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Rare Medium-Sized Rings Prepared via Hydrolytic Imidazoline Ring Expansion (HIRE)

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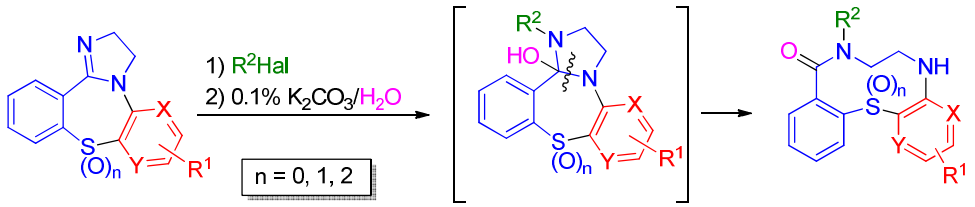


ABSTRACT: The hydrolytic imidazoline ring expansion (HIRE) methodology was extended to readily available tetracyclic [1,4]thiazepines as well as sulfoxide and sulfone analogs thereof. The reactions resulted in the facile formation of a rare medium-sized [1,4,7]thiazecine ring system that has an emerging utility in bioactive compound design. Comparing the HIRE rates for representative compounds in the three groups of substrates allowed drawing some generalizations about the substituent effects on the course of the reaction.

Introduction

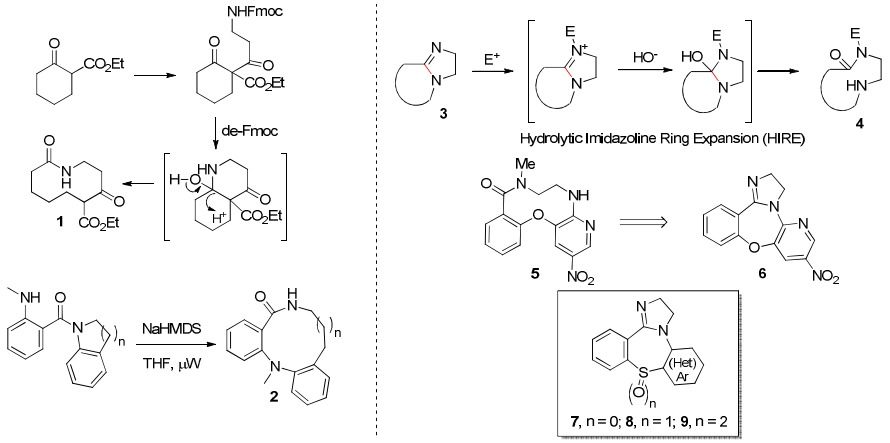
Small-sized (particularly, 5- to 7-membered) rings are omnipresent in existing screening collections for drug discovery.[1] However, due to their reduced flexibility, such compounds can adopt a limited number of conformations, which reduces the chances of finding among them a molecule with an optimal fit for a particular protein target. Excessive conformational flexibility (rotatable bond count) featured in linear scaffolds is also undesired due to impaired cell membrane permeability and intestinal absorption of a future drug.[2] Thus, medium-sized (8- to 11-membered) rings appear to be an optimum scaffold choice for compounds intended for interrogation of biological targets.[3] On the one hand, the cyclic character of such frameworks limits the range of lower-energy conformations the respective compounds can adopt. On the

other hand, this range is sufficiently large for a single compound to optimally present its molecular periphery for a tight and selective binding to a protein.[4] Such multi-conformational small molecule tools are particularly desired when poorly 'druggable' targets are concerned (e. g., protein-protein interactions).[5]

Unfortunately, the area of chemical space corresponding to medium-size rings is quite underpopulated in terms of tangible compounds that can be screened for bioactivity.[6] Most likely, this situation has to do with the difficulty to obtain such compounds via synthesis (which hinders their deposition in screening collections and progression through medicinal chemistry optimization programs).[7] Entropy constraints are the major contributing factor limiting the applicability of ring-closing strategies to construct medium-sized rings; additionally, formation of such rings can be associated with unfavorable enthalpy changes due to destabilizing transannular interactions.[8] An alternative – and significantly more prolific – approach lies in exploring various ring expansion opportunities.[9] The latter are normally recognized in polycyclic systems with some degree of instability which is released via breaking of a central bond which leads to energy-lowering transformations such aromatization or strain relief. Recent illustrative examples include synthesis of 10-membered lactam **1** from readily available 2-oxocyclohexancarboxylic acid by Unsworth and co-workers[3] and conformationally induced Smiles ring expansion synthesis of dibenzodiazepine analogs **2** reported by Clayden and co-workers[10] as well as other examples from these two groups.[11] In recent years, we have been involved[12] in exploring *N*-(hetero)aryl 2-imidazolines as privileged motifs for drug discovery as well as versatile templates for scaffold-oriented synthesis.[13] This led us to an idea of considering polycyclic 2-imidazolines **3** as potential objects for ring expansion driven by hydrolysis and resulting in the formation of lactams **4**. This resulted in the development of an expedited and atom-economical route to [1,4,7]oxadiazecin-9(6*H*)-ones **5** from readily available[14] tetracyclic [1,4]oxazepines **6**.[15] Herein, we describe an extension of the hydrolytic imidazoline ring expansion (HIRE) methodology to tetracyclic [1,4]thiazepines **7** as well as their sulfoxide (**8**)

and sulfone (**9**) analogs) which offers more flexibility with the periphery group variation and provides some insights into substituent effects on the rate of the HIRE reaction (Figure 1).

Figure 1. Recent examples of medium-sized ring synthesis via ring expansion and the substrate focus of the present study.



Results and Discusssion

Preparation of [1,4]thiazepines fused to two aromatic rings and a 2-imidazoline cycles (such as **7**) has been described previously.[16-17] Following a modified procedure for the synthesis of 2-(4,5-dihydro-1*H*-imidazol-2-yl)benzenethiol (**10**) and its condensation with various bis-electrophilic (hetero)aromatic substrates **11a-k**, a set of 2,3-dihydroimidazo[1,2-*d*][1,4]thiazepines **7a-k** was obtained. The regiochemistry of the double S_NAr reaction leading to the formation of **7** is governed by the intermittent Smiles rearrangement which was observed in all similar reactions studies by us[18] and others[16-17] before and also confirmed in this case by a single-crystal X-ray analysis (see Supporting Information) of representative compounds obtained in this work (Scheme 1). The synthesis of tetracyclic compounds **7** was conducted overnight at variable temperature depending on the electrophilicity of the respective aromatic substrate **11** and resulted in good to excellent yields of the target products (Table 1).

Scheme 1. Preparation and the use of thiophenol **10** in the synthesis of 2,3-dihydroimidazo[1,2-*d*][1,4]thiazepines **7a-k**.

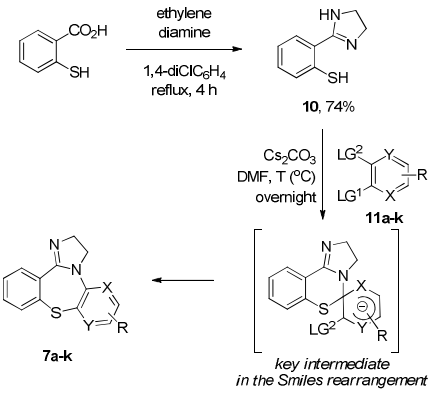
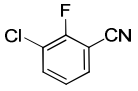
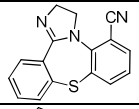
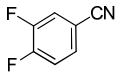
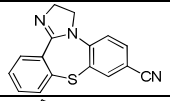
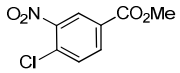
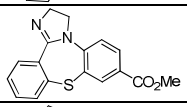
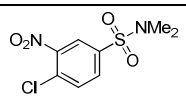
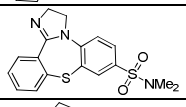
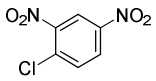
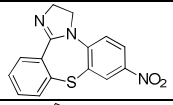
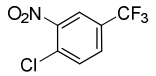
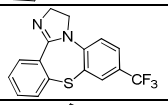
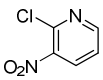
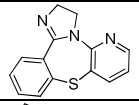
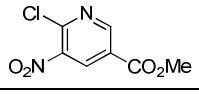
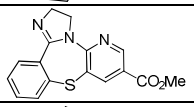
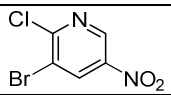
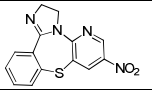
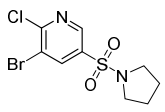
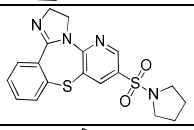
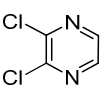
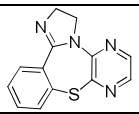


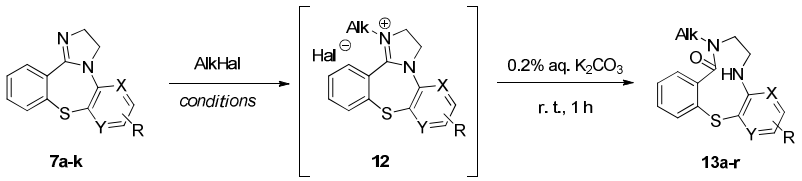
Table 1. 2,3-Dihydroimidazo[1,2-*d*][1,4]thiazepines **7a-k** prepared in this work.

Entry	Compound	Bis-electrophile **11**	Product **7**	Temperature (ºC)	Yield, %
1	**7(11)a**			50	89
2	**7(11)b**			50	87
3	**7(11)c**			75	79
4	**7(11)d**			75	66
5	**7(11)e**			r. t.	91
6	**7(11)f**			50	95
7	**7(11)g**			75	72
8	**7(11)h**			50	51
9	**7(11)i**			50	90
10	**7(11)j**			75	86
11	**7(11)k**			r. t.	76

As it was previously observed for the respective 2,3-dihydroimidazo[1,2-*d*][1,4]oxazepines,[15] tetracycles **7** failed to undergo hydrolytic ring expansion, even on prolonged heating in basic or

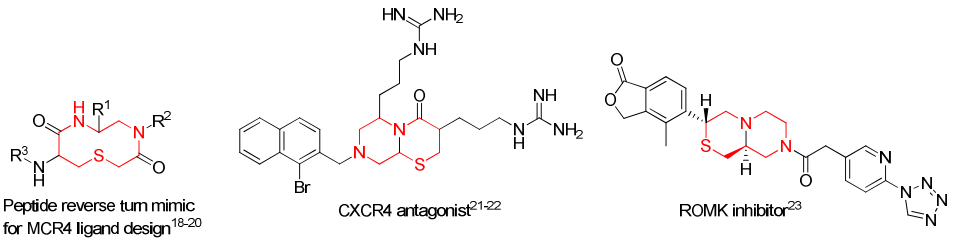
acidic aqueous acetonitrile. Activation of the 2-imidazoline, via N^3-alkylation, towards the nucleophilic attack of hydroxide anion made the respective imidazolinium species **12** quite reactive in the subsequent HIRE reaction as shown in Scheme 2 and the complete conversion of 2,3-dihydroimidazo[1,2-*d*][1,4]thiazepines **7** to the respective [1,4,7]thiadiazecines (**13a-r**) was achieved within 1 h at room temperature. The ring-enlarged products **13a-r** were obtained in moderate to good yields over two steps (Table 2, entries 1-18).

