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 2.5 Hz, 1H), 7.95 (dd, J = 7.7, 1.3 Hz, 1H), 7.89 (dd, J = 7.7, 1.3 Hz, 1H), 7.71 (td, J = 7.6, 1.4 Hz, 1H), 7.64 (td, J = 7.6, 1.3 Hz, 1H), 7.55 (dd, J = 8.7, 2.5 Hz, 1H), 7.43 (d, J = 8.7 Hz, 1H), 5.33 (t, J = 6.2 Hz, 1H), 4.76 (dt, J = 13.6, 3.6 Hz, 1H), 4.11−3.97 (m, 1H), 3.61−3.41 (m, 2H), 1.28 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 155.8, 141.1, 138.9, 138.3, 134.6, 134.4, 132.4, 132.0, 131.6, 131.4, 128.1, 126.6, 124.0, 79.0, 51.6, 39.6, 28.2(3C) ppm. HRMS (ESI), m/z calcd for $C_{20}H_{21}ClN_2O_5SNa$ $[M + Na]^+$ 459.0752, found 459.0758.

*tert-Butyl (2-(5,5-Dioxido-11-oxo-7-(trifluoromethyl)dibenzo-[b,f][1,4]thiazepin-10(11H)-yl)ethyl)carbamate (**11h**).* Yield 122 mg, 65%; white solid; mp 163−165 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 2.1 Hz, 1H), 7.97 (dd, J = 7.8, 1.3 Hz, 1H), 7.90 (dd, J = 7.6, 1.3 Hz, 1H), 7.85 (dd, J = 8.6, 2.2 Hz, 1H), 7.73 (td, J = 7.6, 1.4 Hz, 1H), 7.69−7.61 (m, 2H), 5.28 (t, J = 6.2 Hz, 1H), 4.79 (dt, J = 13.7, 3.4 Hz, 1H), 4.22−4.10 (m, 1H), 3.57−3.47 (m, 2H), 1.23 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 155.8, 143.6, 140.9, 137.5, 134.5, 132.1(2C), 131.7, 131.3 (q, J = 3.6 Hz), 128.6 (q, J = 34.2 Hz), 127.3, 124.4 (q, J = 3.6 Hz), 124.1, 122.7 (q, J = 272.6 Hz), 79.1, 51.8, 39.7, 28.1(3C) ppm. HRMS (ESI), m/z calcd for $C_{21}H_{21}F_3N_2O_5SNa$ $[M + Na]^+$ 493.1015, found 493.1017.

*tert-Butyl (2-(8-Cyano-5,5-dioxido-11-oxodibenzo[b,f][1,4]-thiazepin-10(11H)-yl)ethyl)carbamate (**11i**).* Yield 154 mg, 89%; white solid; mp 204−206 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.1 Hz, 1H), 7.95 (dd, J = 7.8, 1.2 Hz, 1H), 7.90 (dd, J = 7.7, 1.2 Hz, 1H), 7.80 (s, 1H), 7.74 (td, J = 7.6, 1.3 Hz, 1H), 7.69−7.61 (m, 2H), 5.25 (t, J = 6.3 Hz, 1H), 4.78 (dt, J = 13.7, 3.7 Hz, 1H), 4.17−4.03 (m, 1H), 3.61−3.46 (m, 2H), 1.28 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.0, 155.8, 141.4, 140.6, 140.5, 134.8, 132.2, 131.8, 131.3, 130.3, 129.4, 127.9, 124.2, 118.5, 116.1, 79.2, 52.1, 39.6,

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28.2(3C) ppm. HRMS (ESI), m/z calcd for $C_{21}H_{21}N_3O_5SNa$ $[M + Na]^+$ 450.1094, found 450.1096.

*tert-Butyl (2-(7-(N,N-Dimethylsulfamoyl)-5,5-dioxido-11-oxodibenzo[b,f][1,4]thiazepin-10(11H)-yl)ethyl)carbamate (**11j**).* Yield 179 mg, 88%; white solid; mp 194−196 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 2.2 Hz, 1H), 8.01−7.94 (m, 2H), 7.91 (dd, J = 7.7, 1.3 Hz, 1H), 7.74 (td, J = 7.6, 1.5 Hz, 1H), 7.71−7.64 (m, 2H), 5.29 (t, J = 6.5 Hz, 1H), 4.81−4.68 (m, 1H), 4.19−4.03 (m, 1H), 3.66−3.45 (m, 2H), 2.81 (s, 6H), 1.31 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.2, 156.0, 143.7, 140.8, 137.7, 135.0, 134.6, 133.3, 132.2, 131.8, 131.2, 127.3, 126.3, 124.1, 79.2, 52.4, 39.5, 37.8(3C), 28.3(2C) ppm. HRMS (ESI), m/z calcd for $C_{22}H_{27}N_3O_7S_2Na$ $[M + Na]^+$ 532.1183, found 532.1191.

*tert-Butyl (3-(7-(N,N-Dimethylsulfamoyl)-5,5-dioxido-11-oxodibenzo[b,f][1,4]thiazepin-10(11H)-yl)propyl)carbamate (**11k**).* Yield 161 mg, 77%; white solid; R_f = 0.13 (CH_2Cl_2/EtOAc = 20/1); mp 136−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 8.5, 2.2 Hz, 1H), 7.94 (dd, J = 7.7, 1.3 Hz, 1H), 7.88 (dd, J = 7.6, 1.2 Hz, 1H), 7.75−7.68 (m, 1H), 7.69−7.62 (m, 2H), 5.01−4.82 (br s, 1H), 4.78−4.64 (m, 1H), 3.99−3.81 (m, 1H), 3.33−3.15 (m, 2H), 2.82 (s, 6H), 2.07−1.93 (m, 2H), 1.45 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.4, 156.1, 143.0, 140.8, 138.6, 134.8, 134.5, 133.2, 132.1, 131.8, 131.3, 126.9, 126.4, 124.1, 79.2, 49.4, 38.0, 37.8(2C), 28.4(3C), 28.1 ppm. HRMS (ESI), m/z calcd for $C_{23}H_{29}N_3O_7S_2Na$ $[M + Na]^+$ 546.1339, found 546.1344.

*tert-butyl (2-(11,11-Dioxido-5-oxo-9-(trifluoromethyl)benzo[b]-pyrido[3,2-f][1,4]thiazepin-6(5H)-yl)ethyl)carbamate (**11l**).* Yield 141 mg, 75%; white solid; mp 198−200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, J = 4.5 Hz, 1H), 8.44 (s, 1H), 8.31−8.25 (m, 1H), 7.93−7.86 (m, 1H), 7.74−7.64 (m, 2H), 5.21 (t, J = 6.1 Hz, 1H), 4.79 (dt, J = 13.7, 3.5 Hz, 1H), 4.29−4.15 (m, 1H), 3.59−3.46 (m, 2H), 1.23 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.3, 155.7, 151.6, 143.5, 141.0(2C), 135.9, 131.9 (q, J = 3.5 Hz), 129.3 (q, J = 34.0 Hz), 128.7, 128.2, 127.4, 125.9 (q, J = 3.5 Hz), 122.6 (q, J = 272.9 Hz), 79.2, 51.8, 39.7, 28.1(3C) ppm. HRMS (ESI), m/z calcd for $C_{20}H_{20}F_3N_3O_5SNa$ $[M + Na]^+$ 494.0968, found 494.0973.

*tert-Butyl (3-(11,11-Dioxido-5-oxo-9-(trifluoromethyl)benzo[b]-pyrido[3,2-f][1,4]thiazepin-6(5H)-yl)propyl)carbamate (**11m**).* Yield 146 mg, 75%; white solid; R_f = 0.16 (CH_2Cl_2/EtOAc = 20/1); mp 177−179 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, J = 4.7, 1.5 Hz, 1H), 8.43 (d, J = 2.1 Hz, 1H), 8.27 (dd, J = 7.8, 1.7 Hz, 1H), 7.90 (dd, J = 8.5, 2.2 Hz, 1H), 7.77−7.61 (m, 2H), 4.98−4.67 (m, 2H), 3.94−3.80 (m, 1H), 3.32−3.12 (m, 2H), 2.10−1.90 (m, 2H), 1.44 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.5, 156.1, 155.9, 151.5, 142.5, 141.1, 137.0, 131.7 (q, J = 3.5 Hz), 129.4 (q, J = 34.6 Hz), 128.9, 128.2, 127.0, 126.0 (q, J = 3.8 Hz), 122.6 (q, J = 273.0 Hz), 82.8, 49.4, 47.7, 38.0, 28.4(3C) ppm. HRMS (ESI), m/z calcd for $C_{21}H_{22}F_3N_3O_5SNa$ $[M + Na]^+$ 508.1124, found 508.1115.

