Featured Article

Re-thinking Hydrolytic Imidazoline Ring Expansion: A Common Approach to the Preparation of Medium-Sized Rings via Side Chain Insertion into [1.4]Oxa- and [1.4]Thiazepinone Scaffold

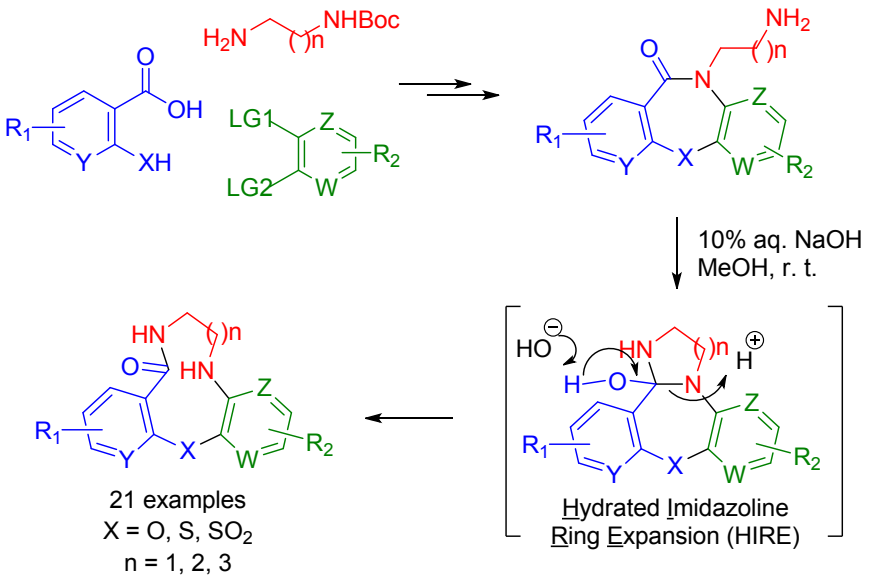
Elena Reutskaya, Angelina Osipyan, Alexander Sapegin, Alexander S. Novikov, and Mikhail Krasavin

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02805 • Publication Date (Web): 19 Dec 2018

Re-thinking Hydrolytic Imidazoline Ring Expansion: A Common Approach to the Preparation of Medium-Sized Rings via Side Chain Insertion into [1.4]Oxa- and [1.4]Thiazepinone Scaffold

Elena Reutskaya, Angelina Osipyan,§ Alexander Sapegin, Alexander S. Novikov, and Mikhail Krasavin*

Saint Petersburg State University, Saint Petersburg 199034, Russian Federation

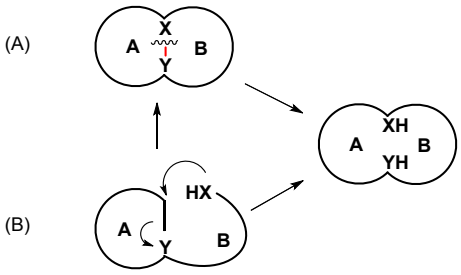


ABSTRACT: The earlier reported ring expansion strategy involving hydrolytically prone imidazoline rings was thought to include the formation of a hydrated imidazoline intermediate. In this work, we accessed the latter *via* the addition of a 2-aminoethyl side chain onto a lactam moiety. This led to an efficient three-atom ring expansion of diarene-fused [1.4]oxazepines and [1.4]thiazepines and led us to propose to term this common approach the hydrated imidazoline ring expansion (HIRE) reaction. The strategy was extended to the insertion of longer (containing up to 5 atoms) side chains and thus larger (11- to 12-membered) diarene-fused rings were obtained *via* the homo-HIRE and homo^2-HIRE reactions, respectively. This underscores the utility of the HIRE reaction for the preparation of medium-sized rings, an important class of chemical tools for interrogation of various biological targets.

INTRODUCTION

Today, small molecules based on medium-sized (8-to-14-membered) cyclic scaffolds are recognized preferred tools for interrogation of biological targets, owing to the optimal balance between conformational rigidity and flexibility present in them, which ultimately enables them to adopt a unique bioactive conformation.[1] Medium-sized rings are particularly useful as a small-molecule platform for lead generation against poorly druggable targets.[2] Unfortunately, medium-sized ring systems are notoriously difficult to prepare via synthesis (due to unfavorable entropy associated with the ring closing in this case and increased enthalpy present in such systems due do destabilizing transannular interactions[3]) and hence are severely underrepresented in today's compound collections intended for biological screening.[4] The more productive (compared to ring closing approach) synthetic strategies based on expansion of smaller rings can, in principle, change the current situation for the better and thus are subject of increased dedicated research efforts in recent years. These strategies broadly fall into one of the following two (mechanistically interrelated) categories: (A) cleavage of a central bond in a fused bicyclic system and (B) insertion of a reactive side chain into a smaller cycle. In both cases a larger ring is formed whose size is the sum of atoms initially present in the two fused rings of in the smaller ring and the side chain (Figure 1).[5]

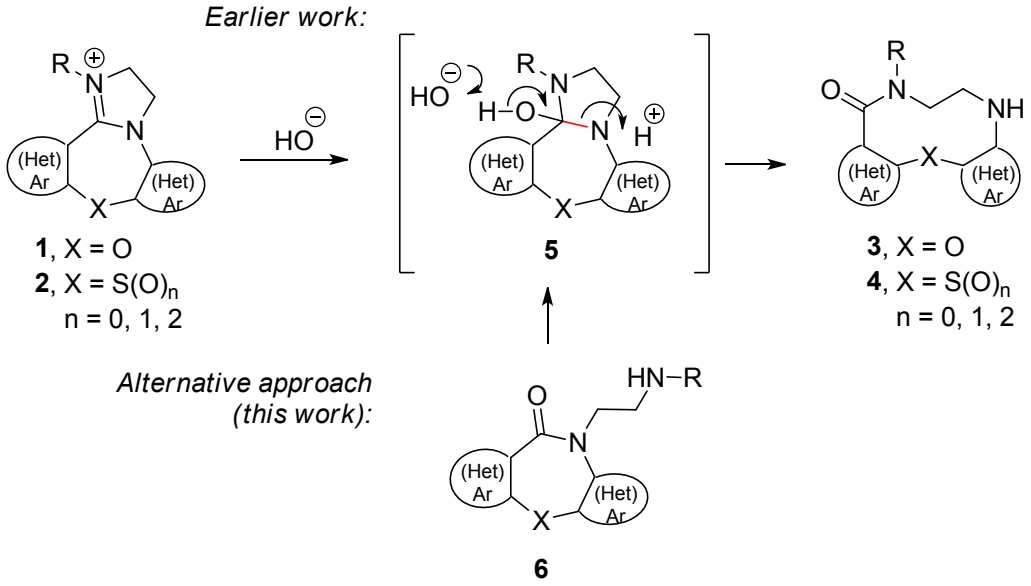
Figure 1. Schematic representation of two principal ring expansion strategies.[5]



Recently, we described a ring expansion strategy involving nucleophilic addition of hydroxide anion to an imidazoline moiety (activated by *N*-alkylation) in diarene-fused [1.4]oxazepines (**1**)[6] or [1.4]thiazepines (**2**)[7] leading to rare, medium-sized [1,4,7]oxazecines **3** and [1,4,7]thiazecines **4**, respectively. Such a ring expansion strategy clearly belongs to type A (Figure 1) as it

presumably involves the breaking of the central bond in putative intermediate **5** through which the ring expansion process is thought to proceed. Initially, we termed this approach "*hydrolytic* imidazoline ring expansion".[6-7] However, herein we propose to switch to a more general designation of this methodology from the mechanistic standpoint, namely, by calling it "*hydrated* imidazoline ring expansion (HIRE)".[8] We reasoned that the same putative hydrated imidazoline intermediate **5** can be formed *via* a possible side chain insertion process involving precursor **6**, which, if successful, would lead to type B ring expansion strategy thereby uniting the two methodological approaches within the same mechanistic framework (Figure 2). We were particularly motivated to investigate such a complementary methodology as we anticipated it to potentially allow involving longer side-chains in a homologous HIRE process which would lead to the formation of 11-membered rings and larger. Previously, we were not able to test the same possibility via the hydration of homologs of **1** and **2** as the latter could not be synthesized. In principle, expansion of β-lactam rings via the insertion of ω-aminoalkyl side chains[9] as well as synthesis of rings as large as 53-membered using the so-called 'zip reaction' employing a polyamine side chain sequential insertion[10] was documented in the literature. However, in the absence of a specific driving force (such as relief of the ring strain) similar reactions either yielded an equilibrium mixture of ring-expanded product and starting material[11] or did not proceed at all.[12] In our case, expulsion of the less nucleophilic anilinic amino group was expected to drive the reaction forward via an irreversible formation of **3**-**4**. Herein, we report our progress in investigating the unified hydrated imidazoline ring expansion (HIRE) process, as described above, and its application to the preparation of 10-membered rings. We also demonstrate the scope and limitations of this methodology with respect to the insertion of longer side chains ("homo^{x}-HIRE").

Figure 2. Alternative approaches to the formation of hydrated imidazoline intermediate **5** and the net result of the unified HIRE reaction.