Scheme 2. The HIRE reaction of tetracycles **7** towards [1,4,7]thiadiazecines **13**.



[1,4,7]Thiadiazecines **13** are representatives of a rare medium-sized ring system. However, its utility as a peptide reverse turn mimic has been recently revealed by the Haskell-Luevano group in the design of melanocortin receptor ligands.[19-21] Constrained bicyclic versions featuring a similar framework have been employed as a scaffold for CXCR4 antagonists[22-23] and ROMK potassium channel blockers[24] (Figure 2).

Figure 2. Examples of bioactive compounds incorporating [1,4,7]thiadiazecine ring system.

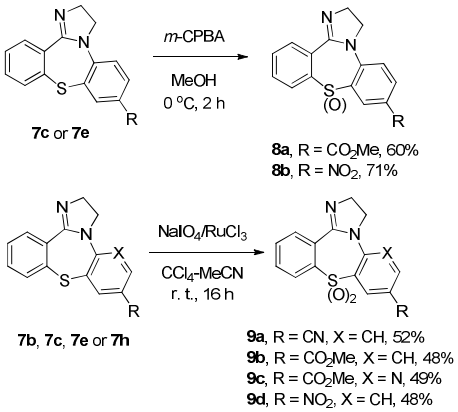


One notable feature of compounds **13** compared to their oxygen counterparts **5** is the greater diversity of substituents (Alk) on the lactam nitrogen atom that can be introduced via alkylation of the 2-imidazoline moiety in the tetracyclic precursors (**7** and **6**, respectively). With compounds **6** as substrates, we did not succeed at introducing any substituents at the imidazoline

N^3 atom besides methyl or ethyl group. On the contrary, 2,3-dihydroimidazo[1,2-*d*][1,4]thiazepines **7** turned out to be quite reactive toward alkyl iodides and bromides – with benzyl bromides reacting on conventional heating (or even ambient temperature – *vide infra*). A general explanation could be in the greater nucleophilicity of the 2-imidazoline moiety in **7** compared to the same in **6**. The difference in electron-donating properties of oxygen atom *vs.* sulfur (**6** *vs.* **7**) is unlikely to be a significant factor: the oxygen atom is likely to be in a better conjugation with the imidazoline's amidine group and thus **6** should have been more nucleophilic. Most likely, the observed higher reactivity of 2-imidazoline moiety in **7** towards alkylating agents has to do with the geometry differences introduced in the tetracyclic system by the larger sulfur atom.

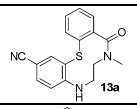
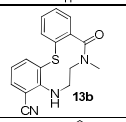
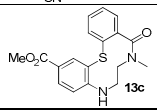
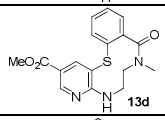
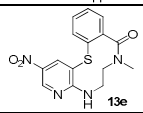
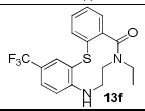
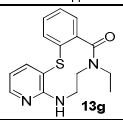
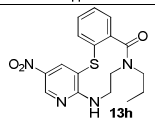
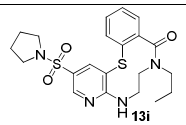
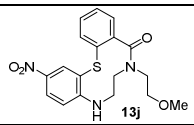
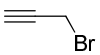
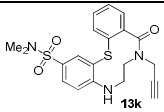
We were also quite curious to see whether oxidation of the sulfur atom in **7** (to produce sulfoxides **8** or sulfones **9**) would have a noticeable effect on the HIRE reaction. To this end, we prepared sulfoxides **8a-b** by brief exposure of the respective sulfide precursors **7** to *m*-CPBA (longer reaction times led to further oxidation to sulfone). Sulfones **9a-d** were prepared using sodium periodate – ruthenium(III) chloride system.[25] Both sets of oxidized substrates for the HIRE reaction were obtained in moderate to good yields (Scheme 3).

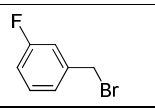
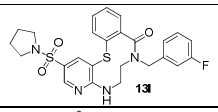
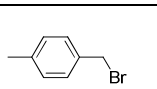
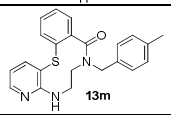
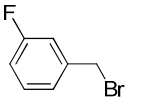
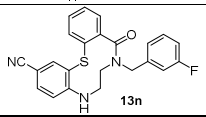
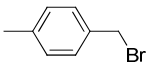
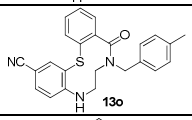
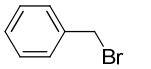
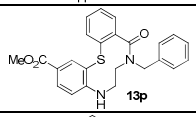
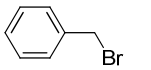
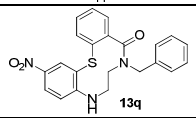
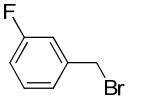
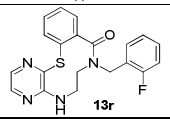
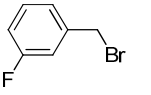
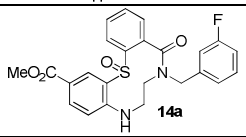
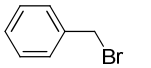
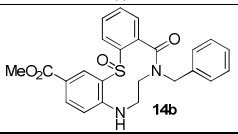
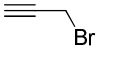
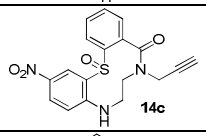
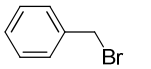
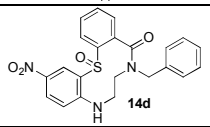
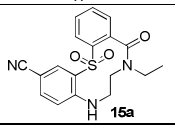
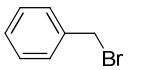
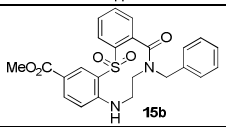
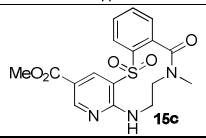
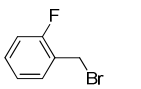
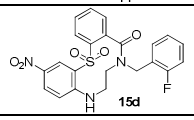
Scheme 3. Synthesis of sulfoxides **8a-b** and sulfones **9a-d**.



All of the sulfoxide (**8a-b**) and sulfone (**9a-d**) substrates thus synthesized displayed good reactivity in the HIRE reaction, upon activation with alkylating agents, under conditions analogous to those shown in Scheme 2 for sulfide substrates **7a-k**. The respective ring-expanded 1,4,7-thiadiazecine-1-oxides **14a-d** and 1,4,7-thiadiazecine 1,1-dioxides **15a-d** were obtained in good yields over two steps (Table 2, entries 19-26).

Table 2. [1,4,7]Thiadiazecines **13a-r**, **14a-d** and **15a-d** prepared in this work.

Entry	Starting material **7**	AlkHal	Product **13**	Alkylation conditions[a]	Yield, %
1	**7b**	MeI	 **13a**	A	64
2	**7a**	MeI	 **13b**	A	58
3	**7c**	MeI	 **13c**	A	67
4	**7h**	MeI	 **13d**	A	40
5	**7i**	MeI	 **13e**	A	65
6	**7f**	EtI	 **13f**	A	43
7	**7g**	EtI	 **13g**	A	47
8	**7i**	*n*-PrI	 **13h**	A	38
9	**7j**	*n*-PrI	 **13i**	A	50
10	**7e**	$MeO(CH_2)_2Br$	 **13j**	A	33
11	**7d**		 **13k**	A	35

12	**7j**		 **13l**	B	60
13	**7g**		 **13m**	B	49
14	**7b**		 **13n**	B	56
15	**7b**		 **13o**	B	42
16	**7h**		 **13p**	B	53
17	**7j**		 **13q**	B	51
18	**7k**		 **13r**	B	41
19	**8a**		 **14a**	B	55
20	**8a**		 **14b**	B	43
21	**8b**		 **14c**	A	38
22	**8b**		 **14d**	B	62
23	**9a**	EtI	 **15a**	A	46
24	**9b**		 **15b**	B	42
25	**9c**	MeI	 **15c**	A	33
26	**9d**		 **15d**	B	50

[a]Conditions – A: AlkHal (1.05 equiv.), MeCN, μW at 120 ºC, 5 h; B: AlkHal (1.05 equiv.), MeCN, 60 ºC, 16 h.

Converting divalent sulfur in substrates **7** into electron-withdrawing sulfoxide and sulfone substituents (as in **8** and **9**) can be expected to significantly influence the course of the HIRE reaction due to the direct conjugation of these groups to the imidazolinium moiety and the nitrogen atom of the 'aniline' leaving group formed as a result of the ring expansion. In order to compare the HIRE rates for the sulfide, sulfoxide and sulfone variants of the tetracyclic HIRE substrates, we prepared pure imidazolinium salts **16a-c** (Scheme 4) and investigated their time-dependent conversion under the HIRE conditions. The data obtained are shown in Figure 3.

Scheme 4. Preparation of imidazolinium salts **16a-c**.

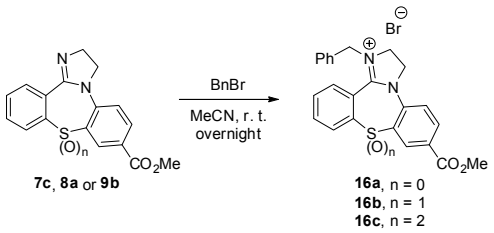
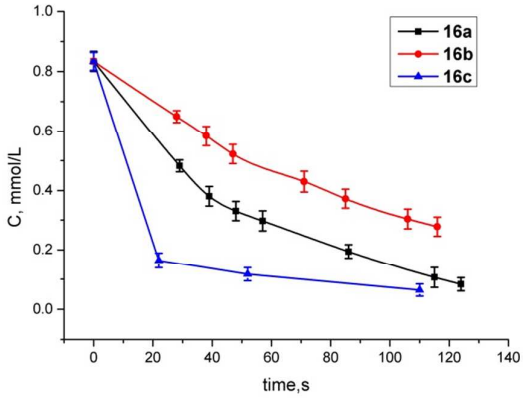


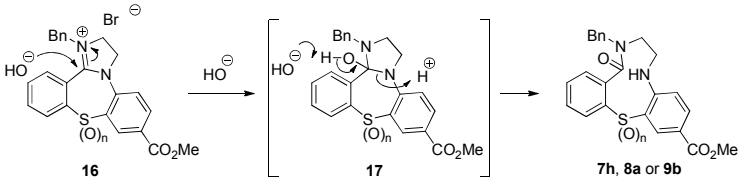
Figure 3. Comparison of HIRE conversion rates for compounds **16a-c**.