*tert-Butyl (2-(5,5-Dioxido-11-oxodibenzo[b,f][1,4]thiazepin-10-(11H)-yl)ethyl)carbamate (**11n**).* Yield 95 mg, 59%; white solid; mp 157−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 7.9, 1.5 Hz, 1H), 7.94 (dd, J = 7.8, 1.3 Hz, 1H), 7.89 (dd, J = 7.6, 1.3 Hz, 1H), 7.68 (td, J = 7.6, 1.3 Hz, 1H), 7.64−7.57 (m, 2H), 7.48 (d, J = 8.1 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 5.49−5.40 (br s, 1H), 4.83−4.74 (m, 1H), 4.12−4.01 (m, 1H), 3.62−3.41 (m, 2H), 1.25 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.3, 155.9, 141.7, 140.5, 137.3, 134.6, 134.0, 132.0, 131.7, 131.3, 126.9, 126.7, 126.5, 123.8, 78.8, 52.0, 39.5, 28.2(3C) ppm. HRMS (ESI), m/z calcd for $C_{20}H_{22}N_2O_5SNa$ $[M + Na]^+$ 425.1142, found 425.1145.

General Procedure for the Preparation of Diarene-fused Medium-size Cycles 12a−n, 13a−n. *Boc*-protected amine **9a−n** or **11a−n** (0.15 mmol) was dissolved in DCM (5 mL) and 4 M solution of HCl in 1,4-dioxane (0.188 mL). The mixture was stirred at room temperature overnight. Volatiles were removed *in vacuo*, and the residue was treated with diethyl ether (1 mL). The solid formed was filtered off and washed with diethyl ether (0.5 mL). The ammonium hydrochloride salt thus obtained was dissolved in a H_2O/MeOH (1:1) mixture (5 mL). Then 10% aq. NaOH (0.45 mmol) was added, and the resulting mixture was stirred under the following conditions: compounds **9a−f**, **9h−m**, **11a−n** at room temperature overnight; compound **9g** at 60 °C for 7 days; compound **9n** at 60 °C for 30 days. The resulting mixture was concentrated *in vacuo* and treated with water (1 mL). The precipitated product was filtered and washed with MeOH (0.5 mL), except compound **12c**—the compound was extracted with $CHCl_3$ (2 mL) and washed with water (3 × 0.5 mL). In addition, compounds **13a−b**, **13e−h**, and **13l−n** were treated with DMSO (0.2 mL) and filtered. The products were dried at 70 °C in vacuum for 24 h.

*2-Nitro-5,6,7,8-tetrahydro-9H-dibenzo[b,i][1,4,7]thiadiazecin-9-one (**12a**).* Yield 39 mg, 82%; yellow solid; mp 206−208 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H, H_{minor}), 8.30 (s, 1H, H_{major}), 8.19−8.03 (m, 3H, $2H_{major}$ + H_{minor}), 7.98−7.83 (m, 2H, H_{major} + H_{minor}), 7.73 (d, J = 7.0 Hz, 1H, H_{minor}), 7.52−7.33 (m, 4H, $2H_{major}$ + $2H_{minor}$), 7.26 (d, J = 7.1 Hz, 1H, H_{major}), 7.18 (d, J = 6.8 Hz, 1H, H_{minor}), 7.07 (d, J = 9.2 Hz, 1H, H_{major}), 6.95 (d, J = 9.2 Hz, 1H, H_{minor}), 6.22−6.08 (m, 2H, H_{major} + H_{minor}), 3.79−3.52 (m, 3H, $3H_{major}$), 3.52−3.36 (m, 1H, H_{major}), 3.27−3.14 (m, 3H, $3H_{minor}$), 3.05−2.96 (m, 1H, H_{minor}) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 169.6 (C_{major}), 158.8 (C_{major}), 138.5 (C_{major}), 133.1 ($2C_{major}$), 131.8 (C_{major}), 130.4 ($2C_{major}$), 129.5 (C_{major}), 127.4 ($2C_{major}$), 121.2 (C_{major}), 115.8 (C_{major}), 45.0 (C_{major}), 37.4 (C_{major}) ppm. **HRMS** (ESI), m/z calcd for $C_{15}H_{13}N_3O_3SNa$ $[M + Na]^+$ 338.0570, found 338.0567.

*2-Nitro-6,7,8,9-tetrahydrodibenzo[b,j][1]thia[4,8]diazacyclo-undecin-10(5H)-one (**12b**).* Yield 80 mg, 81%; yellow solid; mp more than 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (t, J = 6.0 Hz, 1H), 8.27 (d, J = 2.7 Hz, 1H), 8.07−7.96 (m, 2H), 7.52−7.41 (m, 2H), 7.29 (dd, J = 6.7, 2.3 Hz, 1H), 7.21 (t, J = 7.0 Hz, 1H), 6.85 (d, J = 9.3 Hz, 1H), 4.00−3.83 (m, 1H), 3.83−3.67 (m, 1H), 3.56−3.41 (m, 1H), 3.11−2.94 (m, 1H), 1.98−1.78 (m, 1H), 1.66−1.49 (m, 1H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 169.4, 155.1, 142.9, 137.1, 136.3, 133.6, 132.9, 130.8, 130.1, 128.1, 127.5, 119.4, 111.0, 43.3, 39.0, 25.3 ppm. HRMS (ESI), m/z calcd for $C_{16}H_{16}N_3O_3S$ $[M + H]^+$ 330.0907, found 330.0898.

*2-Nitro-5,6,7,8,9,10-hexahydro-11H-dibenzo[b,k][1]thia[4,9]-diazacyclododecin-11-one (**12c**).* Yield 16 mg, 6%; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 2.7 Hz, 1H), 8.21−8.13 (m, 2H), 7.72−7.66 (m, 1H), 7.52 (d, J = 8.9 Hz, 1H), 7.49−7.42 (m, 1H), 7.40−7.30 (m, 2H), 4.81−4.66 (m, 1H), 4.59−4.44 (br s, 1H), 3.75−3.59 (m, 1H), 2.73 (t, J = 6.7 Hz, 2H), 1.84−1.62 (m, 2H), 1.55 (p, J = 7.3 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 167.7, 161.4, 148.9, 144.7, 138.0, 137.3, 132.0, 131.8, 131.6, 129.9, 128.2, 127.7, 125.6, 56.5, 50.2, 27.8, 25.3 ppm. HRMS (ESI), m/z calcd for $C_{17}H_{18}N_3O_3S$ $[M + H]^+$ 344.1063, found 344.1071.

*9-Oxo-6,7,8,9-tetrahydro-5H-dibenzo[b,i][1,4,7]thiadiazecine-2-carbonitrile (**12e**).* Yield 35 mg, 79%; beige solid; mp 216−218 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H, H_{minor}), 8.08 (t, J = 5.7 Hz, 1H, H_{major}), 8.02−7.77 (m, 4H, $2H_{major}$ + $2H_{minor}$), 7.77−7.69 (m, 1H, H_{minor}), 7.61 (d, J = 8.6 Hz, 1H, H_{major}), 7.51−7.34 (m, 4H, $2H_{major}$ + $2H_{minor}$), 7.25 (d, J = 7.1 Hz, 1H, H_{major}), 7.18 (d, J = 6.3 Hz, 1H, H_{minor}), 7.02 (d, J = 8.7 Hz, 1H, H_{major}), 6.95 (d, J = 8.4 Hz, 1H, H_{minor}), 5.93−5.75 (m, 2H, H_{major} + H_{minor}), 3.74−3.45 (m, 3H, $3H_{major}$), 3.45−3.35 (m, 1H, H_{major}), 3.27−3.12 (m, 3H, $3H_{minor}$), 2.70−2.59 (m, 1H, H_{minor}) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 171.4 (C_{minor}), 169.5 (C_{major}), 156.8 (C_{major}), 154.9 (C_{minor}), 141.3 (C_{major} + C_{minor}), 140.5 (C_{minor}), 140.3 (C_{major}), 136.3 (C_{minor}), 135.4 (C_{minor}), 135.1(C_{major} + C_{minor}), 132.1 (C_{major}), 130.6 (C_{major}), 130.2 (C_{major} + C_{minor}), 129.4 (C_{minor}), 129.3 (C_{major}), 127.7 (C_{major}), 127.2 (C_{minor}), 123.8 (C_{minor}), 121.9 (C_{major}), 119.6 (C_{minor}), 119.5 (C_{major}), 117.1 (C_{minor}), 117.0 (C_{major}), 100.6 (C_{minor}), 100.5 (C_{major}), 46.2 (C_{minor}), 45.3 (C_{major}), 40.9 (C_{minor}), 37.4 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{16}H_{13}N_3OSNa$ $[M + Na]^+$ 318.0672, found 318.0669.