RESULTS AND DISCUSSION

The principal substrate type investigated in this work was related to **6**, i. e. it possessed ω-aminoalkyl side chains of various lengths (from 2 to 5 carbon atoms) where 2-aminoethyl side chain was envisioned to be eventually involved in the formation of the putative hydrated imidazoline intermediate **5** while the longer side chains were introduced to test the scope and limitations of the homologous versions of the HIRE approach. To this end, we activated various (hetero)aromatic carboxylic acids **7a-e** (bearing a hydroxy or sulfhydryl groups in *ortho*-position) as respective imidazolides and coupled them to a series of diamines mono-protected with a Boc group (**8a-d**).[13] The amides **9a-j** thus obtained were introduced in the reaction with a range of bis-electrophilic aromatic substrates **10**. The latter underwent, in the presence of K_2CO_3 and at temperatures ranging from ambient to 80 ºC depending on the reactivity of **10**, a double nucleophilic aromatic substitution reaction accompanied by an intermittent Smiles rearrangement (which defines the regiochemical result of the overall ring-forming process)[14] to give diarene-fused [1.4]oxazepines **11a-l** and [1.4]thiazepines **12a-h** in good to excellent yields (Scheme 1, Table 1).

Scheme 1. Preparation of diarene-fused [1.4]oxazepines **11a-l** and [1.4]thiazepines **12a-h** bearing a Boc-protected ω-aminoalkyl side chain.

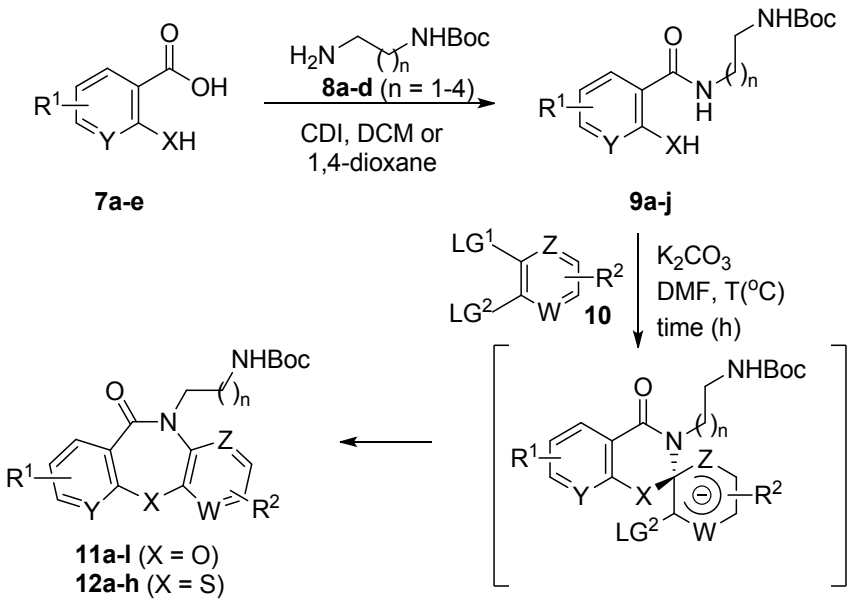
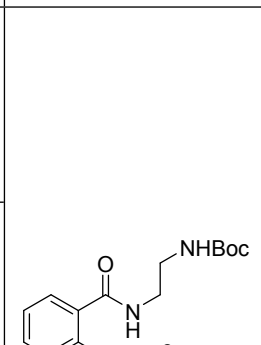
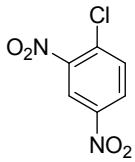
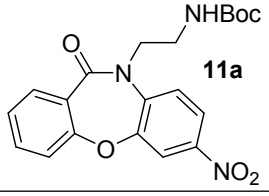
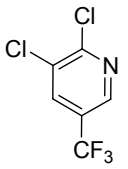
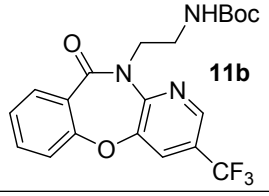
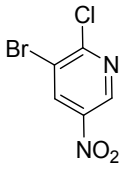
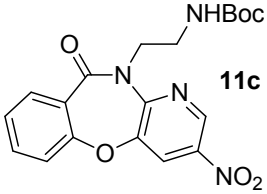
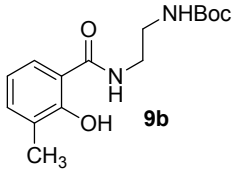
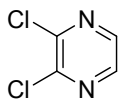
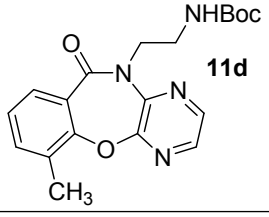
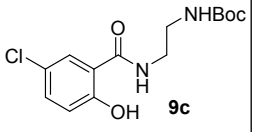
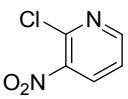
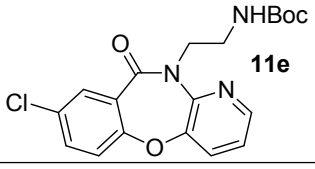
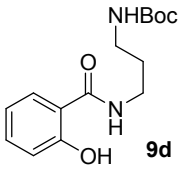
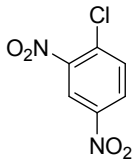
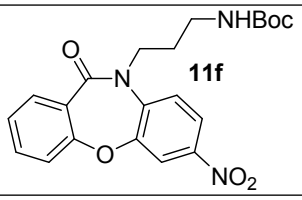
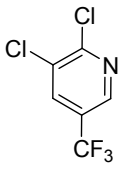
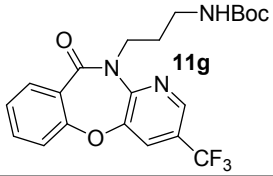
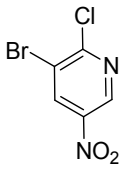
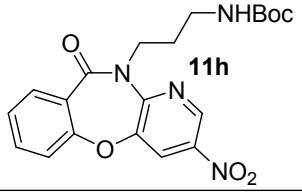
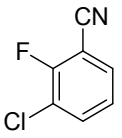
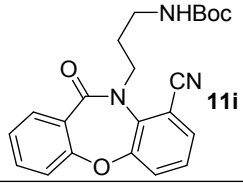
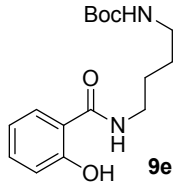
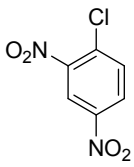
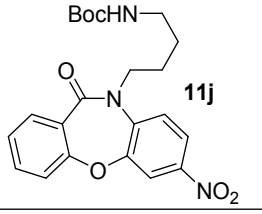
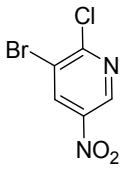
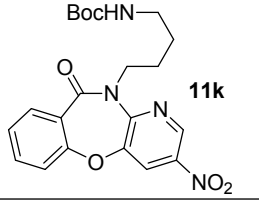
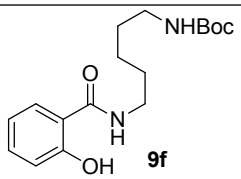
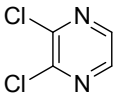
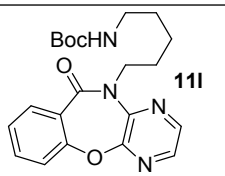
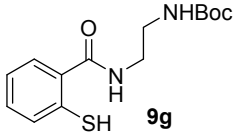
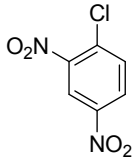
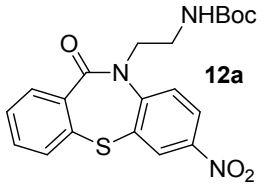
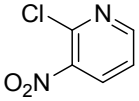
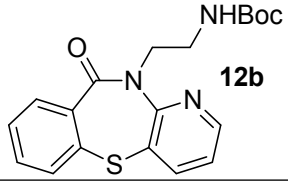
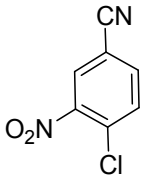
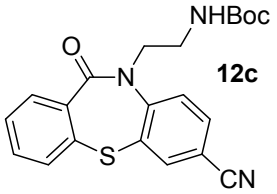
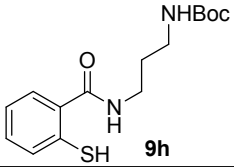
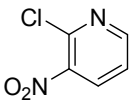
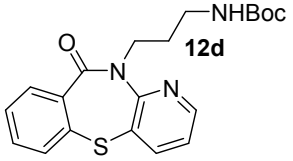
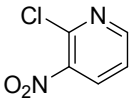
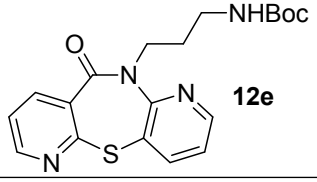
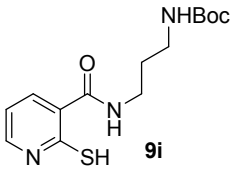
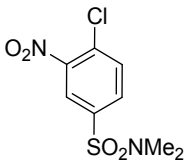
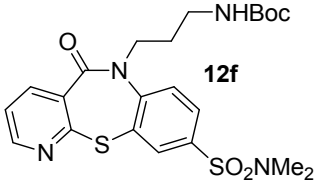
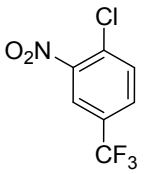
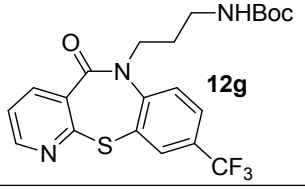
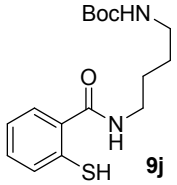
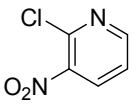
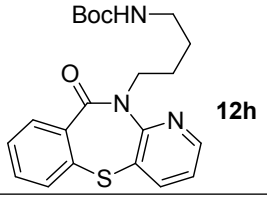


Table 1. Diarene-fused [1.4]oxazepines **11a-l** and [1.4]thiazepines **12a-h** prepared in this work.