As was expected, sulfone **16c** prove to be much more reactive compared to sulfide **16a**, with most of the starting material disappearing within 20 seconds from the reaction start. This is justified both by the increased electrophilicity of the imidazolinium group toward the hydroxide

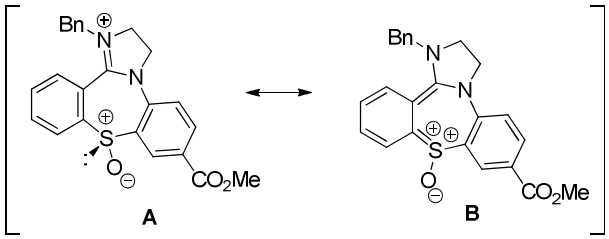
anion (facilitating the formation of tetrahedral intermediate **17**) and the push-pull interaction with the anilinic nitrogen in the HIRE product (Scheme 5).

Scheme 5. Plausible mechanistic pathway for the HIRE reaction of **16a-c**.



However, the fact that sulfoxide **16b** turned out to be even somewhat less reactive than sulfide **16a**, was quite surprising. Such a reactivity pattern can, in principle, be justified by a possible participation of the sulfur unshared electron pair in **16b** in the conjugation with the imidazolinium fragment, which would reduce the electrophilicity of the latter (Figure 4). The lower value of dihedral angle between the imidazolinium ring and the nearby benzene ring in the single-crystal X-ray structure of **16b** compared to that in **16a** (67º and 70º, respectively) argues for the correctness of such an interpretation (see Supporting Information). Additionally, DFT calculations of atomic charges on the amidine carbon atoms of compounds **16a-c** confirmed a lower positive charge in case of sulfoxide **16b** compared to sulfide **16a** (see Supporting Information). This is also in line with the observed relative reactivity of the three substrates under HIRE conditions.

Figure 4. Possible resonance structures in **16b**.



Conclusion

In summary, we described an application of the hydrolytic imidazoline ring expansion (HIRE) reaction to 2,3-dihydroimidazo[1,2-*d*][1,4]thiazepines as well as their sulfoxide and sulfone analogs activated by *N*-alkylation of the 2-imidazoline moiety. The resulting ten-membered lactams contain a rare medium-sized ring system that has recently emerged as a versatile scaffold in bioactive compound design.

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) in DMSO-d_6 or in $CDCl_3$ or in Acetone-d_6 and were referenced to residual solvent proton signals (δ_H = 2.50, 7.26 and 2.05 ppm, respectively) and solvent carbon signals (δ_C = 39.52, 77.00 and 206.26 ppm, respectively). For the HPLC-UV analysis was used chromatograph MiLiChrom A-02 (Econova, Novosibirsk, Russia). Microwave-assisted reactions were performed in the Biotage® Initiator+ microwave synthesizer reactor using a sealed reaction vessel. Mass spectra were recorded with a HRMS-ESI-qTOF spectrometer (ESI ionization). Melting points were determined with an automated heat block instrument and are uncorrected. Single crystal X-ray data were obtained using an Agilent Technologies SuperNova Atlas and an Agilent Technologies Xcalibur Eos diffractometers at a temperature of 100 K. Column chromatography was carried out with silica gel grade 60 (0.040–0.063 mm) 230–400 mesh. Chlorobenzene, dichloromethane and MeCN were distilled over P_2O_5 and stored over molecular sieves 3 Å. THF and 1,4-dioxane were distilled after refluxing with sodium-benzophenone and stored over molecular sieves 3 Å.

Preparation of 2-(4,5-Dihydro-1H-imidazol-2-yl)-benzenethiol 10

To a suspension of thiosalicylic acid (10.00 g, 0.065 mol) in 1,2-dichlorobenzene (100 mL) was added ethylenediamine (11 mL, 0.183 mol) and refluxed under nitrogen for 4 h then cooled to 60°C and methanol (15 mL) was added. The solution was stirred at room temperature overnight

and the resulting yellow crystalline solid was collected and washed with methanol and ether to give pure product.

Yield 8.5g, 74%; yellow solid, mp 247-248 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (br.s, 2H), 7.59 (dd, J = 8.1 Hz, J = 1.3 Hz, 1H), 7.43 (dd, J = 8.2 Hz, J = 1.3 Hz, 1H), 7.01 (ddd, J = 8.2 Hz, J =7.1 Hz, J = 1.5 Hz, 1H), 6.79 (ddd, J = 8.1 Hz, J = 7.1 Hz, J = 1.3 Hz, 1H), 3.89 (s, 4H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 166.7, 137.3, 129.7, 129.1, 129.1, 119.2, 118.7, 43.9, 43.9 ppm. HRMS (ESI), *m/z* calcd for $C_9H_{11}N_2S^+$ $[M+H]^+$ 179.0639, found 179.0637.

General procedure for preparation of 2,3-dihydroimidazo[1,2-d][1,4]thiazepines 7a-k

A solution of **10** (500 mg, 2.800 mmol) and bis-electrophile **11** (1.867 mmol) in anhydrous DMF (10 mL) containing anhydrous Cs_2CO_3 (1370 mg, 5.600 mmol) was heated at a given temperature (Table 1) for overnight. DMF was removed in vacuo and water was added (10 mL). This suspension was stirred 2 h at room temperature, the resulting solid was collected and washed with water, recrystallized from propanol-2/water to provide the analytically pure product.

2,3-Dihydrodibenzo[*b*,*f*]imidazo[1,2-*d*][1,4]thiazepine-5-carbonitrile (7a)

Yield 462 mg, 89%; light beige solid; mp 185-187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (dd, J = 7.8 Hz, J = 1.6 Hz, 1H$_{Ar}$), 7.85 (dd, J = 7.8 Hz, J = 1.6 Hz, 1H), 7.71 – 7.62 (m, 1H), 7.61 – 7.55 (m, 1H), 7.49 – 7.45 (m, 2H), 7.26 (t, J = 7.8 Hz, 1H), 4.81 – 4.72 (m, 1H), 4.13 – 3.81 (m, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 159.4, 144.7, 138.4, 135.5, 134.9, 134.7, 132.3, 131.5, 131.4, 130.8, 129.5, 125.3, 117.1, 107.3, 52.5, 52.4 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{12}N_3S^+$ $[M+H]^+$ 278.0746, found 278.0751.

2,3-Dihydrodibenzo[*b*,*f*]imidazo[1,2-*d*][1,4]thiazepine-7-carbonitrile (7b)

Yield 451 mg, 87%; light beige solid; mp 152-154 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H), 7.69 (dd, J = 7.5 Hz, J = 1.6 Hz, 1H), 7.56

(dd, J = 7.5 Hz, J = 1.6 Hz, 1H), 7.49 (td, J = 7.5 Hz, J = 1.6 Hz, 1H), 7.44 (dd, J = 7.5 Hz, J = 1.6 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 4.17 (s, 2H), 3.93 (t, J = 9.2 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 159.5, 146.8, 137.0, 134.7, 134.6, 133.9, 132.3, 132.0, 132.0, 129.7, 126.3, 120.0, 118.6, 105.0, 52.8, 51.9 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{12}N_3S^+$ $[M+H]^+$ 278.0746, found 278.0750.

Methyl 2,3-dihydrodibenzo[*b,f*]imidazo[1,2-*d*][1,4]thiazepine-7-carboxylate (7c)

Yield 459 mg, 79%; white solid; mp 182-184 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 2.1 Hz, 1H), 7.91 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H), 7.69 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.59 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.47 (td, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.41 (td, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 4.17 (s, 2H), 3.93 (t, J = 9.3 Hz, 2H), 3.82 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 165.0, 159.3, 146.4, 134.3, 133.9, 133.8, 131.7, 131.5, 131.4, 131.1, 129.0, 125.1, 123.5, 118.9, 52.2, 52.1, 51.4 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{15}N_2O_2S^+$ $[M+H]^+$ 311.0849, found 311.0851.

***N,N*-dimethyl-2,3-dihydrodibenzo[*b,f*]imidazo[1,2-*d*][1,4]thiazepine-7-sulfonamide (7d)**

Yield 444 mg, 66%; light yellow solid; mp 211-213 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 2.2 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.61 (dd, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.49 (td, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.43 (td, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 4.19 (s, 2H), 3.94 (t, J = 9.2 Hz, 2H), 2.60 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 159.6, 146.7, 134.8, 134.0, 132.3, 132.3, 132.02, 132.0, 130.1, 129.7, 128.7, 126.2, 119.8, 52.9, 51.9, 38.0 (2C) ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{18}N_3O_2S_2^+$ $[M+H]^+$ 360.0835, found 360.0836.

7-Nitro-2,3-dihydrodibenzo[*b,f*]imidazo[1,2-*d*][1,4]thiazepine (7e)

Yield 505 mg, 91%; yellow solid; mp 214-216 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, J = 2.7 Hz, 1H), 8.22 (dd, J = 9.0 Hz, J = 2.7 Hz, 1H), 7.71 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.62 (dd, J = 7.6 Hz, J = 1.4 Hz, 1H), 7.52 (td, J = 7.5 Hz, J = 1.7 Hz, 1H), 7.45 (td, J = 7.5 Hz, J = 1.4 Hz, 1H), 7.38 (d, J = 9.1 Hz, 1H), 4.22 (s, 2H), 3.98 (t, J = 9.1 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR

(101 MHz, DMSO-d_6) δ 158.8, 148.0, 141.0, 134.2, 133.1, 131.9, 131.6, 131.6, 129.3, 128.1, 125.7, 125.0, 119.1, 52.6, 51.5 ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{12}N_3O_2S^+$ $[M+H]^+$ 298.0645, found 298.0647.

7-(Trifluoromethyl)-2,3-dihydrodibenzo[*b*,*f*]imidazo[1,2-*d*][1,4]thiazepine (7f)

Yield 569 mg, 95%; white solid; mp 169-171 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, J = 2.2 Hz, 1H), 7.70 (td, J = 7.8 Hz, J = 2.0 Hz, 2H), 7.58 (dd, J = 7.6 Hz, J = 1.4 Hz, 1H), 7.48 (td, J = 7.5 Hz, J = 1.8 Hz, 1H), 7.37 – 7.45 (m, 2H), 4.18 (s, 2H), 3.93 (t, J = 9.3 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 159.7, 146.3, 134.7, 134.2, 132.2, 132.0, 132.0, 130.1 (q, J = 3.3 Hz), 129.6, 127.6 (q, J = 3.5 Hz), 126.5, 124.2 (q, J = 271.9 Hz, CF_3), 123.3 (q, J = 32.7 Hz), 120.0, 52.7, 51.8 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{12}F_3N_2S^+$ $[M+H]^+$ 321.0670, found 321.0668.