*5,6,7,8-Tetrahydro-9H-benzo[i]pyrido[3,2-b][1,4,7]thiadiazecin-9-one (**12f**).* Yield 22 mg, 54%; white solid; mp 172−174 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20−8.08 (m, 2H, $2H_{major}$), 8.09−8.02 (m, 2H, $2H_{minor}$), 8.00−7.93 (m, 1H, H_{minor}), 7.85−7.76 (m, 1H, $2H_{major}$), 7.71−7.65 (m, 1H, H_{minor}), 7.64−7.53 (m, 1H, H_{minor}), 7.49−7.31 (m, 3H, $2H_{major}$ + H_{minor}), 7.30−7.19 (m, 1H, H_{major}), 7.20−7.14 (m, 1H, H_{minor}), 6.73−6.66 (m, 1H, H_{minor}), 6.66−6.57 (m,

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1H, H_{major}), 6.04−5.85 (m, 2H, H_{major} + H_{minor}), 4.07−3.84 (m, 1H, H_{major}), 3.78−3.38 (m, 2H, $2H_{major}$), 3.28−3.07 (m, 3H, H_{major} + $2H_{minor}$), 2.73−2.55 (m, 2H, $2H_{minor}$) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 171.5 (C_{minor}), 169.9 (C_{major}), 163.0 (C_{major}), 161.1 (C_{minor}), 150.2 (C_{major}), 150.0 (C_{minor}), 145.7 (C_{major}), 144.3 (C_{minor}), 142.7 (C_{minor}), 136.2 (C_{minor}), 134.8 (C_{minor}), 133.8 (C_{major}), 133.6 (C_{major}), 132.5 (C_{major}), 130.1 (C_{major}), 129.5 (C_{minor}), 129.3 (C_{major}), 129.2 (C_{major}), 127.5 (C_{minor}), 127.4 (C_{minor}), 118.4 (C_{minor}), 116.6 (C_{major}), 115.8 (C_{minor}), 115.5 (C_{major}), 46.3 (C_{minor}), 44.1 (C_{minor}), 43.7 (C_{major}), 37.5 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{14}H_{13}N_3OSNa$ $[M + Na]^+$ 294.0672, found 294.0676.

*2-Chloro-5,6,7,8-tetrahydro-9H-dibenzo[b,i][1,4,7]thiadiazecin-9-one (**12g**).* Yield 18 mg, 38%; white solid; mp 154−156 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.05 (t, J = 5.0 Hz, 1H, H_{major}), 7.81−7.75 (m, 1H, H_{minor}), 7.73−7.65 (m, 2H, H_{major} + H_{minor}), 7.59 (d, J = 2.5 Hz, 1H, H_{major}), 7.56 (dd, J = 7.6, 1.5 Hz, 1H, H_{major}), 7.51−7.35 (m, 7H, $3H_{major}$ + $4H_{minor}$), 7.28 (d, J = 8.9 Hz, 1H, H_{major}), 7.25−7.20 (m, 2H, $2H_{minor}$), 6.97 (d, J = 8.8 Hz, 1H, H_{minor}), 5.39−5.31 (m, 1H, H_{major}), 4.27−3.98 (m, 3H, H_{major} + $2H_{minor}$), 3.96−3.81 (m, 2H, $2H_{major}$), 3.58−3.37 (m, 3H, H_{major} + $2H_{minor}$) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 173.6 (C_{minor}), 164.8 (C_{major}), 156.5 (C_{minor}), 146.7 (C_{major}), 140.6 (C_{minor}), 139.5 (C_{major}), 139.2 (C_{major}), 138.5 (C_{minor}), 137.5 (C_{minor}), 137.2 (C_{major}), 136.8 ($2C_{major}$+C_{minor}), 136.6 (C_{major}), 136.1 (C_{minor}), 135.1 (C_{major}), 134.9 (C_{minor}), 134.3 (C_{major}), 133.6 (C_{minor}), 133.2 (C_{minor}), 133.0 (C_{minor}), 131.5 (C_{major}), 127.3 (C_{major}), 126.0 (C_{major}+C_{minor}), 124.0 (C_{minor}), 57.3 (C_{major}), 56.5 (C_{major}), 50.5 (C_{minor}), 42.0 (C_{minor}) ppm. HRMS (ESI), m/z calcd for $C_{15}H_{13}ClN_2OSNa$ $[M + Na]^+$ 327.0329, found 327.0331.

*2-(Trifluoromethyl)-5,6,7,8-tetrahydro-9H-dibenzo[b,i][1,4,7]-thiadiazecin-9-one (**12h**).* Yield 37 mg, 73%; white solid; mp 214−216 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.15−8.06 (m, 2H, H_{major} + H_{minor}), 8.06−8.01 (m, 1H, H_{minor}), 7.87 (d, J = 7.3 Hz, 1H, H_{major}), 7.82−7.77 (m, 1H, H_{minor}), 7.76−7.71 (m, 1H, H_{major}), 7.53 (dd, J = 8.7, 2.3 Hz, 1H, H_{major}) 7.49−7.35 (m, 5H, $2H_{major}$ + $3H_{minor}$), 7.25 (dd, J = 7.1, 1.9 Hz, 1H, H_{major}), 7.19 (dd, J = 6.5, 2.5 Hz, 1H, H_{minor}), 7.07 (d, J = 8.7 Hz, 1H, H_{major}), 7.02 (d, J = 8.6 Hz, 1H, H_{minor}), 5.76−5.65 (m, 2H, H_{major} + H_{minor}), 3.66−3.35 (m, 5H, $4H_{major}$ + H_{minor}), 3.29−3.12 (m, 2H, $2H_{minor}$), 2.69−2.54 (m, 1H, H_{minor}) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 171.5 (C_{minor}), 169.3 (C_{major}), 156.2 (C_{major}), 154.6 (C_{minor}), 142.3 (C_{minor}), 140.8 (C_{minor}), 136.2 (C_{minor}), 134.1 (q, J = 3.7 Hz, C_{major}), 133.3 (q, J = 3.4 Hz, C_{minor}), 132.3 (C_{major}), 130.8, (C_{minor}), 130.6 (C_{minor}), 130.2 ($2C_{major}$), 129.2, 128.5 (q, J = 3.7 Hz, C_{minor}), 128.4 (q, J = 3.2 Hz, C_{major}), 127.9 (C_{minor}), 126.1 (C_{major}), 125.4 (q, J = 305.8 Hz, C_{minor}), 123.4 (C_{major}), 122.2 (q, J = 302.2 Hz, C_{major}), 121.3 (C_{major}), 119.4 (q, J = 33.2 Hz, C_{major}), 119.3 (q, J = 32.7 Hz, C_{minor}), 119.4 (C_{major}), 117.6 (C_{minor}), 117.1 (C_{major}), 46.9 (C_{minor}), 46.1 (C_{minor}), 45.6 (C_{major}), 37.4 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{16}H_{13}F_3N_2OSNa$ $[M + Na]^+$ 361.0593, found 361.0593.