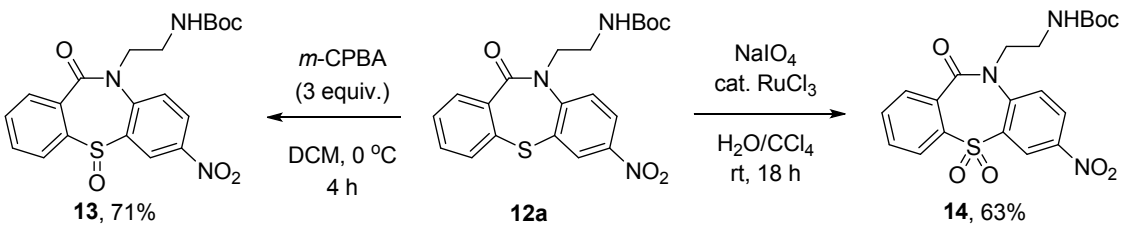
Entry	Compound **9**	Compound **10**	Cyclocondensation product **11** or **12**	Time (h)	T (ºC)	Yield (%)
1				12	RT	89
2				12	RT	82
3				12	50	98
4				16	80	49
5				12	RT	54

6	 **9d**		 **11f**	12	RT	87
7			 **11g**	12	50	84
8			 **11h**	12	50	97
9			 **11i**	18	50	60
10	 **9e**		 **11j**	12	RT	86
11			 **11k**	12	50	92
12	 **9f**		 **11l**	16	80	81
13	 **9g**		 **12a**	5	RT	83
14			 **12b**	18	50	39

15			 **12c**	3	RT	86
16	 **9h**		 **12d**	12	50	64
17			 **12e**	24	RT	40
18	 **9i**		 **12f**	8	RT	89
19			 **12g**	12	RT	70
20	 **9j**		 **12h**	18	50	49

Additionally, we synthesized sulfoxide (**13**) and sulfone (**14**) substrates for further testing in the ring expansion process, by oxidation of compound **12a** with *m*-CPBA and $NaIO_4/RuCl_3$(cat.), respectively (Scheme 2).

Scheme 2. Oxidation of compound **12a**.

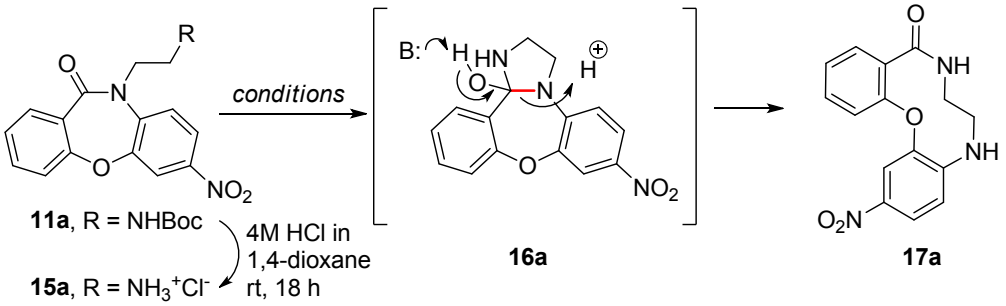


13, 71% **12a** **14**, 63%

Having prepared the diverse set of starting materials for potential hydrated imidazoline ring expansion (HIRE) reactions and its homologous variants, we proceeded to identify the optimal

workable conditions to conduct this process. To this end, the Boc protecting group in **11a** was removed (by treatment with 4M solution of HCl in 1,4-dioxane), the resulting hydrochloride salt **15a** was isolated by simple filtration and used in the ring expansion reactions under a range of conditions which included the variation of the base (thought to promote the scission of the central bond in the putative hydrated imidazoline intermediate **16a**[7]), its quantity as well as solvent system (Table 2).

Table 2. Optimization studies for the HIRE reaction of **15a** prepared from **11a**.



Entry	Solvent system	Base	# of base equiv.	Reaction time (h)[a]	Yield (%)
1	H_2O-MeOH (1:1)	NaOH	4.0	1	68
2		LiOH		1	66
3		K_2CO_3		2	62
4		Et_3N		18[b]	30
5	H_2O-MeCN (1:1)	NaOH	4.0	4	58
6	H_2O-THF (1:1)			24[b]	43
7	H_2O-DMF (1:1)			5	62
8	H_2O-acetone (1:1)			18	41
9	H_2O-MeOH (1:1)	NaOH	1.0	24	62
10			1.5	6	64
11			2.0	3	65
12			3.0	3	68
13	H_2O-MeOH (3:1)	NaOH	3.0	2	44
14	H_2O-MeOH (2:1)			2	48
15	H_2O-MeOH (1:2)			4	45
16	H_2O-MeOH (1:3)			8	48
17	H_2O-MeOH (1:4)			24	48
18	H_2O-MeOH (1:5)			48	50
19	MeOH			72	16

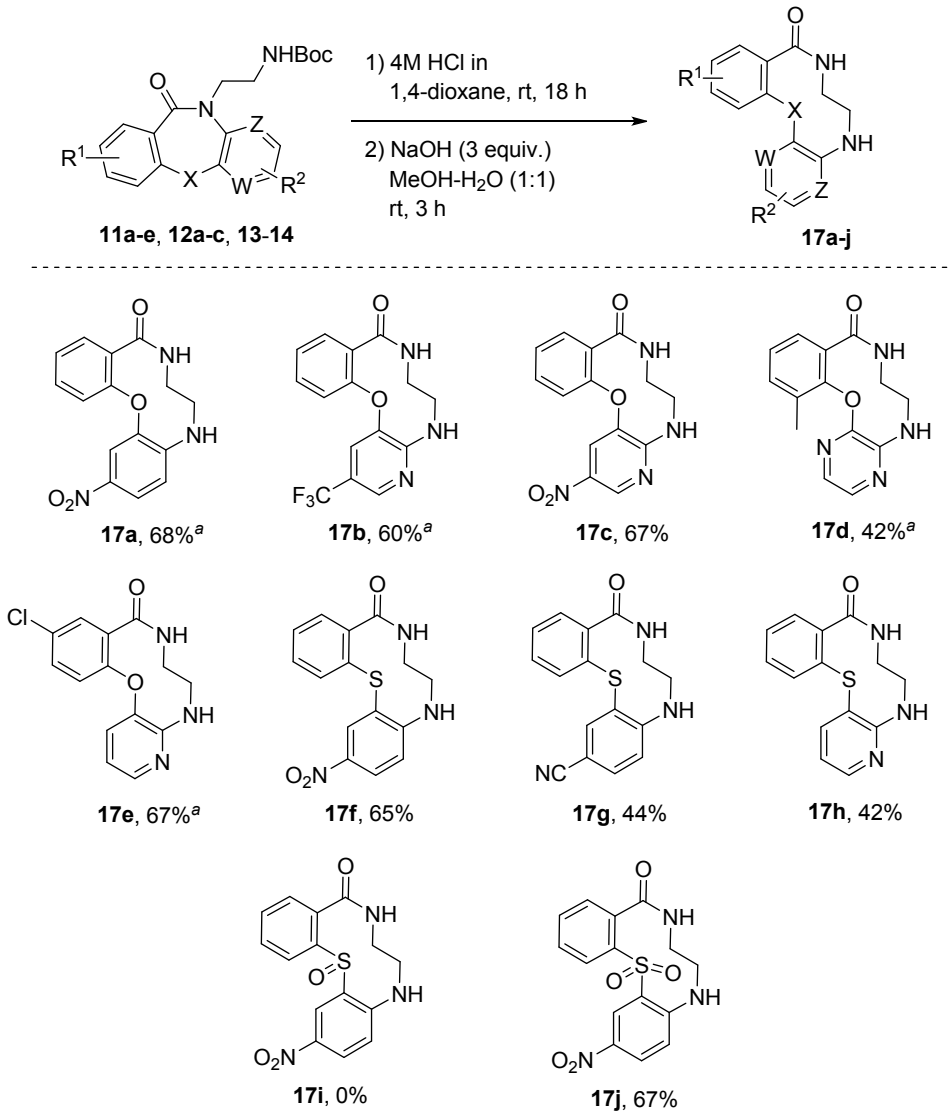
[a] Time to maximum conversion (by TLC analysis).
[b] Reaction was run at 50 ºC.

To our delight, the ring-expanded product which we had expected to arise via the formation of intermediate **16a**, was indeed isolated in all cases studied (this was particularly reassuring since

previously, we were not able to trigger the hydration of imidazoline substrates to form intermediate such as **16a** without activating the imidazoline by *N*-alkylation[6-7]). In principle, the use of the base was not critical for achieving the full conversion of the reaction: by using only 1 equiv. of NaOH (which will only liberate the primary amino group from the salt form) a yield comparable (62%, entry 9) to the optimum yield (68%, entries 1 or 12) was obtained. However, employing additional equivalents of base (up to 3.0) significantly accelerated the reaction (very much in line with the likely participation of the base in the evolution of intermediate **16a**). Other inorganic bases gave comparable results while using Et_3N led to poorer yield and longer reaction time (entry 4). The outcome of the reaction was not sensitive to the concentration of the base (data not shown) but was strongly dependent on the solvent system. Particularly noteworthy is the importance of using 1:1 MeOH-H_2O mixture and the rapid decrease in both the yield and the rate of conversion on going from 25% to 20% H_2O in MeOH and to pure MeOH (Table 1, entries 16-19). Overall, the optimal conditions subsequently employed in all HIRE reactions and their homologous variants described below were identified as using 3.0 equiv. of NaOH in MeOH-H_2O (1:1) as 10 wt. % solution, ambient temperature.

These conditions were applied to other *N*-aminoethyl-substituted 7-membered lactams prepared by Boc group removal from compounds **11a-e**, **12a-c** and **13**-**14** (Scheme 3). The yields of ten-membered lactams **17** were generally good except for sulfoxide **17i** which was not detected in the complex product mixture obtained after exposing **13** to the same reaction conditions.