2,3-Dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido[3,2-*b*][1,4]thiazepine (7g)

Yield 341 mg, 72%; light beige solid; mp 136-138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (dd, J = 4.8 Hz, J = 1.8 Hz, 1H), 7.92 (dd, J = 7.6 Hz, J = 1.8 Hz, 1H), 7.76 (dd, J = 7.6 Hz, J = 1.7 Hz, 1H), 7.57 (dd, J = 7.6 Hz, 1.4 Hz, 1H), 7.48 (td, J = 7.5 Hz, J = 1.7 Hz, 1H), 7.42 (td, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.03 (dd, J = 7.6 Hz, J = 4.8 Hz, 1H), 4.23 (t, J = 9.5 Hz, 2H), 3.90 (t, J = 9.5 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 158.7, 153.9, 148.5, 141.2, 133.8, 133.5, 131.9, 131.7, 131.5, 128.9, 120.2, 118.7, 51.1, 51.0 ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{12}N_3S^+$ $[M+H]^+$ 254.0746, found 254.0750.

Methyl 2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido[3,2-*b*][1,4]thiazepine-7-carboxylate (7h)

Yield 297 mg, 51%; white solid; mp 169-171 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, J = 2.2 Hz, 1H), 8.27 (d, J = 2.1 Hz, 1H), 7.77 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.62 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.53 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.46 (td, J = 7.6 Hz, J = 1.6 Hz, 1H), 4.29 (t, J = 9.2 Hz, 2H), 3.95 (t, J = 9.2 Hz, 2H), 3.85 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 158.3, 144.5, 143.6, 140.3, 138.0, 133.2, 131.4, 131.3, 126.8, 123.0, 121.1, 119.1, 118.5,

77.4, 51.8, 51.5 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{14}N_3O_2S^+$ $[M+H]^+$ 312.0809, found 312.0807.

7-Nitro-2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido[3,2-*b*][1,4]thiazepine (7i)

Yield 502 mg, 90%; light yellow solid; mp 226-228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (d, J = 2.8 Hz, 1H), 8.57 (d, J = 2.8 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.55 (td, J = 7.6 Hz, J = 1.8 Hz, 1H), 7.52 – 7.44 (m, 1H), 4.32 (t, J = 8.9 Hz, 2H), 3.98 (t, J = 8.9 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 157.0, 157.0, 144.3, 138.1, 135.2, 133.4, 131.8 (2C) 131.5, 131.2, 128.9, 118.3, 51.7, 51.1 ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{11}N_4O_2S^+$ $[M+H]^+$ 299.0599, found 299.0597.

7-(Pyrrolidin-1-ylsulfonyl)-2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido[3,2-*b*][1,4]thiazepine (7j)

Yield 607 mg, 86%; light yellow solid; mp 177-179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, J = 2.3 Hz, 1H), 8.16 (d, J = 2.3 Hz, 1H), 7.78 (dd, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.63 (dd, J = 7.6 Hz, 1.5 Hz, 1H), 7.54 (td, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.47 (td, J = 7.6 Hz, J = 1.5 Hz, 1H), 4.29 (t, J = 9.2 Hz, 2H), 3.96 (t, J = 9.2 Hz, 2H), 3.14 – 3.20 (m, 4H), 1.73 – 1.66 (m, 4H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 157.8, 156.2, 147.3, 139.4, 133.7, 132.2 (2C), 132.1, 131.7, 129.3, 126.6, 119.4, 51.80, 51.2, 47.8, 47.8, 24.7, 24.7 ppm. HRMS (ESI), *m/z* calcd for $C_{18}H_{19}N_4O_2S_2^+$ $[M+H]^+$ 387.0940, found 387.0944.

2,3-Dihydrobenzo[*f*]imidazo[1,2-*d*]pyrazino[2,3-*b*][1,4]thiazepine (7k)

Yield 362 mg, 76%; light beige solid; mp 123-125 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, J = 2.6 Hz, 1H), 8.16 (d, J = 2.6 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 4.23 (t, J = 9.3 Hz, 2H), 3.96 (t, J = 9.2 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 158.3, 151.0, 142.8, 142.7, 138.0, 133.6, 132.7 (2C), 132.5, 131.3, 129.7, 51.9, 51.8 ppm. HRMS (ESI), *m/z* calcd for $C_{13}H_{11}N_4S^+$ $[M+H]^+$ 255.0703, found 255.0699.

General procedure for one-pot preparation of [1,4,7]-thiadiazecines 13a-r

To a microwave reaction vial were added the solution of the respective imidazoline-fused [1,4]thiazepine **7a-k** (0.35 mmol) and AlkHal (0.368 mmol) in acetonitrile (10 mL). The resulting mixture was stirred in the microwave for 5 h at 120°C. After cooling to RT, 0.2% aqueous K_2CO_3 (10 mL) was added and stirred for 1 h at room temperature (the reaction was monitored by TLC in THF-Hexane (3:1) or EtOAc). Then CH_2Cl_2 (2x4 mL) were added and the organic layer was separated using centrifuge, washed with water and dried over Na_2SO_4, evaporated and purified by column chromatography eluting with EtOAc.

8-Methyl-9-oxo-6,7,8,9-tetrahydro-5*H*-dibenzo[*b,i*][1,4,7]thiadiazecine-2-carbonitrile (13a)

Yield 69 mg, 64%; white solid; mp 195-197 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.58 (dd, J = 8.6 Hz, J = 2.0 Hz, 1H), 7.37 (td, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.31 (td, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.13 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 5.47 (dd, J = 8.6 Hz, J = 4.2 Hz, 1H), 3.57 (ddt, J = 14.8 Hz, J = 11.0 Hz, J = 3.7 Hz, 1H), 3.31 – 3.13 (m, 3H), 2.91 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 169.2, 154.7, 140.1, 139.5, 135.1, 134.5, 130.8, 130.2, 128.5, 127.6, 121.8, 119.6, 116.8, 100.2, 53.5, 42.8, 32.1 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{16}N_3OS^+$ $[M+H]^+$ 310.1008, found 310.1009.

8-Methyl-9-oxo-6,7,8,9-tetrahydro-5*H*-dibenzo[*b,i*][1,4,7]thiadiazecine-4-carbonitrile (13b)

Yield 63 mg, 58%; white solid; mp 207-209 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (dd, J = 7.7 Hz, J = 1.6 Hz, 1H), 7.80 – 7.74 (m, 1H), 7.68 (dd, J = 7.7 Hz, J = 1.6 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.22 – 7.16 (m, 1H), 6.97 (t, J = 7.7 Hz, 1H), 5.41 (dd, J = 10.5 Hz, J = 1.8 Hz, 1H), 3.74 – 3.61 (m, 1H), 3.51 – 3.40 (m, 1H), 3.18 (ddd, J = 14.3 Hz, J = 3.1 Hz, J = 1.4 Hz, 1H), 3.11 – 3.04 (m, 1H), 3.03 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 169.0, 154.1,

141.6, 141.0, 136.3, 135.1, 129.9, 129.7, 129.1, 126.5, 126.3, 121.1, 117.8, 102.2, 52.3, 44.2, 30.6 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{16}N_3OS^+$ $[M+H]^+$ 310.1005, found 310.1009.

Methyl 8-methyl-6,7,8,9-tetrahydro-5*H*-dibenzo[*b,i*][1,4,7]thiadiazecine-2-carboxylate (13c)

Yield 81 mg, 67%; white solid; mp 174-176 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 2.1 Hz, 1H), 7.76 (dd, J = 8.6 Hz, J = 2.1 Hz, 1H), 7.57 (dd, J = 7.5 Hz, J = 1.4 Hz, 1H), 7.35 (td, J = 7.5 Hz, J = 1.7 Hz, 1H), 7.29 (td, J = 7.5 Hz, J = 1.4 Hz, 1H), 7.11 (dd, J = 7.5 Hz, J = 1.7 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 5.32 (dd, J = 8.3 Hz, J = 4.5 Hz, 1H), 3.80 (s, 3H), 3.58 (ddt, J = 14.5 Hz, J = 9.3 Hz, J = 5.2 Hz, 1H), 3.31 – 3.18 (m, 3H), 2.88 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.7, 165.5, 154.6, 138.7, 137.0, 133.6, 132.1, 130.6, 129.7, 127.8, 127.2, 120.1, 119.3, 115.6, 53.0, 51.7, 42.6, 31.7 ppm. HRMS (ESI), *m/z* calcd for $C_{18}H_{21}N_2O_2S^+$ $[M+H]^+$ 329.1328, found 329.1326.

Methyl 8-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecine-2-carboxylate (13d)

Yield 48 mg, 40%; white solid; mp 153-156 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 2.2 Hz, 1H), 7.49 (dd, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.36 (td, J = 7.6 Hz, 1.5 Hz, 1H), 7.27 (td, J = 7.5 Hz, 1.2 Hz, 1H), 7.09 (dd, J = 7.7 Hz, J = 1.6 Hz, 1H), 6.02 (dd, J = 7.6 Hz, J = 5.0 Hz, 1H), 4.06 – 3.91 (m, 1H), 3.81 (s, 3H), 3.45 – 3.33 (m, 2H), 3.28 (dd, J = 13.7 Hz, 3.1 Hz, 1H), 2.72 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.2, 164.8, 161.7, 150.8, 142.9, 142.9, 136.0, 131.3, 129.4, 129.3, 128.1, 126.7, 115.7, 112.8, 53.5, 51.8, 32.3 ppm. HRMS (ESI), *m/z* calcd for HRMS (ESI), *m/z* calcd for $C_{17}H_{20}N_3O_2S^+$ $[M+H]^+$ 330.1271, found 330.1275.

8-Methyl-2-nitro-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecin-9-one (13e)

Yield 80 mg, 65%; light yellow solid; mp 181-183°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (d, J = 2.6 Hz, 1H), 8.54 (d, J = 2.6 Hz, 1H), 7.53 (dd, J = 8.1 Hz, J = 1.1 Hz, 1H), 7.38 (td, J = 7.7

Hz, *J* = 1.6 Hz, 1H), 7.28 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.11 (dd, *J* = 7.7 Hz, *J* = 1.5 Hz, 1H), 6.64 (t, *J* = 6.1 Hz, 1H), 4.09 – 3.97 (m, 1H), 3.50 – 3.32 (m, 3H), 2.75 (s, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 168.3, 161.7, 146.3, 137.1, 135.8, 135.3, 131.3, 129.4, 128.7, 128.2, 126.8, 113.0, 53.4, 40.6, 32.5 ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{14}N_4NaO_3S^+$ $[M+Na]^+$ 353.0679, found 353.0684.