*9-Oxo-6,7,8,9-tetrahydro-5H-dibenzo[b,i][1,4,7]thiadiazecine-3-carbonitrile (**12i**).* Yield 36 mg, 81%; white solid; mp 233−235 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.06 (t, J = 5.5 Hz, 1H, H_{major}), 8.01−7.93 (m, 2H, $2H_{minor}$), 7.83−7.73 (m, 2H, H_{major} + H_{minor}), 7.55 (d, J = 8.0 Hz, 1H, H_{major}), 7.48−7.32 (m, 6H, $3H_{major}$ + $3H_{minor}$), 7.23 (d, J = 7.2 Hz, 1H, H_{major}), 7.21−7.16 (m, 1H, H_{minor}), 7.14 (d, J = 7.9 Hz, 1H, H_{minor}), 7.04 (d, J = 7.9 Hz, 1H, H_{major}), 5.61−5.51 (m, 1H, H_{major}), 5.50−5.43 (m, 1H, H_{minor}), 3.81−3.36 (m, 4H, $4H_{major}$), 3.25−3.08 (m, 2H, $2H_{minor}$), 2.65−2.54 (m, 2H, $2H_{minor}$) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 168.8 (C_{major}), 153.3 (C_{major}), 138.2 (C_{major}), 134.0 (C_{major}), 133.9 (C_{major}), 132.3 (C_{major}), 130.2 (C_{major}), 129.1 (C_{major}), 128.5 (C_{major}), 127.0 (C_{major}), 122.7 (C_{major}), 120.8 (C_{major}), 119.2 (C_{major}), 113.7 (C_{major}), 45.5 (C_{major}), 37.1 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{16}H_{13}N_3OSNa$ $[M + Na]^+$ 318.0672, found 318.0670.

*N,N-Dimethyl-9-oxo-6,7,8,9-tetrahydro-5H-dibenzo[b,i][1,4,7]-thiadiazecine-2-sulfonamide (**12j**).* Yield 39 mg, 69%; beige solid; mp 179−181 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.13−7.99 (m, 2H, H_{major} + H_{minor}), 7.94 (d, J = 11.6 Hz, 1H, H_{minor}), 7.86−7.72 (m, 2H, H_{major} + H_{minor}), 7.69 (d, J = 6.9 Hz, 1H, H_{minor}), 7.62 (s, 1H, H_{major}), 7.58−7.49 (m, 2H, H_{major} + H_{minor}), 7.47−7.31 (m, 4H, $2H_{major}$ + $2H_{minor}$), 7.23 (d, J = 7.3 Hz, 1H, H_{major}), 7.15 (d, J = 8.9 Hz, 1H, H_{major}), 7.02 (d, J = 8.8 Hz, 1H, H_{minor}), 5.94−5.73 (m, 2H, H_{major} + H_{minor}), 3.79−3.37 (m, 4H, $3H_{major}$ + H_{minor}), 3.31−3.12 (m, 1H, H_{major}), 2.76−2.61 (m, 3H, $3H_{minor}$), 2.58 (s, 6H, $6H_{minor}$), 2.45 (s, 6H, $6H_{major}$) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 168.8 (C_{major}), 156.7 (C_{major}), 136.6 (C_{major}), 133.4 (C_{major}), 132.9 (C_{major}), 130.8 (C_{major}), 130.1 (C_{major}), 128.8 ($2C_{major}$), 124.4 (C_{major}), 121.7 (C_{major}), 117.3 (C_{major}), 45.3 (C_{major}), 37.9 (2C), 37.0 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{17}H_{19}N_3O_3S_2Na$ $[M + Na]^+$ 400.0760, found 400.0759.

*N,N-Dimethyl-10-oxo-5,6,7,8,9,10-hexahydrodibenzo[b,j][1]thia-[4,8]diazacycloundecine-2-sulfonamide (**12k**).* Yield 23 mg, 39%; white solid; mp 196−198 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.95−7.82 (m, 2H), 7.77 (dd, J = 8.5, 2.2 Hz, 1H), 7.65−7.60 (m, 1H), 7.58−7.51 (m, 1H), 7.48−7.40 (m, 3H), 4.75−4.58 (m, 1H), 3.85−3.69 (m, 1H), 2.63 (s, 6H), 2.61−2.54 (m, 2H), 1.73−1.52 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 167.7, 147.3, 138.2, 137.7, 137.0, 132.9, 132.0, 131.9, 131.8, 131.4, 129.7, 129.6, 127.7, 48.5, 39.4, 38.0 (2C), 32.0 ppm. HRMS (ESI), m/z calcd for $C_{18}H_{22}N_3O_3S_2[M + H]^+$ 392.1097, found 392.1087.

*12-(Trifluoromethyl)-6,7,8,9-tetrahydro-5H-benzo[b]pyrido[3,2-i][1,4,7]thiadiazecin-5-one (**12l**).* Yield 27 mg, 54%; white solid; mp 222−224 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.56−8.49 (m, 2H, H_{major} + H_{minor}), 8.12 (d, J = 8.2 Hz, 1H, H_{major}), 7.75 (d, J = 2.2 Hz, 1H, H_{minor}), 7.64−7.56 (m, 4H, $3H_{major}$ + H_{minor}), 7.53 (dd, J = 8.8, 2.2 Hz, 1H, H_{minor}), 7.48 (dd, J = 7.7, 1.9 Hz, 1H, H_{minor}), 7.34 (dd, J = 7.6, 4.7 Hz, 1H, H_{major}), 7.29−7.26 (m, 1H, H_{minor}), 7.23 (d, J = 8.5 Hz, 1H, H_{major}), 7.00 (d, J = 8.8 Hz, 1H, H_{minor}), 5.86−5.76 (m, 1H, H_{major}), 5.34−5.26 (m, 1H, H_{minor}), 3.84−3.65 (m, 2H, $2H_{major}$), 3.50−3.36 (m, 2H, H_{major} + H_{minor}), 3.28−3.19 (m, 1H, H_{minor}), 3.16−3.09 (m, 1H, H_{minor}), 3.04−2.83 (m, 2H, H_{major} + H_{minor}) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 169.0 (C_{minor}), 166.8 (C_{major}), 156.0 (C_{major}), 155.6 (C_{minor}), 150.2 (C_{minor}), 149.8 (C_{major}), 137.8 (C_{major}), 136.9 (C_{minor}), 134.7 (q, J = 3.0 Hz, C_{major}), 133.2 (q, J = 4.3 Hz, C_{minor}), 132.1 (C_{minor}), 129.1 (q, J = 3.7 Hz, C_{major}), 128.5 (q, J = 3.1 Hz, C_{minor}), 127.9 (C_{minor}), 125.7 (C_{major}), 123.5 (C_{major}), 122.3 (C_{major}), 121.4 (C_{minor}), 121.3 (C_{minor}), 120.4 (q, J = 30.1 Hz, C_{major}), 119.7 (q, J = 36.6 Hz, C_{minor}), 118.9 (C_{major}), 118.8 (C_{major}), 117.6 (q, J = 264.4 Hz, C_{major}), 117.2 (q, J = 270.2 Hz, C_{minor}), 116.5 (C_{minor}), 47.0 (C_{minor}), 46.9 (C_{minor}), 45.1 (C_{major}), 36.5 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{15}H_{12}F_3N_3OSNa$ $[M + Na]^+$ 362.0545, found 362.0549.

*13-(Trifluoromethyl)-7,8,9,10-tetrahydrobenzo[b]pyrido[3,2-j]-[1]thia[4,8]diazacycloundecin-5(6H)-one (**12m**).* Yield 25 mg, 48%; white solid; mp 253−255 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.59 (dd, J = 4.8, 1.9 Hz, 1H), 8.40 (t, J = 5.9 Hz, 1H), 7.69 (dd, J = 7.6, 1.9 Hz, 1H), 7.53 (d, J = 2.2 Hz, 1H), 7.50−7.40 (m, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.43 (t, J = 7.0 Hz, 1H), 3.80−3.56 (m, 2H), 3.47−3.36 (m, 1H), 3.20−3.05 (m, 1H), 2.05−1.89 (m, 1H), 1.59−1.46 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 166.9, 154.1, 152.6, 150.5, 138.1, 137.2, 134.0 (q, J = 3.9 Hz), 128.2 (q, J = 3.4 Hz), 124.9 (q, J = 270.5 Hz), 124.0, 117.2, 116.9 (q, J = 32.3 Hz), 112.8, 43.3, 39.3, 24.6 ppm. HRMS (ESI), m/z calcd for $C_{16}H_{14}F_3N_3OSNa$ $[M + Na]^+$ 376.0702, found 376.0702.