Scheme 3. The HIRE reaction of primary amines generated from compounds **11a-e**, **12a-c**, **13-14**.

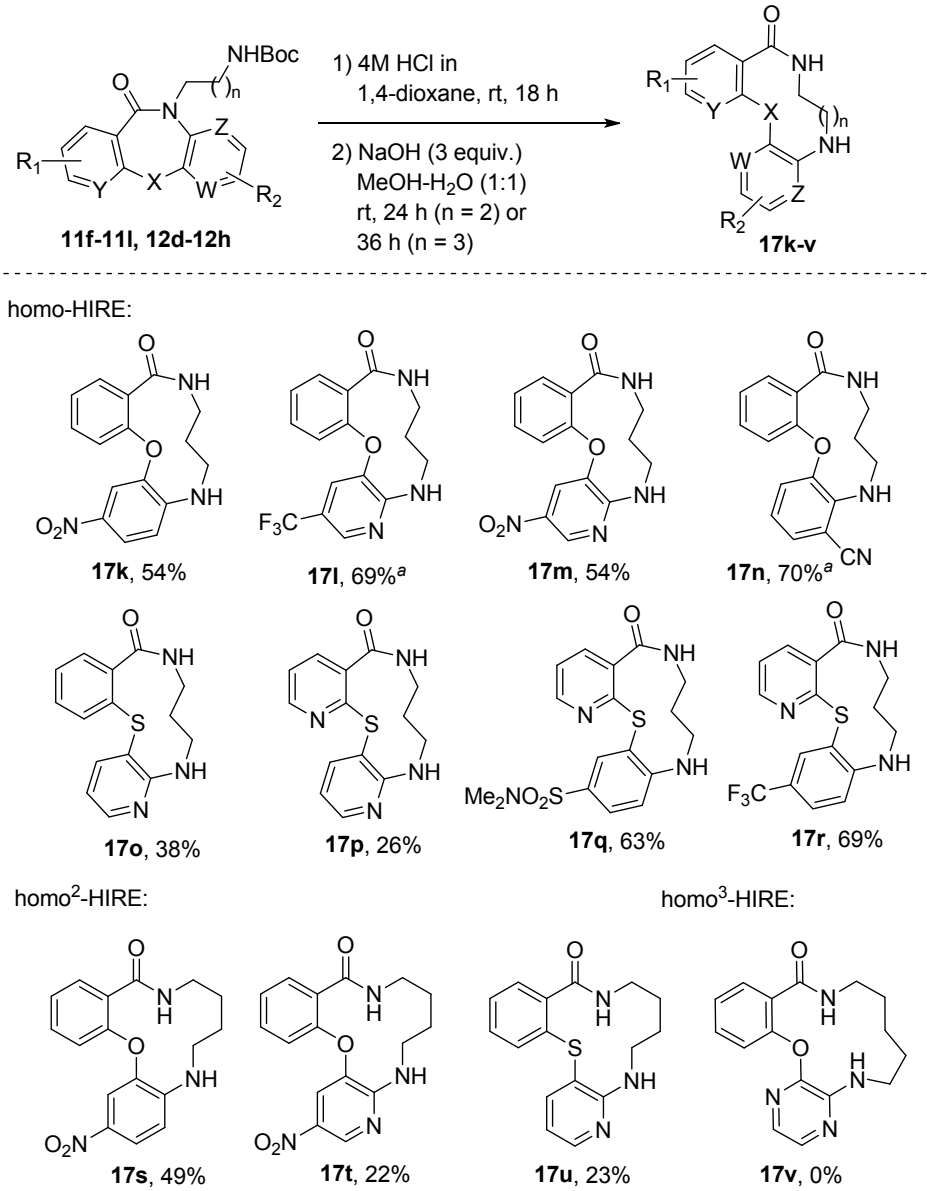


[a] Structure confirmed by single-crystal X-ray analysis.

Encouraged by the successful realization of our strategy to re-construct the hydrated imidazoline intermediate we postulated earlier[6-7] in the *hydrolytic* imidazoline ring expansion (and thus arriving at a unified *hydrated* imidazoline ring expansion process), we were keen to explore the homologous variants of the three-atom side-chain substrates under the same conditions. Previously, we were not able to achieve such a ring expansion process for cyclic amidines larger than imidazoline due to our inability to prepare the respective substrates. With the current 'ω-aminoalkyl side chain' approach, we reasoned, these 'homologous imidazolines' would be also formed, already in the hydrated form, and would be rapidly evolved into respective ring-

expanded products. To our delight, this proved to be true. While the respective homologous hydrated imidazoline ring expansion ('homo^x-HIRE') reactions were markedly slower and took 24-36 h to complete, the respective 11- and 12-lactams were successfully obtained from the respective homo-HIRE and homo^2-HIRE reactions in moderate to good yields. Unfortunately, the same process envisioned for the 6-atom side chain (present in the compound obtained after Boc group removal from **11l**) was not effective, thus defining applicability of the present methodology to 3- to 5-atom lactam ring expansion (Scheme 4).

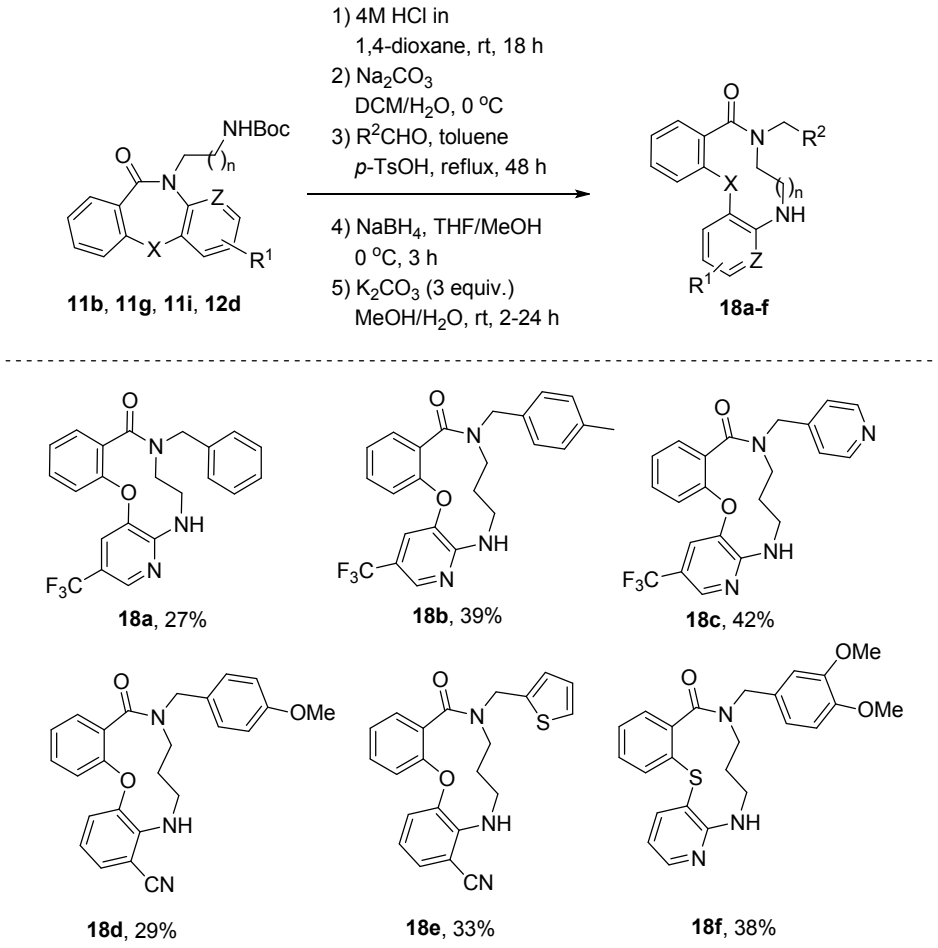
Scheme 4. Deprotection of substrates **11f-11l**, **12d-12h** and subsequent homo-HIRE, homo^2-HIRE and attempted homo^3-HIRE reactions (for n = 2, 3 and 4, respectively).



[a] Structure confirmed by single-crystal X-ray analysis.

We further reasoned that elaboration of primary ω-aminoalkyl side chain (present in substrates obtained by deprotection of compounds **11-14**) into a secondary one should not preclude such systems from undergoing a (homo^x-)HIRE process. The latter was envisioned to furnish ring-expanded lactam products containing an additional substituent (potentially useful as a periphery diversity element for medicinal chemistry optimization).

Scheme 5. Preparation of *N*-substituted (homo-)HIRE lactam products **18a-f** via reductive alkylation.