8-Ethyl-2-(trifluoromethyl)-5,6,7,8-tetrahydro-9*H*-dibenzo[*b,i*][1,4,7]thiadiazecin-9-one (13f)

Yield 55 mg, 43%; white solid; mp 140-142°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, *J* = 2.2 Hz, 1H), 7.65 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 7.50 (dd, *J* = 8.5 Hz, *J* = 2.3 Hz, 1H), 7.36 (td, *J* = 7.6 Hz, *J* = 1.9 Hz, 1H), 7.31 (td, *J* = 7.4 Hz, *J* = 1.5 Hz, 1H), 7.08 (dd, *J* = 7.3 Hz, *J* = 1.8 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 5.31 (dd, *J* = 8.7 Hz, *J* = 3.8 Hz, 1H), 3.67 – 3.50 (m, 2H), 3.31 – 3.21 (m, 2H), 3.14 – 3.05 (m, 2H), 1.18 (t, *J* = 7.0 Hz, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 168.4, 153.9, 139.3, 134.0, 132.6 (d, *J* = 4.1 Hz), 130.1, 129.7, 128.1, 127.9 (q, *J* = 3.6 Hz), 127.1, 124.3 (q, *J* = 270.9 Hz), 121.0, 118.7 (q, *J* = 32.4 Hz), 116.5, 50.4, 43.1, 38.0, 12.7 ppm. HRMS (ESI), m/z calcd for $C_{18}H_{18}F_3N_2OS$ $[M+H]^+$ 367.1086, found 367.1084.

8-Ethyl-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecin-9-one (13g)

Yield 49 mg, 47%; white solid; mp 128-130 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (dd, *J* = 4.8, *J* = 1.8 Hz, 1H), 7.91 (dd, *J* = 7.5, *J* = 1.8 Hz, 1H), 7.54 (dd, *J* = 7.6, *J* = 1.4 Hz, 1H), 7.34 (td, *J* = 7.6, *J* = 1.7 Hz, 1H), 7.29 (td, *J* = 7.6, *J* = 1.4 Hz, 1H), 7.04 (dd, *J* = 7.6 Hz, *J* = 1.7 Hz, 1H), 6.66 (dd, *J* = 7.5, *J* = 4.8 Hz, 1H), 5.47 (dd, *J* = 7.1, *J* = 5.2 Hz, 1H), 3.70 (tdd, *J* = 11.8, *J* = 5.2, *J* = 2.6 Hz, 1H), 3.53 (dq, *J* = 14.0, *J* = 7.1 Hz, 1H), 3.44 – 3.38 (m, 1H), 3.29 (dd, *J* = 14.5, *J* = 2.7 Hz, 1H), 3.20 – 3.11 (m, 1H), 2.94 (dq, *J* = 14.0, *J* = 7.1 Hz, 1H), 1.13 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 168.6, 160.7, 149.7, 143.9, 138.6, 136.8, 133.6, 130.6, 129.9, 127.9 (2C), 115.3, 51.1, 41.3, 38.5, 13.2 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{18}N_3OS^+$ $[M+H]^+$ 300.1165 found 300.1162.

2-Nitro-8-propyl-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecin-9-one (13h)

Yield 48 mg, 38%; light beige solid; mp 197-199 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (d, J = 2.6 Hz, 1H), 8.52 (d, J = 2.6 Hz, 1H), 7.52 (dd, J = 7.7 Hz, J = 1.0 Hz, 1H), 7.38 (td, J = 7.7 Hz, J = 1.4 Hz, 1H), 7.28 (td, J = 7.7 Hz, J = 1.0 Hz, 1H), 7.04 (dd, J = 7.7 Hz, J = 1.4 Hz, 1H), 6.68 – 6.58 (m, 1H), 4.13 – 4.00 (m, 1H), 3.42 – 3.32 (m, 4H), 2.64 (ddd, J = 13.6 Hz, J = 7.8 Hz, J = 5.8 Hz, 1H), 1.62 – 1.41 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.0, 161.8, 146.2, 137.1, 135.7, 135.1, 131.0, 129.3, 128.4, 128.2, 126.7, 112.5, 50.8, 44.8, 41.0, 20.5, 11.1 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{19}N_4O_3S^+$ $[M+H]^+$ 359.1172 found 359.1172.

8-Propyl-2-(pyrrolidin-1-ylsulfonyl)-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7] thiadiazecin-9-one (13i)

Yield 78 mg, 50%; white solid; mp 167-170°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (d, J = 2.3 Hz, 1H), 8.03 (d, J = 2.3 Hz, 1H), 7.47 (dd, J = 8.2 Hz, J = 1.2 Hz, 1H), 7.36 (ddd, J = 8.2 Hz, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.25 (td, J = 7.6, J = 1.2 Hz, 1H), 6.98 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 6.03 (dd, J = 9.0 Hz, J = 4.1 Hz, 1H), 4.16 – 4.04 (m, 1H), 3.39 (ddd, J = 14.9 Hz, J = 11.3 Hz, J = 3.8 Hz, 1H), 3.31 – 3.18 (m, 3H), 3.14 (q, J = 4.0 Hz, 4H), 2.59 (ddd, J = 13.6 Hz, J = 8.2 Hz, J = 5.8 Hz, 1H), 1.72 (q, J = 7.0 Hz, 4H), 1.60 – 1.37 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.0, 161.6, 148.3, 141.6, 134.9, 130.0, 129.1, 128.7, 128.3, 126.2, 121.2, 112.1, 51.1, 47.8, 47.8, 44.9, 41.3, 24.6, 24.6, 20.5, 11.2 ppm. HRMS (ESI), *m/z* calcd for $C_{21}H_{27}N_4O_3S_2^+$ $[M+H]^+$ 447.1519 found 447.1515.

8-(2-Methoxyethyl)-2-nitro-5,6,7,8-tetrahydro-9*H*-dibenzo[*b,i*][1,4,7]thiadiazecin-9-one (13j)

Yield 43 mg, 33%; yellow solid; mp 146-148 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (d, J = 2.8 Hz, 1H), 8.05 (dd, J = 9.2 Hz, J = 2.8 Hz, 1H), 7.58 (dd, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.36 (td, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.31 (td, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.04 (dd, J = 7.6 Hz, J = 1.6

Hz, 1H), 6.98 (d, *J* = 9.2 Hz, 1H), 5.84 (t, *J* = 6.5 Hz, 1H), 3.72 – 3.46 (m, 4H), 3.40 – 3.32 (m, 2H), 3.29 (s, 3H), 3.20 – 3.08 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 168.5, 155.9, 137.4, 137.2, 132.6, 131.4, 129.6, 129.5, 127.6, 127.4, 126.8, 118.6, 114.2, 69.5, 58.2, 51.7, 43.2, 42.5 ppm. HRMS (ESI), *m/z* calcd for $C_{18}H_{20}N_3O_4S^+$ $[M+H]^+$ 374.1169 found 374.1171.

_N,N_-dimethyl-9-oxo-8-(prop-2-yn-1-yl)-6,7,8,9-tetrahydro-5_H_-dibenzo[_b,i_][1,4,7] thiadiazecine-2-sulfonamide (13k)

Yield 54 mg, 35%; light beige solid; mp 196-198 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, *J* = 2.3 Hz, 1H), 7.60 (dd, *J* = 7.7 Hz, *J* = 1.4 Hz, 1H), 7.52 (dd, *J* = 8.6 Hz, *J* = 2.3 Hz, 1H), 7.38 (td, *J* = 7.7 Hz, *J* = 1.6 Hz, 1H), 7.32 (td, *J* = 7.5 Hz, *J* = 1.4 Hz, 1H), 7.07 (dd, *J* = 7.5 Hz, *J* = 1.6 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 5.46 (dd, *J* = 8.1 Hz, *J* = 5.0 Hz, 1H), 4.26 (dd, *J* = 17.6 Hz, *J* = 2.4 Hz, 1H), 4.04 (dd, *J* = 17.6 Hz, *J* = 2.5 Hz, 1H), 3.74 – 3.64 (m, 1H), 3.46 – 3.35 (m, 2H), 3.32 (s, 1H), 3.26 – 3.16 (m, 1H), 2.57 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 168.3, 154.3, 137.4, 135.5, 133.3, 130.5, 130.5, 129.9, 127.9, 127.1, 123.1, 120.1, 115.8, 79.6, 74.5, 51.3, 42.7, 37.7, 37,7, 33.2 ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}N_3NaO_3S_2^+$ $[M+Na]^+$ 438.0917, found 438.0921.

General procedure for one-pot preparation of [1,4,7]-thiadiazecines 13l-r

To a solution of respective compound **7a-k** (0.35 mmol) in acetonitrile (10 mL) 0.368 mmol of $BrCH_2Ar$ was added. The resulting mixture was stirred overnight at 60°C (the reaction was monitored by TLC in THF-Hexane (3:1) or EtOAc). Then 0.2% aqueous K_2CO_3 (10 mL) was added at room temperature. After 1 h, CH_2Cl_2 (2x4 mL) was added, the organic layer was separated, washed with water, dried over Na_2SO_4, evaporated and purified by column chromatography eluting with EtOAc.

8-(3-Fluorobenzyl)-2-(pyrrolidin-1-ylsulfonyl)-5,6,7,8-tetrahydro-9_H_-benzo[_i_]pyrido[3,2-_b_][1,4,7]thiadiazecin-9-one (13l)

Yield 108 mg, 60%; white solid; mp 206-208 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.3 Hz, 1H), 8.07 (d, J = 2.3 Hz, 1H), 7.50 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.28 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.19 – 7.07 (m, 3H), 7.04 (dd, J = 7.6 Hz, J = 1.3 Hz, 1H), 6.19 (dd, J = 8.8 Hz, J = 4.2 Hz, 1H), 4.51 (d, J = 15.3 Hz, 1H), 4.26 – 4.12 (m, 1H), 3.88 (d, J = 15.3 Hz, 1H), 3.51 – 3.40 (m, 1H), 3.29 – 3.20 (m, 2H), 3.18 – 3.11 (m, 4H), 1.75 – 1.60 (m, 4H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.4, 162.3 (d, J = 243.9 Hz), 161.5, 148.4, 141.7, 140.8 (d, J = 7.1 Hz), 134.2, 130.6 (d, J = 8.4 Hz), 130.2, 129.3, 129.0, 128.3, 126.3, 123.3 (d, J = 2.7 Hz), 121.3, 114.2 (d, J = 21.7 Hz), 114.0 (d, J = 21.2 Hz), 112.1, 51.3, 47.8, 47.8, 46.0, 40.8, 24.6 (2C) ppm. HRMS (ESI), *m/z* calcd for $C_{25}H_{26}FN_4O_3S_2^+$ $[M+H]^+$ 513.1425 found 513.1428.