*5,6,7,8-Tetrahydro-9H-dibenzo[b,i][1,4,7]thiadiazecin-9-one (**12n**).* Yield 15 mg, 37%; white solid; mp 175−177 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.07−7.96 (m, 2H, H_{major} + H_{minor}), 7.86−7.78 (m, 2H, $2H_{minor}$), 7.74 (dd, J = 7.7, 1.3 Hz, 1H, H_{major}), 7.44−7.32 (m, 5H, $3H_{major}$ + $2H_{minor}$), 7.27−7.19 (m, 3H, $2H_{major}$ + H_{minor}), 7.20−7.15 (m, 1H, H_{minor}), 6.94 (dd, J = 8.3, 1.3 Hz, 1H, H_{major}), 6.93−6.87 (m, 1H, H_{minor}), 6.82−6.76 (m, 1H, H_{minor}), 6.69−6.62 (m, 1H, H_{major}), 5.37−5.30 (m, 2H, H_{major} + H_{minor}), 3.58−3.35 (m, 4H, $3H_{major}$ + H_{minor}), 3.30−3.19 (m, 2H, H_{major} + H_{minor}), 3.20−3.12 (m, 1H, H_{minor}), 3.10−3.02 (m, 1H, H_{minor}) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 171.7 (C_{minor}), 168.9 (C_{major}), 152.6 (C_{major}), 151.8 (C_{minor}), 141.4 (C_{minor}), 141.3 (C_{minor}), 137.3 (C_{major}), 136.7 (C_{minor}), 136.5 (C_{minor}), 133.7 (C_{major}), 133.5 (C_{major}), 131.7 (C_{minor}), 131.6 (C_{minor}), 131.4 (C_{major}), 130.4 (C_{minor}), 129.9 (C_{major}), 129.5 (C_{minor}), 128.5 (C_{major}), 128.4 (C_{major}), 126.8 (C_{major}), 124.6 (C_{minor}), 121.1 (C_{major}), 120.8 (C_{minor}), 120.0 (C_{major}), 119.2 (C_{minor}), 117.9

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(C_{major}), 48.3 (C_{minor}), 46.0 (C_{major}), 45.5 (C_{minor}), 37.4 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{15}H_{14}N_2OSNa$ $[M + Na]^+$ 293.0719, found 293.0718.

*2-Nitro-5,6,7,8-tetrahydro-9H-dibenzo[b,i][1,4,7]thiadiazecin-9-one 14,14-Dioxide (**13a**).* Yield 41 mg, 78%; yellow solid; mp 197−198 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 2.7 Hz, 1H, H_{minor}), 8.42 (d, J = 2.7 Hz, 1H, H_{major}), 8.36−8.28 (m, 1H, H_{major}), 8.28−8.17 (m, 3H, $2H_{major}$ + H_{minor}), 7.96 (dd, J = 8.1, 1.2 Hz, 1H, H_{minor}), 7.83−7.69 (m, 3H $2H_{major}$ + $2H_{minor}$), 7.64−7.58 (m, 1H, H_{minor}), 7.47 (dd, J = 7.4, 1.4 Hz, 2H, H_{major}), 7.38 (dd, J = 7.7, 1.3 Hz, 1H, H_{minor}), 7.31−7.20 (m, 4H, $3H_{major}$ + H_{minor}), 7.17 (d, J = 9.3 Hz, 1H, H_{minor}), 3.97−3.86 (m, 1H, H_{major}), 3.84−3.64 (m, 3H, H_{major} + $2H_{minor}$), 3.29−3.20 (m, 2H, H_{major} + H_{minor}), 3.13−3.02 (m, 1H, H_{major}), 2.79−2.66 (m, 1H, H_{minor}) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 169.1 (C_{minor}), 167.2 (C_{major}), 155.7 (C_{minor}), 152.8 (C_{major}), 138.2 (C_{major}), 138.0 (C_{minor}), 137.8 (C_{major}), 137.7 (C_{minor}), 136.3 (C_{minor}), 136.1 (C_{major}), 134.9 (C_{major} + C_{minor}), 131.6 (C_{minor}), 131.0 (C_{major}), 130.8 (C_{minor}), 130.7 (C_{major}), 130.5 (C_{minor}), 129.1 (C_{major}), 129.0 (C_{major}), 128.7 (C_{minor}), 127.7 (C_{major}), 126.2 (C_{minor}), 124.8 (C_{minor}), 123.9 (C_{major}), 119.2 (C_{major}), 118.2 (C_{minor}),46.4 (C_{major}), 45.3 (C_{minor}), 43.1 (C_{major}), 36.6 (C_{minor}) ppm. HRMS (ESI), m/z calcd for $C_{15}H_{13}N_3O_5SNa$ $[M + Na]^+$ 370.0468, found 370.0462.

*2-Nitro-6,7,8,9-tetrahydrodibenzo[b,j][1]thia[4,8]diazacyclo-undecin-10(5H)-one 15,15-Dioxide (**13b**).* Yield 40 mg, 74%; yellow solid; mp 254−256 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 2.7 Hz, 1H), 8.31−8.21 (m, 2H), 8.18 (dd, J = 9.6, 2.7 Hz, 1H), 8.02 (dd, J = 8.4, 4.7 Hz, 1H), 7.79−7.69 (m, 2H), 7.46 (dd, J = 6.5, 2.2 Hz, 1H), 7.11 (d, J = 9.6 Hz, 1H), 3.97−3.74 (m, 2H), 3.61−3.47 (m, 1H), 3.14−3.01 (m, 1H), 2.06−1.89 (m, 1H), 1.72−1.60 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 166.2, 152.5, 139.4, 138.0, 136.2, 134.5, 130.5, 130.2, 129.9, 128.7(2C), 120.8, 115.6, 43.6, 39.4, 25.6 ppm. HRMS (ESI), m/z calcd for $C_{16}H_{15}N_3O_5SNa$ $[M + Na]^+$ 384.0625, found 384.0623.

*9-Oxo-6,7,8,9-tetrahydro-5H-dibenzo[b,i][1,4,7]thiadiazecine-2-carbonitrile 14,14-Dioxide (**13e**).* Yield 29 mg, 60%; white solid; mp 232−233 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31−8.18 (m, 3H, $2H_{major}$ + H_{minor}), 8.13 (s, 1H, H_{major}), 8.01 (d, J = 8.1 Hz, 1H, H_{minor}), 7.95−7.84 (m, 1H, H_{minor}), 7.83−7.67 (m, 5H, $3H_{major}$ + $2H_{minor}$), 7.61 (t, J = 7.6 Hz, 1H, H_{minor}), 7.49−7.31 (m, 2H, H_{major} + H_{minor}), 7.23−7.12 (m, 2H, H_{major} + H_{minor}), 7.12−7.04 (m, 1H, H_{minor}), 7.02−6.92 (m, 1H, H_{major}), 3.99−3.83 (m, 1H, H_{major}), 3.74−3.56 (m, 3H, $2H_{major}$ + H_{minor}), 3.30−3.14 (m, 2H, $2H_{minor}$), 3.09−2.93 (m, 1H, H_{major}), 2.72−2.58 (m, 1H, H_{minor}) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 169.2 (C_{major}), 167.2 (C_{minor}), 154.2 (C_{minor}), 151.4-(C_{major}), 138.7 (C_{major}), 138.6 (C_{minor}), 138.4 (C_{major}), 137.9 (C_{minor}), 136.5 (C_{minor}), 136.2 (C_{minor}), 136.1 (C_{major}), 134.7 (C_{major}), 134.7 (C_{minor}), 134.5 (C_{major}), 131.5 (C_{minor}), 130.9 (C_{major}), 130.3 ($2C_{major}$), 129.4 (C_{minor}), 128.9 (C_{major}), 128.5 (C_{minor}), 126.2 (C_{minor}), 125.2 (C_{minor}), 120.1 (C_{major}), 119.3 (C_{major}), 118.8 (C_{minor}), 100.3 (C_{major}), 100.1 (C_{minor}), 46.6 (C_{minor}), 45.6 (C_{minor}), 43.6 (C_{major}), 36.9 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{16}H_{13}N_3O_3SNa$ $[M + Na]^+$ 350.0570, found 350.0574.