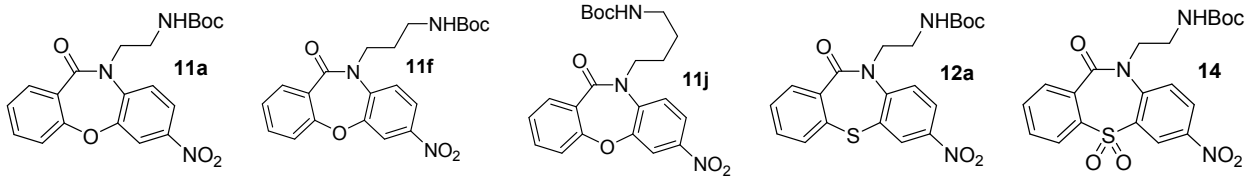


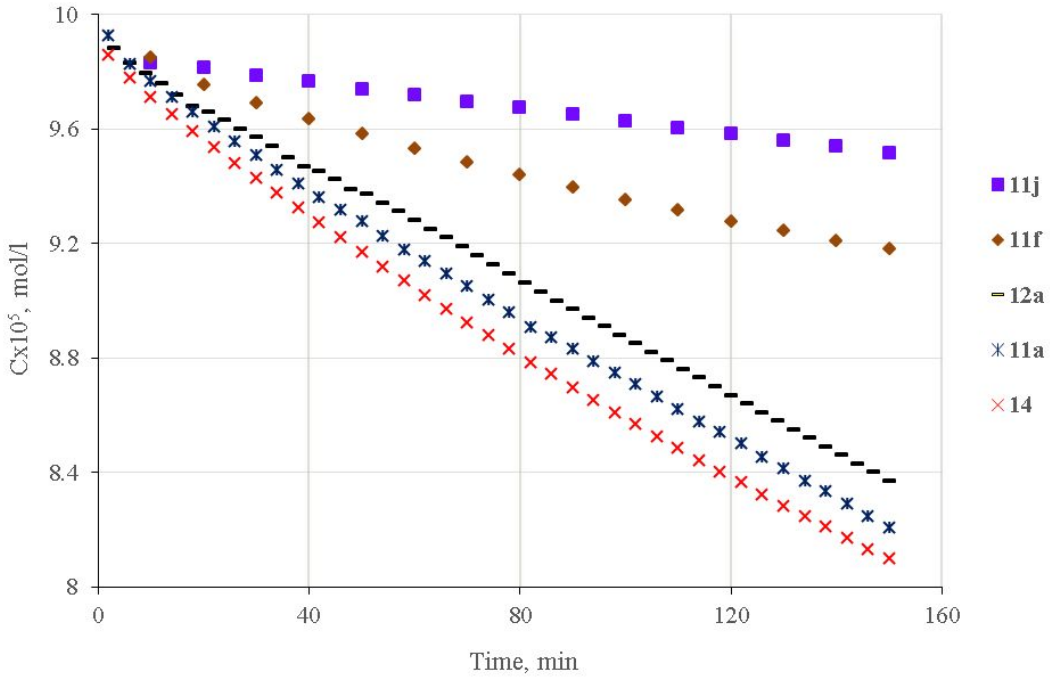
We tested and confirmed this possibility for compounds **11b**, **11g**, **11i** and **12d**. Without intermittent purification, these compounds were subjected to Boc group removal, Schiff base formation (which, surprisingly, turned out to be particularly sluggish in this case), reduction of the latter with sodium borohydride and triggering the (homo-)HIRE event. The latter, again, was found to be markedly slower for the formation of 11-membered lactams **18b-f** compared to their 10-membered counterpart **18a** (24 h vs. 2 h to achieve a complete conversion, respectively). The

target compounds **18a-f** were isolated in 27-42% yields, which we consider rather efficient taking into account the number chemical events involved in this syntheses (Scheme 5).

Aiming to better understand the structural factors influencing the rate of the (homo^{x}-)HIRE process, we compared the initial rates of conversion observed UV-spectrophotometrically for the HIRE reactions (performed in solutions 1000-fold more dilute compared to the preparative reactions described above) for five similarly substituted substrates (generated by deprotection of **11a**, **11f**, **11j**, **12a** and **14**).

Figure 3. Comparative initial rates of conversion for (homo^{x}-)HIRE substrates obtained by deprotection of **11a**, **11f**, **11j**, **12a** and **14**.

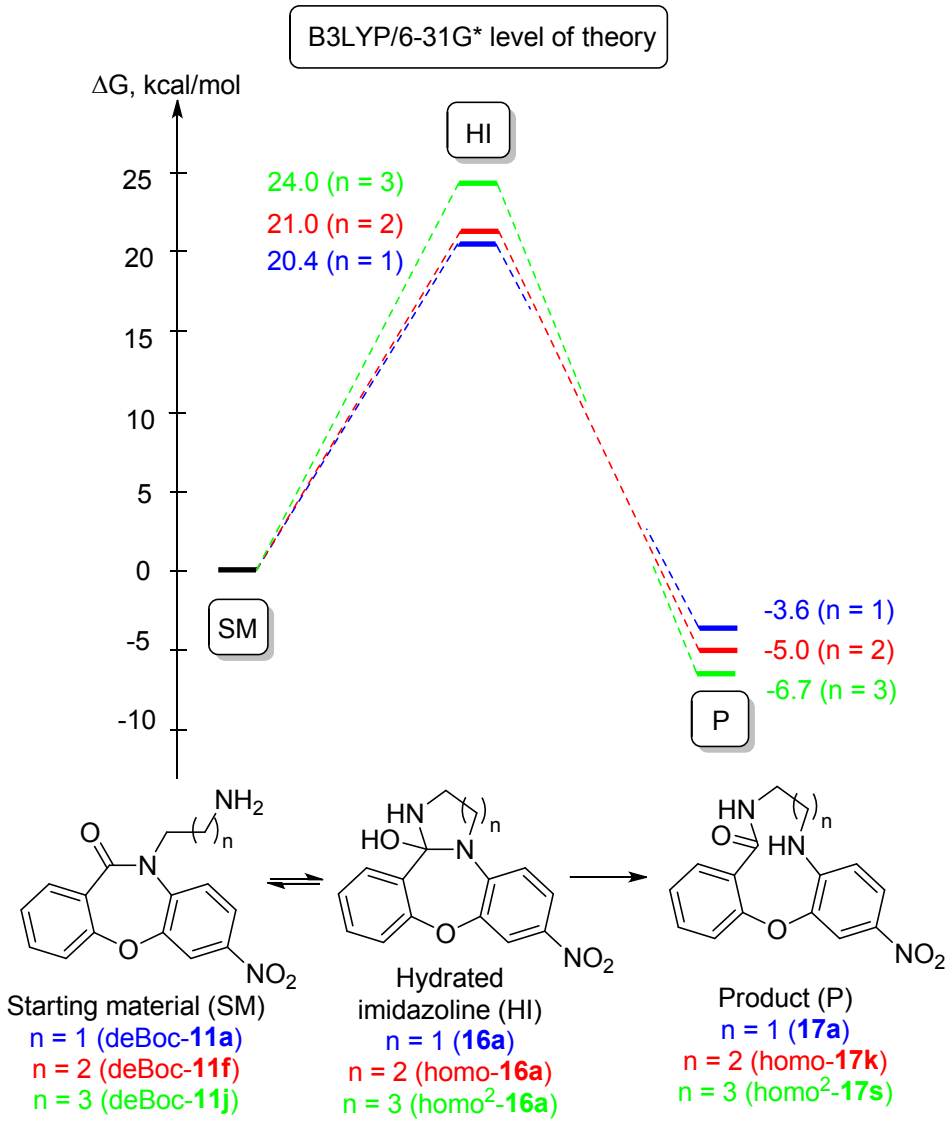




As it is evident form the data plotted in Figure 3, the rates of conversion were virtually insensitive to the nature of the linker atom (group) between the two aromatic rings (cf. deprotected **11a**, **12a** and **14**). This finding is contrast to our earlier observations made for the hydrolytic imidazoline ring expansion reaction[7] and suggests that the electrophilicity of the

lactam carbonyl carbon atom (which is influenced by the nature of the X group, being in direct conjugation with it) in present case has no significant bearing on the rate of reaction. On the contrary, what does have a substantial effect on the reaction rate is the length of the side chain (cf. significant slowing of the conversion for deprotected **11a→11f→11j**).

Figure 4. Energy diagram for the (homo^x)-HIRE reaction proceeding via the formation of hydrated imidazoline and its homologs.

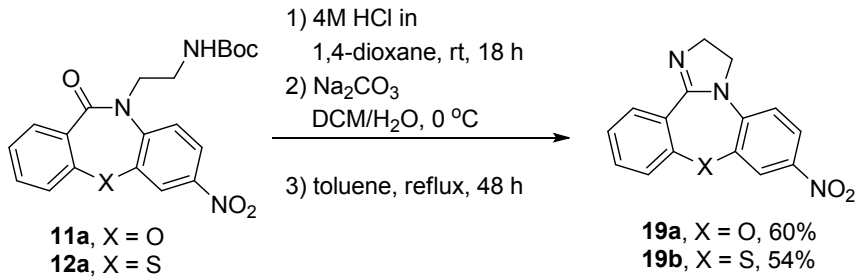


Theoretical calculations performed at the B3LYP/6-31G* theory level confirmed that elongation of the side chain in deprotected starting material (**11a→11f→11j**) led to a substantial *increase* of the energy level of the respective hydrated imidazoline intermediate and its homologs ((homo^x)-**16a**). Increase entropy loss associated with the formation of the latter is the likely reason for the observed reactivity trend (also corroborated by the energy calculations) rather than the relative

energy levels of the reactions products which were calculated to *decrease* in the same order (**17a→17k→17s**). The energy diagram summarizing the results of the theoretical calculations is presented in Figure 4. Interestingly, in this case, calculations gave more reliable results compared to the M06-2X/6-31G* theory level (Tables S3-S4). The computational results and the resulting conclusions obtained in present work are similar to those described in two recent conceptually related publications by Yudin[15] and Unsworth[16] on ring expansion (also using the B3LYP/6-31G* theory level calculations). Additionally, the ring expansions described in this paper are also related to other methodologies recently described by Unsworth and co-workers.[17]

The intermediacy of the hydrated imidazoline and its homologs in the reactions described herein suggests that if these reactions are conducted in aprotic, dehydrating medium in the absence of base, the hydrated imidazoline can be dehydrated to form stable imidazoline product. This was indeed observed for deprotected compounds **11a** and **12a** on reflux in toluene with azeotropic removal of water (Scheme 6). Interestingly, that previously described compounds **19a**[6] and **19b**[7] need to be activated by *N*-alkylation in order to form the hydrated imidazoline intermediate and, as the result, undergo the HIRE process, as we observed earlier.[6-7]

Scheme 6. Formation of imidazolines **19a-b** from deprotected **11a** and **12a** under dehydrative conditions.