8-(4-Methylbenzyl)-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecin-9-one (13m)

Yield 54 mg, 49%; white solid; mp 144-146 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (dd, J = 4.8 Hz, J = 1.8 Hz, 1H), 7.91 (dd, J = 7.5 Hz, J = 1.8 Hz, 1H), 7.56 (dd, J = 7.9 Hz, J = 1.3 Hz, 1H), 7.36 (td, J = 7.6 Hz, J = 1.7 Hz, 1H), 7.32 – 7.29 (m, 1H), 7.27 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 7.07 (dd, J = 7.5 Hz, J = 1.8 Hz, 1H), 6.67 (dd, J = 7.5 Hz, J = 4.8 Hz, 1H), 5.48 (t, J = 6.3 Hz, 1H), 4.80 (d, J = 14.9 Hz, 1H), 3.99 (d, J = 14.9 Hz, 1H), 3.79 (tdd, J = 11.7 Hz, J = 5.9 Hz, J = 3.0 Hz, 1H), 3.42 – 3.34 (m, 1H), 3.27 – 3.18 (m, 1H), 3.10 (dd, J = 14.2 Hz, 2.9 Hz, 1H), 2.29 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.7, 160.1, 149.2, 143.4, 137.3, 136.4, 134.7, 132.8, 130.3, 129.5, 129.2 (2C), 127.7 (2C), 127.4 (2C), 114.8, 114.5, 50.7, 45.5, 40.3, 20.7 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{22}N_3OS^+$ $[M+H]^+$ 376.1478, found 376.1479.

8-(3-Fluorobenzyl)-9-oxo-6,7,8,9-tetrahydro-5*H*-dibenzo[*b,i*][1,4,7]thiadiazecine-2-carbonitrile (13n)

Yield 79 mg, 56%; white solid; mp 205-207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 7.9 Hz, J = 1.3 Hz, 1H), 7.60 (dd, J = 8.7 Hz, J = 2.0 Hz, 1H), 7.48 –

7.37 (m, 2H), 7.34 (td, J = 7.5 Hz, J = 1.3 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.17 – 7.10 (m, 2H), 6.99 (d, J = 8.7 Hz, 1H), 5.51 (dd, J = 7.9 Hz, J = 4.8 Hz, 1H), 4.86 (d, J = 15.2 Hz, 1H), 4.23 (d, J = 15.2 Hz, 1H), 3.62 (tt, J = 9.9 Hz, J = 4.8 Hz, 1H), 3.30 – 3.14 (m, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 169.0, 162.3 (d, J = 243.8 Hz), 154.1, 140.7 (d, J = 7.1 Hz), 139.6, 137.9, 134.6, 133.6, 130.6 (d, J = 8.3 Hz), 130.1, 129.8, 127.9, 127.2, 123.6 (d, J = 2.8 Hz), 120.5, 119.1, 115.9, 114.4 (d, J = 21.6 Hz), 114.1 (d, J = 20.9 Hz), 99.6, 50.9, 45.6, 42.2 ppm. HRMS (ESI), *m/z* calcd for $C_{23}H_{19}FN_3OS^+$ $[M+H]^+$ 404.1221, found 404.1227.

8-(4-methylbenzyl)-9-oxo-6,7,8,9-tetrahydro-5H-dibenzo[b,i][1,4,7]thiadiazecine-2-carbonitrile (13o)

Yield 59 mg, 42%; white solid; mp 221-223 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 7.9 Hz, J = 1.3 Hz, 1H), 7.60 (dd, J = 8.6 Hz, 2.0 Hz, 1H), 7.38 (td, J = 7.6 Hz, J = 1.7 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.19 (d, J = 7.9 Hz, 2H), 7.09 (dd, J = 7.6 Hz, J = 1.7 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 5.51 (dd, J = 8.3 Hz, J = 4.5 Hz, 1H), 4.86 (d, J = 14.8 Hz, 1H), 4.16 (d, J = 14.8 Hz, 1H), 3.65 – 3.54 (m, 1H), 3.27 – 3.12 (m, 3H), 2.30 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 169.3, 154.6, 140.1, 138.8, 136.9, 135.2, 135.2, 134.2, 130.6, 130.3, 129.7, 129.7, 128.5, 128.3, 128.3, 127.6, 121.2, 119.6, 116.6, 100.1, 51.1, 46.2, 42.7, 21.2 ppm. HRMS (ESI), *m/z* calcd for $C_{24}H_{22}N_3OS^+$ $[M+H]^+$ 400.1483, found 400.1478.

Methyl 8-benzyl-9-oxo-6,7,8,9-tetrahydro-5*H*-dibenzo[*b,i*][1,4,7]thiadiazecine-2-carboxylate (13p)

Yield 82 mg, 53%; white solid; mp 183-186 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 2.0 Hz, 1H), 7.78 (dd, J = 8.7 Hz, 2.0 Hz, 1H), 7.57 (dd, J = 7.9 Hz, J = 1.3 Hz, 1H), 7.41 – 7.28 (m, 7H), 7.11 (dd, J = 7.5 Hz, J = 1.6 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 5.38 (dd, J = 7.5 Hz, J = 5.1 Hz, 1H), 4.87 (d, J = 15.0 Hz, 1H), 4.17 (d, J = 15.0 Hz, 1H), 3.80 (s, 3H), 3.69 – 3.58 (m, 1H), 3.28 – 3.10 (m, 3H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 168.9, 165.5, 154.5, 137.9, 137.7, 137.0, 133.2, 132.1, 130.5, 129.7, 128.7 (2C), 127.7, 127.6 (2C), 127.3, 127.2,

119.4, 119.2, 115.4, 51.7, 50.7, 45.9, 42.4 ppm. HRMS (ESI), *m/z* calcd for $C_{24}H_{22}N_2NaO_3S^+$ $[M+Na]^+$ 441.1243 found 441.1242.

8-Benzyl-2-nitro-5,6,7,8-tetrahydro-9*H*-dibenzo[*b,i*][1,4,7]thiadiazecin-9-one (13q)

Yield 72 mg, 51%; light yellow solid; mp 228-230°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 2.7 Hz, 1H), 8.11 – 8.06 (m, 1H), 7.61 (dd, J = 7.9 Hz, J = 1.3 Hz, 1H), 7.41 – 7.29 (m, 7H), 7.11 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.03 (d, J = 9.2 Hz, 1H), 5.88 (t, J = 6.5 Hz, 1H), 4.86 (d, J = 15.1 Hz, 1H), 4.12 (d, J = 15.1 Hz, 1H), 3.81 – 3.68 (m, 1H), 3.33 – 3.25 (m, 2H), 3.19 (dd, J = 13.5 Hz, J = 3.2 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.7, 155.8, 137.7, 137.3, 137.3, 132.9, 131.4, 129.8, 129.7, 129.7, 128.7, 128.7, 128.7, 127.6, 127.6, 127.4, 127.3, 126.8, 118.8, 50.7, 46.1, 42.1 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{20}N_3O_3S^+$ $[M+H]^+$ 406.1228, found 406.1225.

8-(2-Fluorobenzyl)-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrazino[2,3-*b*][1,4,7]thiadiazecin-9-one (13r)

Yield 58 mg, 41%; light beige solid; mp 177-179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 2.6 Hz, 1H), 7.84 (d, J = 2.6 Hz, 1H), 7.48 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.36 – 7.28 (m, 2H), 7.24 – 7.18 (m, 2H), 7.11 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 5.62 (dd, J = 8.2 Hz, 4.9 Hz, 1H), 4.69 (d, J = 15.4 Hz, 1H), 4.04 (dddd, J = 14.2 Hz, J = 11.5 Hz, J = 8.5 Hz, J = 3.2 Hz, 1H), 3.94 (d, J = 15.4 Hz, 1H), 3.39 – 3.35 (m, 1H), 3.27 – 3.21 (m, 1H), 3.18 (dd, J = 14.6 Hz, J = 3.2 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 169.3, 160.9 (d, J = 244.8 Hz), 155.7, 142.1, 137.3, 135.8, 134.2, 131.5, 130.2 (d, J = 4.3 Hz), 129.9, 129.8 (d, J = 8.2 Hz), 129.2, 128.5, 127.3, 125.1 (d, J = 3.4 Hz), 124.7 (d, J = 14.5 Hz), 115.8 (d, J = 21.2 Hz), 51.4, 41.1 (d, J = 3.8 Hz), 40.0 ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{17}FN_4NaOS^+$ $[M+Na]^+$ 403.0999, found 403.1005.

General procedure for preparation of sulfoxides 8a-b

To a solution of 0.67 mmol of thiazepine in methanol was added a solution of *m*-CPBA (289.4 mg, 1.68 mmol) in methanol at 0°C. This suspension was stirred for 2 h at room temperature and the resulting solid was filtered off, washed with methanol. Crystallized from DMF to provide the analytically pure product.

Methyl 2,3-dihydrodibenzo[*b,f*]imidazo[1,2-*d*][1,4]thiazepine-7-carboxylate 9-oxide (8a)

Yield 131 mg, white solid; yield 60%; mp 281-283 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 2.1 Hz, 1H), 8.03 (dd, J = 8.4 Hz, J = 2.1 Hz, 1H), 7.85 – 7.70 (m, 3H), 7.59 (ddd, J = 8.7 Hz, J = 6.6 Hz, J = 2.3 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 4.47 – 4.36 (m, 1H), 4.10 – 3.98 (m, 2H), 3.97 – 3.80 (m, 4H) ppm. ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.7, 158.3, 144.2, 139.5, 136.6, 132.7, 132.3, 130.8 (2C), 126.5, 124.3, 124.1, 120.7, 77.4, 52.4, 52.3, 51.4 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{15}N_2O_3S^+$ $[M+H]^+$ 327.0798, found 327.0801.

7-Nitro-2,3-dihydrodibenzo[*b,f*]imidazo[1,2-*d*][1,4]thiazepine 9-oxide (8b)

Yield 149 mg, 71 %; yellow solid; mp 230-232 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 (d, J = 2.6 Hz, 1H), 8.29 (dd, J = 8.8 Hz, J = 2.7 Hz, 1H), 7.92 (td, J = 7.9 Hz, J = 1.2 Hz, 2H), 7.75 (td, J = 7.7 Hz, J = 1.2 Hz, 1H), 7.56 (td, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 4.51 – 4.38 (m, 1H), 4.30 – 4.10 (m, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, Chloroform-d) δ 158.3, 144.5, 143.6, 140.3, 138.0, 133.2, 131.4, 131.2, 126.8, 123.0, 121.1, 119.1, 118.5, 51.8, 51.5. HRMS (ESI), *m/z* calcd for $C_{15}H_{12}N_3O_3S^+$ $[M+H]^+$ 314.0599, found 314.0594.