*5,6,7,8-Tetrahydro-9H-benzo[i]pyrido[3,2-b][1,4,7]thiadiazecin-9-one 14,14-Dioxide (**13f**).* Yield 27 mg, 59%; white solid; mp 165−168 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42−8.33 (m, 1H, H_{major}), 8.33−8.21 (m, 3H, H_{major} + $2H_{minor}$), 8.19 (dd, J = 7.8, 1.8 Hz, 1H, H_{minor}), 8.14 (d, J = 7.9 Hz, 1H, H_{major}), 8.00 (d, J = 7.9 Hz, 1H, H_{major}), 7.85 (dd, J = 8.2, 1.2 Hz, 1H, H_{minor}), 7.78−7.65 (m, 3H, $2H_{major}$ + H_{minor}), 7.64−7.56 (m, 1H, H_{minor}), 7.43 (d, J = 7.3 Hz, 1H, H_{major}), 7.36 (dd, J = 7.6, 1.3 Hz, 1H, H_{minor}), 7.17−7.09 (m, 1H, H_{minor}), 6.94−6.85 (m, 2H, H_{major} + H_{minor}), 6.83 (dd, J = 7.9, 4.7 Hz, 1H, H_{major}), 4.17 (q, J = 11.2, 8.9 Hz, 1H, H_{major}), 4.05−3.87 (m, 2H, H_{major} + H_{minor}), 3.47−3.36 (m, 1H, H_{major}), 3.28−3.21 (m, 1H, H_{minor}), 3.13−3.03 (m, 1H, H_{minor}), 3.04−2.93 (m, 1H, H_{major}), 2.70−2.54 (m, 1H, H_{minor}) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 169.3 (C_{major}), 167.4 (C_{minor}), 158.7 (C_{major}), 156.7 (C_{minor}), 155.0 (C_{major}), 154.8 (C_{minor}), 140.3 (C_{major}), 138.9 (C_{minor}), 138.8 (C_{major}), 137.9 (C_{minor}), 137.0 (C_{minor}), 136.1 (C_{minor}), 134.5 (C_{minor}), 130.9 (C_{minor}), 130.8 (C_{major}), 130.2 ($2C_{major}$), 129.1 (C_{major}), 128.8 (C_{minor}), 128.6 (C_{major}), 121.1 (C_{major}), 120.2 (C_{minor}), 115.4 (C_{minor}), 114.9 (C_{major}), 46.6 (C_{minor}), 43.2 (C_{minor}), 41.4 (C_{major}), 36.8 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{14}H_{13}N_3O_3SNa$ $[M + Na]^+$ 326.0570, found 326.0576.

*2-Chloro-5,6,7,8-tetrahydro-9H-dibenzo[b,i][1,4,7]thiadiazecin-9-one 14,14-Dioxide (**13g**).* Yield 45 mg, 89%; brown solid; mp 138−140 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31−8.07 (m, 3H, $2H_{major}$ + H_{minor}), 7.99 (d, J = 8.1 Hz, 1H, H_{minor}), 7.87 (d, J = 2.6 Hz, 1H, H_{minor}), 7.81−7.67 (m, 3H, $2H_{major}$ + H_{minor}), 7.67−7.56 (m, 2H, H_{major} + H_{minor}), 7.54−7.40 (m, 3H, $2H_{major}$ + H_{minor}), 7.36 (d, J = 7.6 Hz, 1H, H_{minor}), 7.11 (d, J = 9.5 Hz, 2H, H_{major} + H_{minor}), 6.58 (d, J = 11.5 Hz, 1H, H_{minor}), 6.53−6.34 (m, 1H, H_{major}), 4.02−3.79 (m, 1H, H_{major}), 3.63−3.42 (m, 3H, $2H_{major}$ + H_{minor}), 3.25−3.10 (m, 2H, $2H_{minor}$), 3.06−2.90 (m, 1H, H_{major}), 2.76−2.56 (m, 1H, H_{minor}) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 169.2 (C_{major}), 167.0 (C_{minor}), 150.5 (C_{major} + C_{minor}), 147.9 (C_{major}), 147.6 (C_{minor}), 138.8 (C_{minor}), 137.1 (C_{minor}), 137.0 (C_{minor}), 136.2 (C_{major}), 135.9 (C_{major}), 134.6 (C_{major}), 134.5 (C_{minor}), 131.0 (C_{major}), 130.9 (C_{major}), 130.3 ($2C_{major}$), 129.5 (C_{minor}), 129.2 (C_{minor}), 129.0 (C_{major}), 128.6 (C_{minor}), 128.3 (C_{major}), 127.8 (C_{minor}), 123.0 (C_{minor}), 122.5 (C_{major}), 122.4 (C_{minor}), 47.2 (C_{minor}), 46.6 (C_{minor}), 40.9 (C_{major}), 37.4 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{15}H_{13}ClN_2O_3SNa$ $[M + Na]^+$ 359.0228, found 359.0227.

*2-(Trifluoromethyl)-5,6,7,8-tetrahydro-9H-dibenzo[b,i][1,4,7]-thiadiazecin-9-one 14,14-Dioxide (**13h**).* Yield 50 mg, 90%; gray solid; mp 201−202 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37−8.16 (m, 3H, $2H_{major}$ + H_{minor}), 8.10 (s, 1H, H_{minor}), 7.94 (d, J = 8.1 Hz, 1H, H_{minor}), 7.89 (s, 1H, H_{major}), 7.84−7.66 (m, 5H, $3H_{major}$ + $2H_{minor}$), 7.65−7.56 (m, 1H, H_{minor}), 7.53−7.32 (m, 2H, H_{major} + H_{minor}), 7.30−7.15 (m, 2H, H_{major} + H_{minor}), 6.94 (d, J = 11.1 Hz, 1H, H_{minor}), 6.88−6.75 (m, 1H, H_{major}), 4.01−3.82 (m, 1H, H_{major}), 3.75−3.53 (m, 3H, $2H_{major}$ + H_{minor}), 3.30−3.14 (m, 2H, $2H_{minor}$), 3.11−2.95 (m, 1H, H_{major}), 2.66 (q, J = 11.2 Hz, 1H, H_{minor}) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 169.3 (C_{major}), 167.2 (C_{minor}), 154.1 (C_{minor}), 151.5 (C_{major}), 138.7 (C_{major}), 138.0 (C_{minor}), 136.7 (C_{major}), 136.3 (C_{minor}), 134.7 (C_{major}), 134.6 (C_{minor}), 132.5 (q, J = 3.1 Hz, C_{minor}), 132.3 (C_{minor}), 131.1 (C_{major}), 130.9 (C_{major}), 130.4 (C_{major}), 129.1 (C_{minor}), 129.0 (C_{major}), 128.6 (C_{minor}), 128.2 (q, J = 2.7 Hz, C_{major}), 126.7 (q, J = 3.7 Hz, C_{minor}), 125.8 (C_{minor}), 125.5 (q, J = 275.5 Hz, C_{minor}), 124.4 (q, J = 2.2 Hz, C_{major}), 124.3 (q, J = 269.6 Hz, C_{major}), 120.3 (C_{minor}), 119.9 (C_{major}), 118.9 (q, J = 32.6 Hz, C_{major}), 118.5 (q, J = 33.0 Hz, C_{minor}), 46.6 (C_{minor}), 46.0 (C_{minor}), 43.8 (C_{major}), 37.1 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{16}H_{13}F_3N_2O_3SNa$ $[M + Na]^+$ 393.0491, found 393.0494.