11a, X = O
12a, X = S

19a, X = O, 60%
19b, X = S, 54%

CONCLUSION

In summary, we have presented a novel ring expansion strategy involving insertion of an ω-aminoalkyl side chain in [1.4]oxazepinone and [1.4]thiazepinone nucleus. The reaction of 2-aminoethyl derivatives is thought to proceed via a hydrated imidazoline intermediate and thus has a common mechanistic foundation with the earlier described expansion of imidazoline rings

activated by alkylation. We therefore propose to term this common ring expansion approach the hydrated imidazoline ring expansion or HIRE. This methodology was found applicable to insertion of longer side chains (up to 5 atoms) and thus can also furnish 11- to 12-membered medium-sized rings via a "homo^{x}-HIRE" approach. The HIRE reaction itself was found to be markedly faster compared to its homologous variant which, according to theoretical calculations of the respective energy profiles, has to do with the least entropy loss associated with the formation of hydrated imidazoline among its homologs. The new approach to the construction of medium-sized cycles will add significantly to the modern arsenal of methods to assemble such rings. The development of common mechanistic view on the ring expansion process will significantly facilitate our ongoing quest for yet unexplored opportunities for three-atom ring expansion via the HIRE reaction. The results of these studies will be reported as they become available.

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 $CDCl_3$ and were referenced to residual solvent signals (δ_H = 2.50, 7.26 ppm respectively) and solvent carbon signals (δ_C = 39.52, 77.00 ppm respectively). Mass spectra were recorded on microTOF spectrometers (ESI ionization). Melting points were determined in open capillary tubes on Stuart SMP50 Melting Point Apparatus. 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. Spectrophotometric measurements were performed on a UV-1800 Shimadzu double beam spectrophotometer (Japan) using 10.00 mm quartz cells. Column chromatography was carried out with silica gel grade 60 (0.040–0.063 mm) 230–400 mesh. HPLC preparative chromatography was performed with Agilent PrepHT XDB-C18 preparative cartridge 21.2x150 mm 5-micron. All commercial reagents and solvents were used without further purification, unless otherwise noted. DMF for the synthesis was distilled over CaH_2 and stored under nitrogen

over freshly activated molecular sieves 4Å. Potassium carbonate was dried at 200 °C for 5 hours prior to use.

General Procedure for the Preparation of Amides 9a-j

To a suspension of **7** (35 mmol) in CH_2Cl_2 (**9a-f**) or 1,4-dioxane (**9g-j**) (25 mL) CDI (5.83 g, 36 mmol) was added. The mixture was stirred at room temperature for 1.5-2 h. Mono-Boc-protected diaminoalkane **8** (35 mmol) was added at 0 ˚C. The resulting mixture was stirred at 0 ºC for 2 h and then at room temperature overnight. The reaction mixture was washed with sat. aq. K_2CO_3 (3×20 mL), water, dried over Na_2SO_4 and concentrated under reduced pressure. Compounds **9a, 9e, 9f** were purified by column chromatography. Compounds **9h-i** were crystallized from EtOAc.

All other compounds were sufficiently pure to be used in the step without further purification.

***tert*-Butyl (2-(2-hydroxybenzamido)ethyl)carbamate (9a)**

Yield 6.48 g, 66%; white solid; mp 75-78 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.51 (br s, 1H), 7.89 – 7.68 (br s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.86 (t, J = 8.4 Hz, 1H), 5.04 (s, 1H), 3.56 (td, J = 6.0, 4.6 Hz, 2H), 3.50 – 3.39 (m, 2H), 1.46 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.6, 161.5, 158.1, 134.0, 126.0, 118.6, 118.3, 114.2, 80.4, 42.4, 39.5, 28.3(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{20}N_2NaO_4$ $[M+Na]^+$ 303.1315, found 303.1326.

***tert*-Butyl (2-(2-hydroxy-3-methylbenzamido)ethyl)carbamate (9b)**

Yield 5.15 g, 50%; white solid; R_f (Hexane/EtOAc = 4/1): 0.19; mp 118-120 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.89 – 12.71 (br s, 1H), 7.73 – 7.60 (br s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 7.3 Hz, 1H), 6.76 (t, J = 7.7 Hz, 1H), 5.13 – 4.96 (br s, 1H), 3.59 – 3.50 (m, 2H), 3.48-3.41 (m, 2H), 2.28 (s, 3H), 1.46 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.0, 160.0, 158.0, 134.8, 127.3, 123.4, 117.9, 113.3, 80.4, 42.3, 39.6, 28.3 (3C), 15.7 ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{22}N_2NaO_4$ $[M+Na]^+$ 317.1472, found 317.1471.

***tert*-Butyl (2-(5-chloro-2-hydroxybenzamido)ethyl)carbamate (9c)**

Yield 5.73 g, 42%; white solid; R_f (Hexane/EtOAc = 2/1): 0.27; mp 159-161 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.57 – 12.36 (br s, 1H), 8.11 – 7.96 (br s, 1H), 7.51 (d, J = 2.5 Hz, 1H), 7.32 (dd, J = 8.9, 2.5 Hz, 1H), 6.92 (d, J = 8.9 Hz, 1H), 5.19 – 5.01 (br s, 1H), 3.58 – 3.50 (m, 2H), 3.50 – 3.41 (m, 2H), 1.48 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.4, 160.1, 158.4, 133.8, 125.7, 123.3, 119.7, 115.1, 80.8, 42.8, 39.3, 28.3(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{20}ClN_2O_4$ $[M+H]^+$ 315.1106, found 315.1097.

***tert*-Butyl (3-(2-hydroxybenzamido)propyl)carbamate (9d)**

Yield 7.21 g, 70%; white solid; mp 87-90 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.64 (br s, 1H), 7.95 – 7.78 (br s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.40 (td, J = 7.2, 1.6 Hz, 1H), 6.99 (dd, J = 8.3, 1.3 Hz, 1H), 6.89 (td, J = 7.6, 1.3 Hz, 1H), 4.86 (s, 1H), 3.52 (q, J = 6.1 Hz, 2H), 3.29 (q, J = 6.3 Hz, 2H), 1.78 – 1.68 (m, 2H), 1.49 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.1, 161.6, 157.4, 133.9, 125.9, 118.7, 118.3, 114.5, 79.9, 36.9, 35.4, 30.1, 28.4(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{22}N_2NaO_4$ $[M+Na]^+$ 317.1472, found 317.1480.

***tert*-Butyl (4-(2-hydroxybenzamido)butyl)carbamate (9e)**

Yield 2.91 g, 27%; white solid; R_f (CH_2Cl_2/EtOAc = 9/1): 0.33; mp 100-102 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.65 – 12.47 (br s, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.39 (td, J = 7.2, 1.6 Hz, 1H), 7.18 – 7.04 (br s, 1H), 6.98 (dd, J = 8.3, 1.2 Hz, 1H), 6.83 (td, J = 7.3, 1.2 Hz, 1H), 4.74 (s, 1H), 3.50 (q, J = 6.4 Hz, 2H), 3.18 (q, J = 6.6 Hz, 2H), 1.72 – 1.56 (m, 4H), 1.47 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 161.5, 156.4, 134.0, 125.8, 118.5, 118.4, 114.4, 79.4, 39.8, 39.2, 28.4(3C), 27.9, 27.4 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{24}N_2NaO_4$ $[M+Na]^+$ 331.1628, found 331.1635.

***tert*-Butyl (5-(2-hydroxybenzamido)pentyl)carbamate (9f)**

Yield 8.38 g, 75%; white solid; mp 105-107 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.63 – 12.47 (br s, 1H), 7.53 (d, J = 7.4 Hz, 1H), 7.39 (td, J = 7.2, 1.6 Hz, 1H), 6.99 (dd, J = 8.3, 1.2 Hz, 1H), 7.02 – 6.84 (br s, 1H), 6.88 – 6.82 (m, 1H), 4.69 – 4.57 (br s, 1H), 3.45 (q, J = 6.6 Hz, 2H), 3.15

(q, J = 6.4 br Hz, 2H), 1.69-1.59 (m, 2H), 1.53 – 1.35 (m, 13H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 207.0, 170.0, 161.5, 156.3, 133.9, 125.7, 118.5, 114.6, 79.2, 39.8, 38.9, 30.9, 30.1, 28.4(3C), 25.7 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{26}N_2NaO_4$ $[M+Na]^+$ 345.1785, found 345.1788.

***tert*-Butyl (2-(2-mercaptobenzamido)ethyl)carbamate (9g)**

Yield 7.88 g, 76%; white solid; mp 185-188 ˚C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.59 (t, J = 5.6 Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.45 (td, J = 7.7, 1.4 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 6.90 (t, J = 5.8 Hz, 1H), 3.32 (q, J = 6.3 Hz, 2H), 3.15 (q, J = 6.3 Hz, 2H), 1.39 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 167.4, 156.2, 137.2, 134.2, 131.5, 128.5, 126.3, 126.1, 78.2, 40.4, 39.8, 28.7(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{20}N_2NaO_3S$ $[M+Na]^+$ 319.1087, found 319.1084.

***tert*-Butyl (3-(2-mercaptobenzamido)propyl)carbamate (9h)**

Yield 5.87 g, 54%; white solid; mp 164-165 ˚C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.58 (t, J = 5.7 Hz, 1H), 7.69 – 7.60 (m, 2H), 7.45 (td, J = 7.7, 1.5 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 6.82 (t, J = 5.9 Hz, 1H), 3.28 (q, J = 6.7 Hz, 2H), 3.02 (q, J = 6.6 Hz, 2H), 1.72 – 1.62 (m, 2H), 1.39 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 167.3, 156.1, 137.1, 134.5, 131.5, 128.3, 126.4, 126.2, 78.0, 38.2, 37.5, 30.0, 28.7(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{22}N_2NaO_3S$ $[M+Na]^+$ 333.1243, found 333.1250.