General procedure for preparation of sulfones 9a-d

To a stirred solution of 0.360 mmol of thiazepine, in 2 mL of carbon tetrachloride, 2 mL of acetonitrile, and 4 mL of water was added 231 mg (1.080 mmol) of sodium periodate. Once all of the sodium periodate had dissolved, 0.2 mg (0.018 mmol) of ruthenium trichloride hydrate was added, and the reaction mixture was stirred vigorously overnight at room temperature. It was then extracted with CH_2Cl_2; the combined organic extracts were dried over Na_2SO_4 and

evaporated. The crude product was purified by column chromatography eluting with THF-Hexane (4:1).

2,3-Dihydrodibenzo[*b,f*]imidazo[1,2-*d*][1,4]thiazepine-7-carbonitrile 9,9-dioxide (9a)

Yield 58 mg, 52%; light beige solid; mp 226-228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.95 – 7.81 (m, 3H), 7.49 (d, J = 8.7 Hz, 1H), 4.47 (dt, J = 11.1 Hz, J = 11.3 Hz, 1H), 4.15 – 3.90 (m, 3H) ppm. ^{13}C{^{1}H} NMR (400 MHz, Chloroform-d) δ 120.9, 104.1, 101.6, 100.3, 97.3, 94.9, 94.5, 94.3, 93.2, 90.1, 87.6, 82.0, 79.8, 67.8, 15.0, 14.6, ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{12}N_3O_2S^+$ $[M+H]^+$ 310.0642, found 310.0645.

Methyl 2,3-dihydrodibenzo[*b,f*]imidazo[1,2-*d*][1,4]thiazepine-7-carboxylate 9,9-dioxide (9b)

Yield 59 mg, 48%; white solid; mp 205-207 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 2.1 Hz, 1H), 8.20 (dd, J = 8.7 Hz, J = 2.1 Hz, 1H), 8.02 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.95 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.88 (td, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.82 (td, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 4.51 (q, J = 10.7 Hz, 1H), 4.16 – 3.93 (m, 3H), 3.87 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.5, 157.7, 141.6, 138.6, 135.8, 135.1, 132.5, 132.2, 128.5, 127.6, 127.3, 124.2, 122.5, 120.2, 52.4, 52.1, 51.6 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{15}N_2O_4S^+$ $[M+H]^+$ 343.0744, found 343.0747.

Methyl 2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido[3,2-*b*][1,4]thiazepine-7-carboxylate 9,9-dioxide (9c)

Yield 61 mg, white solid; 49%; mp 199-201°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (d, J = 2.2 Hz, 1H), 8.54 (d, J = 2.2 Hz, 1H), 8.03 (ddd, J = 9.5 Hz, J = 7.6 Hz, J = 1.4 Hz, 2H), 7.91 (td, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.86 (td, J = 7.6 Hz, J = 1.5 Hz, 1H), 4.53 – 4.27 (m, 1H), 4.06 (s, 2H), 4.12 – 3.92 (m, 3H), 3.88 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.1, 156.7, 155.2, 151.2, 138.2, 136.9, 135.9, 133.5, 132.9, 127.6, 125.0, 122.9, 119.2, 53.0, 52.0 (2C). HRMS (ESI), *m/z* calcd for $C_{16}H_{14}N_3O_4S^+$ $[M+H]^+$ 344.0698, found 344.0700.

7-Nitro-2,3-dihydrodibenzo[b,f]imidazo[1,2-d][1,4]thiazepine 9,9-dioxide (9d)

Yield 57 mg, 48%; yellow solid; mp 237-239 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, J = 2.7 Hz, 1H), 8.45 (dd, J = 9.1 Hz, 2.8 Hz, 1H), 8.02 (dd, J = 7.7 Hz, 1.4 Hz, 1H), 7.94 (dd, J = 7.6 Hz, 1.5 Hz, 1H), 7.89 (td, J = 7.5 Hz, 1.5 Hz, 1H), 7.83 (td, J = 7.5 Hz, 1.6 Hz, 1H), 7.51 (d, J = 9.2 Hz, 1H), 4.49 (dt, J = 12.3 Hz, 10.3 Hz, 1H), 4.17 (td, J = 9.7 Hz, 3.5 Hz, 1H), 4.13 – 4.05 (m, 1H), 4.03 – 3.92 (m, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 157.4, 142.7, 140.2, 137.9, 135.4, 132.7, 132.3, 130.2, 128.0, 127.2, 124.4, 122.6, 120.7, 52.4, 51.8 ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{12}N_3O_4S^+$ $[M+H]^+$ 330.0555, found 330.0553.

All the lactams **14a-d** and **15a-d** were prepared according to general procedures for preparation of compounds **13a-r**.

Methyl 8-(3-fluorobenzyl)-9-oxo-6,7,8,9-tetrahydro-5*H*-dibenzo[*b,i*][1,4,7]thiadiazecine-2-carboxylate 14-oxide (14a)

Yield 87 mg, white solid; 55%; mp 180-182 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (d, J = 2.1 Hz, 1H), 7.77 (dd, J = 8.5 Hz, J = 2.1 Hz, 1H), 7.61 (dd, J = 7.7 Hz, J = 1.7 Hz, 1H), 7.53 – 7.43 (m, 3H), 7.29 (dd, J = 10.4 Hz, J = 4.7 Hz, 2H), 7.25 (dd, J = 7.2 Hz, J = 1.7 Hz, 1H), 7.19 – 7.12 (m, 1H), 6.88 (d, J = 8.5 Hz, 1H), 6.04 (dd, J = 9.6 Hz, J = 3.5 Hz, 1H), 5.36 (d, J = 15.3 Hz, 1H), 4.18 (d, J = 15.3 Hz, 1H), 3.83 (s, 3H), 3.51 – 3.44 (m, 1H), 3.28 (d, J = 5.0 Hz, 1H), 3.15 (dd, J = 9.0 Hz, J = 3.4 Hz, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.9, 165.4, 162.3 (d, J = 243.7 Hz), 148.4, 143.0, 140.7 (d, J = 7.2 Hz), 135.4, 135.3, 132.7, 131.2, 130.6 (d, J = 8.3 Hz), 130.3, 125.8, 124.6, 123.7 (d, J = 2.6 Hz), 123.0, 120.6 (2C), 115.7, 114.5 (d, J = 21.5 Hz), 114.0 (d, J = 20.9 Hz), 51.8, 50.3, 45.7 ppm. HRMS (ESI), *m/z* calcd for $C_{24}H_{22}FN_2O_4S^+$ $[M+H]^+$ 453.1277, found 453.1279.

Methyl 8-benzyl-9-oxo-6,7,8,9-tetrahydro-5H-dibenzo[b,i][1,4,7]thiadiazecine-2-carboxylate 14-oxide (14b)

Yield 52 mg, 34%; white solid; mp 193-195 °C. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (d, *J* = 2.0 Hz, 1H), 7.77 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1H), 7.63 (dd, *J* = 7.7 Hz, *J* = 1.5 Hz, 1H), 7.50 – 7.39 (m, 6H), 7.35 – 7.30 (m, 1H), 7.22 (dd, *J* = 7.3 Hz, *J* = 1.5 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 5.97 (dd, *J* = 9.7 Hz, *J* = 3.4 Hz, 1H), 5.40 (d, *J* = 15.1 Hz, 1H), 4.15 (d, *J* = 15.1 Hz, 1H), 3.83 (s, 3H), 3.49 – 3.42 (m, 1H), 3.31 – 3.25 (m, 1H), 3.18 – 3.05 (m, 2H) ppm. ^{13}C{^{1}H} (101 MHz, DMSO-d_6) δ 168.8, 165.5, 148.4, 143.0, 137.6, 135.6, 135.2, 132.7, 131.2, 130.2, 128.7 (2C), 127.7 (2C), 127.3, 125.8, 124.6, 123.1, 120.6, 115.8, 51.9, 50.1, 46.0, 39.9. HRMS (ESI), *m/z* calcd for $C_{24}H_{23}N_2O_4S^+$ $[M+H]^+$ 435.1373, found 435.1379.

2-Nitro-8-(prop-2-yn-1-yl)-5,6,7,8-tetrahydro-9*H*-dibenzo[*b,i*][1,4,7]thiadiazecin-9-one 14-oxide (14c)

Yield 54 mg, 38%; yellow solid; mp 208-210 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 2.7 Hz, 1H), 8.07 (dd, *J* = 9.0 Hz, *J* = 2.7 Hz, 1H), 7.66 (dd, *J* = 7.7 Hz, *J* = 1.5 Hz, 1H), 7.51 (pd, *J* = 7.3 Hz, *J* = 1.5 Hz, 2H), 7.21 (dd, *J* = 7.3 Hz, *J* = 1.5 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 1H), 6.41 (dd, *J* = 9.9 Hz, 3.5 Hz, 1H), 4.78 (dd, *J* = 17.7 Hz, *J* = 2.5 Hz, 1H), 4.08 (dd, *J* = 17.7 Hz, *J* = 2.5 Hz, 1H), 3.68 – 3.56 (m, 1H), 3.49 (dd, *J* = 14.1 Hz, *J* = 2.5 Hz, 1H), 3.31 – 3.27 (m, 1H), 3.19 (ddd, *J* = 15.1 Hz, *J* = 11.6 Hz, *J* = 3.5 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.1, 149.8, 142.5, 139.5, 135.5, 135.1, 131.6, 130.7, 127.6, 125.8, 124.8, 118.1, 115.3, 79.2, 75.3, 50.1, 39.4, 33.3 ppm. HRMS (ESI), *m/z* calcd for $C_{18}H_{15}N_3KO_4S^+$ $[M+K]^+$ 408.0428, found 408.0430.

8-Benzyl-2-nitro-5,6,7,8-tetrahydro-9*H*-dibenzo[*b,i*][1,4,7]thiadiazecin-9-one 14-oxide (14d)

Yield 64 mg, 43%; light yellow solid; mp 234-236 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, *J* = 2.7 Hz, 1H), 8.06 (dd, *J* = 9.0 Hz, *J* = 2.7 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.52 – 7.40 (m, 6H), 7.36 – 7.31 (m, 1H), 7.26 – 7.22 (m, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 6.68 (dd, *J* = 9.5 Hz, *J* = 2.8 Hz, 1H), 5.41 (d, *J* = 15.2 Hz, 1H), 4.14 (d, *J* = 15.2 Hz, 1H), 3.60 – 3.51 (m, 1H), 3.38 (ddd, *J* = 14.4, *J* = 8.9 Hz, *J* = 3.5 Hz, 1H), 3.23 – 3.11 (m, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.6, 149.9, 142.4, 139.4, 137.6, 135.7, 135.5, 131.5, 130.5, 128.7, 128.7, 127.7 (3C),

127.3, 125.9, 124.8, 118.1, 115.1, 50.0, 46.0, 39.6 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{20}N_3O_4S^+$ $[M+H]^+$ 422.1166, found 422.1169.