*9-Oxo-6,7,8,9-tetrahydro-5H-dibenzo[b,i][1,4,7]thiadiazecine-3-carbonitrile 14,14-Dioxide (**13i**).* Yield 7 mg, 15%; white oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26−8.13 (m, 3H, $2H_{major}$ + H_{minor}), 8.03 (d, J = 8.2 Hz, 1H, H_{minor}), 7.90 (dd, J = 8.1, 1.2 Hz, 1H, H_{minor}), 7.84−7.67 (m, 5H, $3H_{major}$ + $2H_{minor}$), 7.65−7.57 (m, 2H, H_{major} + H_{minor}), 7.45 (d, J = 7.4 Hz, 1H, H_{major}), 7.37 (dd, J = 7.7, 1.3 Hz, 1H, H_{minor}), 7.27 (dd, J = 8.2, 1.5 Hz, 1H, H_{minor}), 7.17 (dd, J = 8.4, 1.5 Hz, 1H, H_{major}), 6.76−6.68 (m, 1H, H_{minor}), 6.68−6.58 (m, 1H, H_{major}), 4.01−3.79 (m, 1H, H_{major}), 3.72−3.49 (m, 3H, $2H_{major}$ + H_{minor}), 3.23−3.09 (m, 1H, H_{major}), 3.09−3.00 (m, 2H, $2H_{minor}$), 2.68−2.56 (m, 1H, H_{minor}) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 169.1 (C_{major}), 167.0 (C_{minor}), 151.5 (C_{minor}), 148.9 (C_{major}), 138.5 (C_{minor}), 138.1 (C_{minor}), 136.5 (C_{minor}), 136.4 (C_{minor}), 134.8 (C_{major} + C_{minor}), 132.2 (C_{major}), 131.1 (C_{major}), 130.9 (C_{major}), 130.7 (C_{major}), 130.4 ($2C_{major}$), 130.0 (C_{minor}), 129.2 (C_{minor}), 129.1 (C_{major}), 128.6 (C_{minor}), 128.3 (C_{minor}), 124.1 (C_{minor}), 123.9 (C_{major}), 121.7 (C_{major}), 121.1 (C_{minor}), 118.3 (C_{major}), 118.1 (C_{major} + C_{minor}), 46.7 (C_{major}), 44.1 (C_{minor}), 40.9 (C_{major}), 37.2 (C_{minor}) ppm. HRMS (ESI), m/z calcd for $C_{16}H_{13}N_3O_3SNa$ $[M + Na]^+$ 350.0570, found 350.0577.

*N,N-Dimethyl-9-oxo-6,7,8,9-tetrahydro-5H-dibenzo[b,i][1,4,7]-thiadiazecine-2-sulfonamide 14,14-Dioxide (**13j**).* Yield 44 mg, 72%; white solid; mp 212−214 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34−8.26 (m, 1H, H_{major}), 8.26−8.13 (m, 2H, H_{major} + H_{minor}), 8.08 (d, J = 2.3 Hz, 1H, H_{minor}), 7.93−7.82 (m, 2H, H_{major} + H_{minor}), 7.81−7.66 (m, 5H, $3H_{major}$ + $2H_{minor}$), 7.67−7.58 (m, 1H, H_{minor}), 7.53−7.32 (m, 2H, H_{major} + H_{minor}), 7.29−7.16 (m, 2H, H_{major} + H_{minor}), 7.06−6.89 (m, 2H, H_{major} + H_{minor}), 4.00−3.79 (m, 1H, H_{major}), 3.78−

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3.56 (m, 3H, $2H_{major}$ + H_{minor}), 3.28−3.15 (m, 2H, $2H_{minor}$), 3.11−3.00 (m, 2H, H_{major}), 2.76−2.63 (m, 1H, H_{minor}), 2.59 (s, 6H, $6H_{minor}$), 2.51 (s, 6H, $6H_{major}$) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 169.2 (C_{major}), 167.2 (C_{minor}), 154.2 (C_{major}), 151.7 (C_{minor}), 138.6 (C_{major}), 137.8 (C_{minor}), 134.7 (C_{major}), 134.6 (C_{minor}), 134.5 (C_{major} + C_{minor}), 131.2 (C_{major}), 130.9 (C_{major}), 130.8 (C_{minor}), 130.4 (C_{major} + C_{minor}), 129.4 (C_{minor}), 129.1 (C_{major}), 128.9 (C_{minor}), 128.7 (C_{major}), 125.5 (C_{minor}), 125.3 (C_{minor}), 124.2 (C_{major}), 123.8 (C_{minor}), 123.4 (C_{major}), 119.7 (C_{major}), 119.3 (C_{minor}), 46.6 (C_{minor}), 45.7 (C_{minor}), 43.3 (C_{major}), 38.1 ($2C_{major}$), 38.0 ($2C_{minor}$), 36.8 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{17}H_{19}N_3O_5S_2Na$ $[M + Na]^+$ 432.0658, found 432.0654.

*N,N-Dimethyl-10-oxo-5,6,7,8,9,10-hexahydrodibenzo[b,j][1]thia-[4,8]diazacycloundecine-2-sulfonamide 15,15-Dioxide (**13k**).* Yield 32 mg, 50%; white solid; mp 246−248 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.25−8.13 (m, 2H), 7.78−7.59 (m, 5H), 7.46 (dd, J = 6.5, 2.2 Hz, 1H), 7.11 (d, J = 9.1 Hz, 1H), 3.91−3.68 (m, 2H), 3.54−3.41 (m, 1H), 3.32 (s, 6H), 3.15−3.01 (m, 1H), 2.09−1.91 (m, 1H), 1.68−1.53 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO- d_6) δ 166.1, 151.1, 139.8, 137.9, 134.2, 133.9, 132.1, 130.3, 129.8, 128.3, 120.9, 120.8, 115.7, 43.3, 39.4, 37.9(2C), 25.4 ppm. HRMS (ESI), m/z calcd for $C_{18}H_{21}N_3O_5S_2Na$ $[M + Na]^+$ 446.0815, found 446.0818.

*12-(Trifluoromethyl)-6,7,8,9-tetrahydro-5H-benzo[b]pyrido[3,2-i][1,4,7]thiadiazecin-5-one 14,14-Dioxide (**13l**).* Yield 45 mg, 80%; white solid; mp 243−245 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.85 (d, J = 4.7 Hz, 1H, H_{minor}), 8.79 (d, J = 4.6 Hz, 1H, H_{major}), 8.41−8.29 (m, 1H, H_{major}), 8.30−8.16 (m, 1H, H_{minor}), 8.10−7.62 (m, 8H, $4H_{major}$ + $4H_{minor}$), 7.27−7.15 (m, 2H, H_{major} + H_{minor}), 7.08−6.89 (m, 1H, H_{major}), 6.85−6.73 (m, 1H, H_{minor}), 4.09−3.92 (m, 1H, H_{minor}), 3.69−3.47 (m, 2H, $2H_{major}$), 3.29−3.11 (m, 3H, H_{major} + $2H_{minor}$), 3.10−2.96 (m, 1H, H_{minor}), 2.66−2.53 (m, 1H, H_{major}) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 167.7 (C_{major}), 165.7 (C_{minor}), 154.5 (C_{minor}), 154.1 (C_{minor}), 152.0 (C_{minor}), 151.6 (C_{minor}), 151.5 (C_{major}), 150.3 (C_{major}), 138.5 (C_{major}), 137.9 (C_{minor}), 134.7 (C_{minor}), 132.9 (q, J = 3.3 Hz, C_{major}), 132.8 (q, J = 3.2 Hz, C_{minor}), 128.6 (q, J = 2.9 Hz, (C_{minor})), 128.5 (C_{major} + C_{minor}), 128.4 (C_{major}), 128.2 (q, J = 3.9 Hz, C_{major}), 124.4 (q, J = 270.9 Hz, C_{major}), 124.3 (q, J = 269.1 Hz, C_{minor}), 122.6 (C_{minor}), 122.5 (C_{major}), 121.1 (C_{major}), 119.9 (C_{major}), 118.5 (q, J = 33.4 Hz, C_{minor}), 118.4 (q, J = 33.6 Hz, C_{major}), 46.8 (C_{major}), 46.0 (C_{major}), 45.0 (C_{minor}), 37.5 (C_{minor}) ppm. HRMS (ESI), m/z calcd for $C_{15}H_{12}F_3N_3O_3SNa$ $[M + Na]^+$ 394.0444, found 394.0447.