***tert*-Butyl (3-(2-mercaptonicotinamido)propyl)carbamate (9i)**

Yield 6.21 g, 57%; yellow solid; mp 125-127 ˚C. ^1H NMR (400 MHz, $CDCl_3$) δ 13.23 – 12.84 (br s, 1H), 10.98 – 10.74 (br s, 1H), 8.81 (dd, J = 7.7, 1.9 Hz, 1H), 7.77 (d, J = 6.1 Hz, 1H), 6.95 (t, J = 7.7 Hz, 1H), 5.19 – 5.07 (br s, 1H), 3.59 (q, J = 6.3 Hz, 2H), 3.27 (q, J = 6.4 Hz, 2H), 1.99 – 1.71 (m, 2H), 1.45 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 174.7, 164.1, 156.2, 143.3, 139.3, 133.7, 113.9, 79.1, 37.9, 37.0, 29.8, 28.5(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{22}N_3O_3S$ $[M+H]^+$ 312.1376, found 312.1380.

***tert*-Butyl (4-(2-mercaptobenzamido)butyl)carbamate (9j)**

Yield 2.95 g, 26%; white solid; mp 193-195 ˚C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (t, J = 5.6 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.44 (td, J = 6.2, 1.5 Hz, 1H), 7.29 (td, J = 7.4, 1.2 Hz, 1H), 6.80 (t, J = 5.8 Hz, 1H), 3.27 (q, J = 5.8 Hz, 2H), 2.96 (q, J = 6.4 Hz, 2H), 1.59 – 1.41 (m, 4H), 1.38 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.2, 156.1, 137.1, 134.6, 131.4, 128.3, 126.3, 126.2, 77.8, 40.0, 39.4, 28.8(3C), 27.5, 26.9 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{24}N_2NaO_3S$ $[M+Na]^+$ 347.1400, found 347.1395.

General Procedure for Preparation of [1.4]Oxazepinones 11 and [1.4]Thiazepinones 12

To a solution of amide **9** (0.70 mmol) in anhydrous DMF (5 mL) the respective 1,2-dihaloarene or 1-halo-2-nitroarene **10** (0.70 mmol) and freshly calcinated K_2CO_3 (290 mg, 2.10 mmol) were added. The mixture was stirred the appropriate temperature (Table 1) overnight. DMF was removed *in vacuo* and the residue was partitioned between water (5 mL) and CH_2Cl_2 (5 mL). The organic layer was separated, washed with water (3 x 5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

Compounds **11a, 11c, 11d, 11e, 11k, 12c, 12e, 12f** were purified by column chromatography. Compound **11g** was crystallized from Hexane/EtOAc = 4/1.

***tert*-Butyl (2-(7-nitro-11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)ethyl)carbamate (11a)**

Yield 248.8 mg, 89%; green solid; R_f (CH_2Cl_2/Acetone = 20/1): 0.21; mp 159-161 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 2.5 Hz, 1H), 8.12 (dd, J = 8.9, 2.5 Hz, 1H), 7.85 (dd, J = 7.7, 1.7 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.54 (td, J = 7.8, 1.7 Hz, 1H), 7.32 – 7.25 (m, 2H), 5.04 – 4.84 (br s, 1H), 4.25 (t, J = 6.6 Hz, 2H), 3.57 (q, J = 6.2 Hz, 2H), 1.40 (s, 9H) ppm. ^{13}C{^{1}H} (101 MHz, $CDCl_3$) δ 166.1, 159.7, 156.0, 153.5, 145.0, 141.6, 134.3, 132.2, 126.1, 125.9, 123.6, 121.5, 119.8, 117.5, 79.7, 49.6, 39.0, 28.3(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}N_3NaO_6$ $[M+Na]^+$ 422.1323, found 422.1319.

***tert*-Butyl (2-(10-oxo-3-(trifluoromethyl)benzo[*f*]pyrido[3,2-*b*][1,4]oxazepin-11(10*H*)-yl)ethyl)carbamate (11b)**

Yield 243.0 mg, 82%; white solid; mp 106-108 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 0.9 Hz, 1H), 7.90 (dd, J = 7.8, 1.6 Hz, 1H), 7.80 (d, J = 1.8 Hz, 1H), 7.54 (td, J = 8.0, 1.6 Hz, 1H), 7.31 (td, J = 7.7, 0.9 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 5.37 – 5.19 (br s, 1H), 4.48 (t, J = 5.7 Hz, 2H), 3.60 (q, J = 5.7 Hz, 2H), 1.40 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.9, 158.8, 155.9, 151.1, 147.7, 141.7 (q, J = 4.1 Hz), 134.3, 132.7, 127.2, 126.2, 125.8, 124.5, 122.7 (d, J = 272.5 Hz), 119.5, 79.1, 46.7, 39.8, 28.3(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}F_3N_3O_4$ $[M+H]^+$ 424.1479, found 424.1486.

***tert*-Butyl (2-(3-nitro-10-oxobenzo[*f*]pyrido[3,2-*b*][1,4]oxazepin-11(10*H*)-yl)ethyl)carbamate (11c)**

Yield 274.7 mg, 98%; yellow solid; R_f (CH_2Cl_2): 0.18; mp 179-181 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, J = 2.2 Hz, 1H), 8.35 (d, J = 2.3 Hz, 1H), 7.89 (dd, J = 7.8, 1.4 Hz, 1H), 7.56 (td, J = 6.9, 1.4 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 6.9 Hz, 1H), 5.21 – 5.03 (br s, 1H), 4.51 (t, J = 5.9 Hz, 2H), 3.59 (q, J = 5.9 Hz, 2H), 1.39 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.7, 158.3, 155.9, 152.9, 147.1, 141.1, 140.5, 134.6, 132.7, 126.4, 125.6, 125.1, 119.6, 79.3, 46.8, 39.5, 28.3(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{20}N_4NaO_6$ $[M+Na]^+$ 423.1275, found 423.1270.

***tert*-Butyl (2-(6-methyl-10-oxobenzo[*f*]pyrazino[2,3-*b*][1,4]oxazepin-11(10*H*)-yl)ethyl)carbamate (11d)**

Yield 127.1 mg, 49%; white solid; R_f (CH_2Cl_2/EtOAc = 40/1): 0.13; mp 159-161 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 2.5 Hz, 1H), 8.08 (d, J = 2.5 Hz, 1H), 7.69 (dd, J = 7.8, 1.6 Hz, 1H), 7.41 (dd, J = 7.6, 1.5 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 5.29 – 5.01 (br s, 1H), 4.43 (t, J = 5.9 Hz, 2H), 3.57 (q, J = 5.8 Hz, 2H), 2.59 (s, 3H), 1.40 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.2, 155.9, 155.1, 153.5, 144.7, 139.9, 137.8, 135.3, 130.4, 129.7, 125.8, 125.7, 79.2,

46.4, 39.6, 28.4(3C), 16.3 ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{22}N_4NaO_4$ $[M+Na]^+$ 393.1533, found 393.1540.

***tert*-Butyl (2-(8-chloro-10-oxobenzo[*f*]pyrido[3,2-*b*][1,4]oxazepin-11(10*H*)-yl)ethyl)carbamate (11e)**

Yield 147.4 mg, 54%; yellow solid; R_f (Hexane/EtOAc = 2/1): 0.27; mp 159-161 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, J = 4.6, 1.5 Hz, 1H), 7.85 (d, J = 2.6 Hz, 1H), 7.58 (dd, J = 7.9, 1.5 Hz, 1H), 7.43 (dd, J = 8.6, 2.6 Hz, 1H), 7.18 – 7.12 (m, 2H), 5.54 (t, J = 5.6 Hz, 1H), 4.41 (t, J = 5.9 Hz, 2H), 3.59 (q, J = 5.7 Hz, 2H), 1.41 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.9, 157.9, 156.0, 148.5, 147.6, 145.0, 133.6, 132.2, 131.2, 129.8, 127.6, 121.7, 121.0, 79.0, 46.9, 39.8, 28.4(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{20}ClN_3NaO_4$ $[M+Na]^+$ 412.1035, found 412.1042.

***tert*-Butyl (3-(7-nitro-11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)propyl)carbamate (11f)**

Yield 256.3 mg, 87%; yellow solid; mp 129-131 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 2.6 Hz, 1H), 8.10 (dd, J = 9.0, 2.6 Hz, 1H), 7.85 (dd, J = 7.7, 1.8 Hz, 1H), 7.63 – 7.48 (m, 1H), 7.46 (d, J = 9.0 Hz, 1H), 7.33 – 7.24 (m, 2H), 4.91 (br s, 1H), 4.24 (t, J = 7.0 Hz, 2H), 3.34 – 3.21 (m, 2H), 2.05 – 1.87 (m, 2H), 1.44 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.0, 159.7, 154.2, 145.0, 140.9, 134.1, 132.2, 126.0(2C), 125.9, 123.2, 121.3, 119.7, 117.1, 77.3, 53.4, 46.5, 30.9, 28.3(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{21}H_{23}N_3NaO_6$ $[M+Na]^+$ 436.1479, found 436.1472.