8-Ethyl-9-oxo-6,7,8,9-tetrahydro-5H-dibenzo[*b,i*][1,4,7]thiadiazecine-2-carbonitrile 14,14-dioxide (15a)

Yield 57 mg, 46%; white solid; mp 181-183 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, J = 2.0 Hz, 1H$_{Ar}$), 7.97 (dd, J = 8.2 Hz, J = 1.3 Hz, 1H), 7.80 (dd, J = 8.8 Hz, J = 2.1 Hz, 1H), 7.70 (td, J = 7.5 Hz, J = 1.3 Hz, 1H), 7.60 (ddd, J = 8.5 Hz, J = 7.4 Hz, J = 1.4 Hz, 1H), 7.30 (dd, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 7.7 Hz, 1H), 3.70 (dq, J = 14.1 Hz, J = 6.7 Hz, 1H), 3.58 – 3.47 (m, 2H), 3.41 – 3.32 (m, 2H), 3.08 – 2.99 (m, 1H), 1.23 (t, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.8, 150.9, 138.2, 136.4, 136.0, 134.1, 133.9, 131.0, 130.3, 128.3, 125.5, 118.8, 118.3, 99.7, 51.4, 42.4, 40.2, 12.5 ppm. HRMS (ESI), *m/z* calcd for $C_{18}H_{17}N_3NaO_3S^+$ $[M+Na]^+$ 378.0883, found 378.0885.

Methyl 8-benzyl-9-oxo-6,7,8,9-tetrahydro-5H-dibenzo[*b,i*][1,4,7]thiadiazecine-2-carboxylate 14,14-dioxide (15b)

Yield 52 mg, 42%; white solid; mp 202-205 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 2.1 Hz, 1H), 7.92 (dd, J = 8.8 Hz, J = 2.1 Hz, 1H), 7.85 (dd, J = 8.2 Hz, J = 1.2 Hz, 1H), 7.71 (td, J = 7.5 Hz, J = 1.2 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.50 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.36 – 7.30 (m, 2H), 7.08 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 5.03 (d, J = 15.0 Hz, 1H), 4.58 (d, J = 15.0 Hz, 1H), 3.83 (s, 3H), 3.52 – 3.37 (m, 2H), 3.28 – 3.22 (m, 1H), 3.18 – 3.10 (m, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.6, 164.9, 151.2, 137.7, 136.5, 135.7, 134.0, 130.7, 130.5, 130.5, 128.7, 128.7, 128.2, 127.9, 127.9, 127.4, 126.4, 124.7, 118.9, 118.0, 52.1, 51.5, 46.5, 41.9. HRMS (ESI), *m/z* calcd for $C_{24}H_{22}N_2KO_5S^+$ $[M+K]^+$ 489.0881 found 489.0883.

Methyl 8-methyl-9-oxo-6,7,8,9-tetrahydro-5H-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecine-2-carboxylate 14,14-dioxide (15c)

Yield 43 mg, 33%; white solid; mp 175-177 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 2.3 Hz, 1H), 8.48 (d, J = 2.3 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.70 (td, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.61 (td, J = 7.6 Hz, J = 1.4 Hz, 1H), 7.35 (dd, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.17 (s, 1H), 3.85 (s, 4H), 3.67 (s, 1H), 3.37 – 3.32 (m, 1H), 3.24 – 3.15 (m, 1H), 3.02 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 166.9, 164.1, 158.0, 155.2, 138.9, 136.3, 134.1, 130.5 (2C), 130.4, 128.4, 119.2, 116.1, 53.4, 52.2, 40.0 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{18}N_3O_5S^+$ $[M+H]^+$ 376.0960, found 376.0962.

8-(2-Fluorobenzyl)-2-nitro-5,6,7,8-tetrahydro-9H-dibenzo[b,i][1,4,7]thiadiazecin-9-one 14,14-dioxide (15d)

Yield 80 mg, 50%; light yellow solid; mp 252-254 °C. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.61 (d, J = 2.8 Hz, 1H), 8.22 (dd, J = 9.3 Hz, J = 2.8 Hz, 1H), 8.02 – 7.92 (m, 1H), 7.74 (td, J = 7.5 Hz, J = 1.3 Hz, 1H), 7.62 (td, J = 7.8 Hz, J = 1.3 Hz, 1H), 7.56 (td, J = 7.8 Hz, J = 1.8 Hz, 1H), 7.40 (dtd, J = 7.6 Hz, J = 6.3 Hz, J = 5.4 Hz, J = 1.9 Hz, 1H), 7.35 – 7.22 (m, 3H), 7.18 (d, J = 9.3 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 5.18 (d, J = 15.4 Hz, 1H), 4.52 (d, J = 15.4 Hz, 1H), 3.59 (t, J = 6.8 Hz, 2H), 3.30 – 3.18 (m, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.3, 160.4 (d, J = 244.9 Hz), 152.1, 137.5, 135.9, 135.8, 134.4, 131.2, 130.7, 130.3, 130.0 (d, J = 4.1 Hz), 129.6 (d, J = 8.2 Hz), 128.2, 125.7, 124.8 (d, J = 3.2 Hz), 124.1, 123.9 (d, J = 14.6 Hz), 117.7, 115.5 (d, J = 21.4 Hz), 51.3, 41.6, 40.6 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{19}FN_3O_5S^+$ $[M+H]^+$ 456.1029, found 456.1027.

Preparation of imidazolinium salts 16a-c

Compound **7c, 8a, 9b** (0.322 mmol) and BnBr (58 mg, 0.38 mmol) were combined in dry acetonitrile in a glass test tube with a screw cap. The resulting mixture was stirred overnight at 60°C, then the reaction was monitored by TLC (ethyl acetate/hexane 8:2). After completion of the reaction, the mixture was concentrated *in vacuo*, diluted with 3 mL of Et_2O, filtered and air-dried.

1-benzyl-7-(methoxycarbonyl)-2,3-dihydrodibenzo[b,f]imidazo[1,2-d][1,4]thiazepin-1-ium bromide (16a)

Yield 132 mg, 86%; light beige solid; mp 211-213 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 – 8.35 (m, 1H), 8.27 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 8.5 Hz, J = 1.8 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.73 – 7.64 (m, 1H), 7.59 (dtd, J = 14.4 Hz, J = 7.5 Hz, J = 1.8 Hz, 2H), 7.43 – 7.32 (m, 3H), 7.29 – 7.22 (m, 2H), 5.53 (dt, J = 13.4 Hz, J = 9.9 Hz, 1H), 4.97 (s, 1H), 4.87 (ddd, J = 13.4 Hz, J = 11.5 Hz, J = 7.3 Hz, 1H), 4.16 (ddd, J = 11.5 Hz, J = 9.9 Hz, J = 7.3 Hz, 1H), 3.91 (s, 3H), 3.79 – 3.90 (m, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.1, 163.9, 141.7, 138.1, 134.9, 134.8, 133.3, 133.2, 132.2 (2C), 132.1, 130.4, 130.3, 129.6 (2C), 129.4, 128.4 (2C), 125.6, 124.3, 52.9, 52.8, 52.1, 47.5 ppm. HRMS (ESI), m/z calcd for $C_{24}H_{21}N_2O_2S^+$ [M^+] 401.1324, found 401.1318.

1-Benzyl-7-(methoxycarbonyl)-2,3-dihydrodibenzo[b,f]imidazo[1,2-d][1,4]thiazepin-1-ium 9-oxide bromide (16b)

Yield 111 mg, 70 % white solid; mp 273-275 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.19 (td, J = 8.8 Hz, J = 8.3 Hz, J = 2.0 Hz, 2H), 8.11 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H), 8.04 (td, J = 7.7 Hz, 1.3 Hz, 1H) 7.78 (dd, J = 8.3 Hz, J = 6.9 Hz, 2H), 7.68 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.53 – 7.34 (m, 5H), 5.05 (t, J = 10.8 Hz, 1H), 4.96 – 4.87 (m, 2H), 4.48 – 4.41 (m, 1H), 4.29 (tt, J = 12.3 Hz, J = 6.0 Hz, 2H), 3.89 (s, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 164.3, 161.8, 148.1, 142.2, 141.2, 137.9, 135.9, 134.9, 132.9, 131.8, 131.3, 129.5 (2C), 129.0, 128.3 (2C), 128.2, 125.4, 122.2, 114.8, 53.3, 52.5, 51.0, 49.1 ppm. HRMS (ESI), *m/z* calcd for $C_{24}H_{21}N_2O_3S^+$ [M^+] 417.1267, found 417.1271.

1-Benzyl-7-(methoxycarbonyl)-2,3-dihydrodibenzo[b,f]imidazo[1,2-d][1,4]thiazepin-1-ium 9,9-dioxide bromide (16c)

Yield 125 mg, 76%; white solid; mp 238-240 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 – 8.15 (m, 2H), 8.14 – 8.03 (m, 1H), 8.00 – 7.87 (m, 3H), 7.87 – 7.76 (m, 1H), 7.55 – 7.33 (m, 5H), 5.24 – 5.07 (m, 1H), 5.09 – 4.95 (m, 2H), 4.52 (ddt, J = 17.8 Hz, J = 11.0 Hz, J = 6.2 Hz, 1H),

4.34 – 4.25 (m, 1H), 4.16 – 3.93 (m, 1H), 3.93 – 3.85 (m, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) 164.3, 161.8, 148.2, 142.3. 141.2, 137.9, 136.5, 135.8, 134.8, 134.3, 132.9, 129.5 (2C), 128.4 (2C), 128.2, 125.4, 122.2, 121.3, 114.8, 53.3, 52.5, 51.0, 49.1 ppm. HRMS (ESI), *m/z* calcd for $C_{24}H_{21}N_2O_4S^+$ [M^+] 433.1217, found 433.1222.

Comparison of HIRE conversion rates for compounds 16a-c

The conversion was monitored using high-performance liquid chromatography (HPLC). Measurements were performed at 35˚C with a flow rate of 200 μL/min (H_2O with 0.1% TFA; HPLC grade MeCN with 0.1% TFA). The absorbance was measured at 254 nm.

The solutions of imidazolinium salts **16a-c** were prepared by dissolving 0.042 mmol of the respective compound in 10 mL of MeCN-H_2O system (1:1), then the volume was made up to 50 mL. The calibration curves were generated for solutions of salts **16a-c** at 4 concentrations: 0.83 mmol/L, 0.42 mmol/L, 0.21 mmol/L, 0.10 mmol/L.

To start measurements, the solution of compound **16a-c** was placed into the test tube into the constant-temperature bath to maintain the reaction temperature at 25.0 ± 0.1 °C. Then K_2CO_3 was added (2 mg) and 200 μL of the reaction mixture was sampled at specific intervals into the chromatography vial containing 2 μL of acetic acid. The conversion of the starting materials was evaluated using calibration curves.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic information for compounds **9c, 13a, 13p**, **14b, 15d, 16a and 16b** details of DFT calculations, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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