*13-(Trifluoromethyl)-7,8,9,10-tetrahydrobenzo[b]pyrido[3,2-j][1]thia[4,8]diazacycloundecin-5(6H)-one 15,15-Dioxide (**13m**).* Yield 34 mg, 59%; white solid; mp 215−217 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.85 (dd, J = 4.7, 1.6 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H), 8.00 (dd, J = 7.7, 1.7 Hz, 1H), 7.85 (d, J = 2.2 Hz, 1H), 7.76 (dd, J = 7.7, 4.6 Hz, 1H), 7.70 (dd, J = 9.1, 2.3 Hz, 1H), 7.64 (dd, J = 9.0, 4.4 Hz, 1H), 7.14 (d, J = 9.0 Hz, 1H), 3.95−3.81 (m, 1H), 3.82−3.68 (m, 1H), 3.51−3.38 (m, 1H), 3.11−3.00 (m, 1H), 2.01−1.86 (m, 1H), 1.72−1.60 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 164.5, 154.8, 150.8, 150.2, 138.9, 134.3, 132.2 (q, J = 3.3 Hz), 129.4 (q, J = 4.3 Hz), 128.1, 124.6 (q, J = 270.4 Hz), 118.6, 116.1 (q, J = 33.0 Hz), 115.9, 42.9, 39.4, 26.0 ppm. HRMS (ESI), m/z calcd for $C_{16}H_{14}F_3N_3O_3SNa$ $[M + Na]^+$ 408.0600, found 408.0604.

*5,6,7,8-Tetrahydro-9H-dibenzo[b,i][1,4,7]thiadiazecin-9-one 14,14-Dioxide (**13n**).* Yield 39 mg, 87%; white solid; mp 216−218 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.30−8.04 (m, 3H, H_{major} + $2H_{minor}$), 7.98−7.81 (m, 2H, H_{major} + H_{minor}), 7.78−7.52 (m, 5H, $3H_{major}$ + $2H_{minor}$), 7.52−7.26 (m, 4H, $3H_{major}$ + H_{minor}), 7.15−6.97 (m, 2H, H_{major} + H_{minor}), 6.92 (t, J = 7.7 Hz, 1H, H_{minor}), 6.81 (t, J = 7.8 Hz, 1H, H_{major}), 6.60 (d, J = 11.5 Hz, 1H, H_{minor}), 6.44 (s, 1H, H_{minor}), 4.06−3.76 (m, 1H, H_{major}), 3.73−3.40 (m, 4H, $2H_{major}$ + $2H_{minor}$), 3.27−3.09 (m, 2H, H_{major} + H_{minor}), 3.09−2.86 (m, 1H, H_{minor}) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 169.4 (C_{major}), 151.6 (C_{minor}), 149.1 (C_{major}), 137.8 (C_{minor}), 136.1 (C_{major} + C_{minor}), 136.0 (C_{major}), 134.2 (C_{major} + C_{minor}), 134.0 (C_{minor}), 131.0 (C_{minor}), 130.7 (C_{major} + C_{minor}), 130.6 (C_{major}), 130.2 (C_{major} + C_{minor}), 129.6 (C_{major}), 128.9 (C_{major} + C_{minor}), 128.6 (C_{minor}), 126.9 (C_{major}), 120.5 (C_{major} + C_{minor}), 120.2 (C_{minor}), 119.7 (C_{major}), 118.9 (C_{minor}), 47.3 (C_{minor}), 46.6 (C_{minor}), 40.9 (C_{major}), 37.6 (C_{major}) ppm. HRMS (ESI), m/z calcd for $C_{15}H_{14}N_2O_3SNa$ $[M + Na]^+$ 325.0617, found 325.0629.

Hydrolysis Products 14a−c. *2-((2-((5-Aminopentyl)amino)-5-nitrophenyl)thio)benzoic Acid (**14a**).* Yield 38 mg, 68%; yellow solid; mp more than 250 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.70−8.60 (br s, 1H), 8.42 (d, J = 2.7 Hz, 1H), 8.10 (dd, J = 9.3, 2.8 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.28−7.11 (m, 3H), 6.65 (d, J = 9.3 Hz, 1H), 3.17 (q, J = 5.1 Hz, 2H), 2.82 (t, J = 6.0 Hz, 2H), 1.70−1.53 (m, 4H), 1.55−1.39 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 171.7, 157.8, 155.1, 144.5, 135.0, 133.2, 130.7, 128.6, 128.2, 128.0, 127.1, 117.9, 109.1, 42.9, 31.2, 28.4, 27.5, 27.0 ppm. HRMS (ESI), m/z calcd for $C_{18}H_{22}N_3O_4S$ $[M + H]^+$ 376.1326, found 376.1331.

*2-((2-((4-Aminobutyl)amino)-5-nitrophenyl)sulfonyl)benzoic Acid (**14b**).* Yield 47 mg, 79%; yellow solid; mp more than 250 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, J = 2.8 Hz, 1H), 8.13 (dd, J = 9.5, 2.8 Hz, 1H), 7.58−7.50 (m, 2H), 7.36−7.26 (m, 2H), 6.83 (d, J = 9.6 Hz, 1H), 3.26 (t, J = 6.9 Hz, 2H), 2.42 (t, J = 6.9 Hz, 2H), 1.43 (p, J = 7.1 Hz, 2H), 1.16−1.04 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 171.0, 151.0, 146.4, 134.6, 133.8, 133.6, 130.0, 129.2, 128.5, 127.3, 127.1, 122.7, 112.5, 43.1, 41.6, 30.5, 25.7 ppm. HRMS (ESI), m/z calcd for $C_{17}H_{19}N_3O_6SNa$ $[M + Na]^+$ 416.0887, found 416.0886.

*2-((2-((5-Aminopentyl)amino)-5-nitrophenyl)sulfonyl)benzoic Acid (**14c**).* Yield 57 mg, 94%; yellow solid; mp more than 250 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, J = 2.8 Hz, 1H), 8.13 (dd, J = 9.4, 2.8 Hz, 1H), 7.57−7.46 (m, 2H), 7.33−7.23 (m, 2H), 6.82 (d, J = 9.5 Hz, 1H), 3.26 (t, J = 6.8 Hz, 2H), 2.42 (t, J = 6.9 Hz, 2H), 1.39 (p, J = 7.0 Hz, 2H), 1.24 (p, J = 7.1 Hz, 2H), 1.09−0.97 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 170.9, 150.8, 146.5, 134.1, 133.8, 133.0, 130.2, 129.4, 128.3, 127.2, 127.1, 122.2, 112.5, 42.9, 41.7, 33.0, 27.8, 23.7 ppm. HRMS (ESI), m/z calcd for $C_{18}H_{21}N_3O_6SNa$ $[M + Na]^+$ 430.1043, found 430.1040.

Spectrophotometric Monitoring of the Conversion Rates in the HIRE Reaction. The conversion was monitored using a UV-1800 Shimadzu double-beam spectrophotometer using 10.00 mm quartz cells. Measurements were performed at room temperature (23 °C). The solutions of ammonium hydrochloride salts obtained by deprotection of **9a−n** or **11a−n** were prepared by dissolving 0.01 mmol of the respective compound in 1:1 H_2O/MeOH (10 mL) and making up the total volume to 100 mL. The calibration curves were generated at four concentrations: 0.1, 0.05, 0.025, and 0.0125 mM. To start the measurements, the starting solution prepared as described above (3 mL) was placed in a 10.00 mm quartz cell. Then 10% aq NaOH solution (100 μL) was added, and the monitoring was started. The UV spectra were run at equal time intervals. The conversion of the starting materials was evaluated using calibration curves. The first-order reaction rate constants were calculated graphically.

Sample Preparation for the Crystal Growth. The solutions of the compounds **12a**, **12e**, **12n**, **13a**, **13b**, **13e**, **13f**, **13h**, **13l**, **13n**, **14b**, and **14c** in DMSO-d_6 after NMR experiments were filtered through a syringe filter and left in open vials until crystals grew.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00236.

X-ray crystallographic information for compounds **12a**, **12e**, **12n**, **13a**, **13b**, **13e**, **13f**, **13h**, **13l**, **13n**, **14b**, and **14c**; example of k_{obs} calculation for compound **9a**; copies of ^1H and ^{13}C NMR spectra; NMR assignment of compound **13a**; EXSY/NOESY spectra; results of variable temperature NMR; NOE-based distance calculations; Monte Carlo conformational search; ensemble atom coordinates (PDF)

Accession Codes

CCDC 2046962−2046963, 2046965, 2046967−2046972, and 2046974−2046976 contain the supplementary crystallographic

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data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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