***tert*-Butyl (3-(10-oxo-3-(trifluoromethyl)benzo[*f*]pyrido[3,2-*b*][1,4]oxazepin-11(10*H*)-yl)propyl)carbamate (11g)**

Yield 257.2 mg, 84%; white solid; mp 122-124 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.89 (d, J = 7.1 Hz, 1H), 7.80 (s, 1H), 7.54 (t, J = 7.3 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 5.23 – 5.07 (br s, 1H), 4.42 (t, J = 6.4 Hz, 2H), 3.24 (q, J = 5.7 Hz, 2H), 2.05 – 1.94 (m, 2H), 1.46 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.8, 158.8, 156.0, 151.1,

147.8, 141.7 (q, J = 4.2 Hz), 134.2, 132.6, 127.2, 126.2, 126.0, 124.4, 122.7 (d, J = 267.7 Hz), 119.5, 79.1, 44.4, 37.8, 30.9, 28.4(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{21}H_{22}F_3N_3NaO_4$ $[M+Na]^+$ 460.1455, found 460.1461.

***tert*-Butyl (3-(3-nitro-10-oxobenzo[*f*]pyrido[3,2-*b*][1,4]oxazepin-11(10*H*)-yl)propyl)carbamate (11h)**

Yield 281.4 mg, 97%; yellow solid; mp 141-143 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, J = 2.4 Hz, 1H), 8.35 (d, J = 2.4 Hz, 1H), 7.88 (dd, J = 7.8, 1.7 Hz, 1H), 7.57 (td, J = 7.8, 1.7 Hz, 1H), 7.33 (td, J = 8.1, 1.8 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 5.13 – 4.97 (br s, 1H), 4.43 (t, J = 6.8 Hz, 2H), 3.24 (q, J = 6.0 Hz, 2H), 2.07 – 1.97 (m, 2H), 1.46 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.6, 158.3, 156.0, 152.9, 147.1, 141.1, 140.6, 134.5, 132.6, 126.4, 125.7, 125.1, 119.5, 79.2, 44.8, 37.8, 28.7, 28.4(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{23}N_4O_6$ $[M+H]^+$ 415.1612, found 415.1620.

***tert*-Butyl (3-(9-cyano-11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)propyl)carbamate (11i)**

Yield 165.2 mg, 60%; beige solid; crystallized from 20% ethyl acetate in hexane; mp 172-174 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.7, 1.5 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.47 (td, J = 8.1, 1.7 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.20 (d, J = 8.1 Hz, 1H), 4.92 (dt, J = 14.0, 6.8 Hz, 1H), 4.91 – 4.83 (br s, 1H), 3.91 – 3.81 (m, 1H), 3.35 – 3.21 (m, 1H), 3.08 (td, J = 12.7, 6.0 Hz, 1H), 1.98 – 1.88 (m, 1H), 1.76 – 1.68 (m, 1H), 1.41 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.4, 160.9, 157.6, 155.8, 137.8, 133.8, 132.2, 131.5, 127.8, 126.6, 126.2, 126.1, 119.7, 116.1, 109.8, 79.1, 47.6, 37.3, 28.5, 28.4(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{23}N_3NaO_4$ $[M+Na]^+$ 416.1581, found 416.1575.

***tert*-Butyl (4-(7-nitro-11-oxodibenzo[*b*,*f*][1,4]oxazepin-10(11*H*)-yl)butyl)carbamate (11j)**

Yield 86% (264.7 mg, 0.62 mmol); yellow solid; mp 101-105 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 2.5 Hz, 1H), 8.11 (dd, J = 9.0, 2.5 Hz, 1H), 7.86 (dd, J = 7.8, 1.6 Hz, 1H), 7.53 (td, J = 7.9, 1.7 Hz, 1H), 7.45 (d, J = 8.9 Hz, 1H), 7.34 – 7.25 (m, 1H), 4.71 – 4.46 (br s, 1H), 4.19 (t, J

= 7.2 Hz, 2H), 3.25 – 3.07 (m, 2H), 1.88 – 1.75 (m, 2H), 1.67 – 1.53 (m, 2H), 1.44 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.7, 159.7, 155.9, 154.0, 144.9, 141.1, 134.0, 132.3, 126.0(2C), 123.34, 121.2, 119.6, 117.7, 79.2, 53.4, 48.7, 28.3, 27.3, 25.1(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{25}N_3NaO_6$ $[M+Na]^+$ 450.1636, found 450.1632.

tert-Butyl (4-(3-nitro-10-oxobenzo[*f*]pyrido[3,2-*b*][1,4]oxazepin-11(10*H*)-yl)butyl)carbamate (11k)

Yield 275.9 mg, 92%; yellow solid; mp 115-118˚C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (d, *J* = 2.4 Hz, 1H), 8.32 (d, *J* = 2.4 Hz, 1H), 7.87 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.54 (td, *J* = 8.0, 1.6 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 4.80 – 4.65 (br s, 1H), 4.39 – 4.28 (m, 2H), 3.18 (q, *J* = 6.0 Hz, 2H), 1.94 – 1.77 (m, 2H), 1.68 – 1.49 (m, 2H), 1.43 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.2, 158.3, 155.9, 153.0, 146.9, 141.9, 140.6, 134.4, 132.7, 126.4, 125.7, 125.0, 119.5, 79.1, 46.9, 40.0, 28.4(3C), 27.3, 25.4 ppm. HRMS (ESI), *m/z* calcd for $C_{21}H_{25}N_4O_6$ $[M+H]^+$ 429.1769, found 429.1773.

tert-Butyl (5-(10-oxobenzo[*f*]pyrazino[2,3-*b*][1,4]oxazepin-11(10*H*)-yl)pentyl)carbamate (11l)

Yield 226.8 mg, 81%; pink solid; mp 83-86 ˚C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 2.4 Hz, 1H), 8.07 (d, *J* = 2.4 Hz, 1H), 7.94 – 7.87 (m, 1H), 7.57 – 7.51 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.27 (m, 1H), 4.54 (br s, 1H), 4.33 – 4.24 (m, 2H), 3.15 – 3.07 (m, 2H), 1.88 – 1.63 (m, 2H), 1.53 – 1.32 (m, 13H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.1, 156.8, 156.0, 153.4, 144.4, 140.2, 137.6, 134.1, 132.3, 126.1, 125.8, 120.5, 79.0, 46.8, 40.5, 28.4(3C), 28.0, 26.6, 26.4 ppm. HRMS (ESI), *m/z* calcd for $C_{21}H_{26}N_4NaO_4$ $[M+Na]^+$ 421.1846, found 421.1849.

tert-Butyl (2-(7-nitro-11-oxodibenzo[*b*,*f*][1,4]thiazepin-10(11*H*)-yl)ethyl)carbamate (12a)

Yield 241.4 mg, 83%; yellow solid; mp 125-127 ˚C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.6 Hz, 1H), 8.19 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.73 – 7.66 (m, 1H), 7.56 (d, *J* = 8.9 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.41 – 7.35 (m, 2H), 4.99 (t, *J* = 6.3 Hz, 1H), 4.66 (dt, *J* = 13.3, 5.2 Hz, 1H), 3.98

(dt, J = 13.8, 6.7 Hz, 1H), 3.62 – 3.37 (m, 2H), 1.32 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.3, 155.7, 149.7, 144.7, 137.4, 137.2, 137.1, 131.5 (2C), 131.2, 129.3, 128.2, 126.4, 124.9, 79.4, 51.4, 39.2, 28.2(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}N_3NaO_5S$ $[M+Na]^+$ 438.1094, found 438.1095.

***tert*-Butyl (2-(10-oxobenzo[*f*]pyrido[3,2-*b*][1,4]thiazepin-11(10*H*)-yl)ethyl)carbamate (12b)**

Yield 101.4 mg, 39%; yellow solid; mp 159-161 ˚C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, J = 4.7, 1.8 Hz, 1H), 7.93 (dd, J = 7.6, 1.8 Hz, 1H), 7.74 – 7.68 (m, 1H), 7.48 – 7.43 (m, 1H), 7.39 – 7.33 (m, 2H), 7.10 (dd, J = 7.6, 4.7 Hz, 1H), 5.57 – 5.41 (br s, 1H), 4.53 (dt, J = 13.7, 5.5 Hz, 1H), 4.40 (dt, J = 13.6, 5.8 Hz, 1H), 3.61 – 3.46 (m, 2H), 1.39 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.7, 155.9, 148.8, 141.8, 138.1, 137.1, 131.8, 131.2(2C), 130.7, 130.1, 129.0, 121.4, 78.9, 48.6, 39.6, 28.4(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{21}N_3NaO_3S$ $[M+Na]^+$ 394.1196, found 394.1202.

***tert*-Butyl (2-(7-cyano-11-oxodibenzo[*b*,*f*][1,4]thiazepin-10(11*H*)-yl)ethyl)carbamate (12c)**

Yield 238.1 mg, 86%; yellow solid; R_f (CH_2Cl_2/EtOAc = 4/1): 0.25; mp 159-161 ˚C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 2.0 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.63 (dd, J = 8.4, 2.0 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.42 – 7.34 (m, 2H), 5.09 – 4.91 (br s, 1H), 4.64 (dt, J = 13.6, 5.1 Hz, 1H), 3.95 (dt, J = 14.0, 6.6 Hz, 1H), 3.59 – 3.47 (m, 2H), 1.34 (s, 9H) ppm. $^{13}C\{^1H\}$ 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 $C_{21}H_{21}N_3NaO_3S$ $[M+Na]^+$ 418.1196, found 418.1201.

***tert*-Butyl (3-(10-oxobenzo[*f*]pyrido[3,2-*b*][1,4]thiazepin-11(10*H*)-yl)propyl)carbamate (12d)**

Yield 172.7 mg, 64%; yellow solid; mp 159-161 ˚C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, J = 4.7, 1.8 Hz, 1H), 7.93 (dd, J = 7.7, 1.8 Hz, 1H), 7.69 (dd, J = 7.3, 2.0 Hz, 1H), 7.45 (dd, J = 7.2, 1.8 Hz, 1H), 7.47 – 7.29 (m, 2H), 7.09 (dd, J = 7.7, 4.7 Hz, 1H), 4.62 – 4.34 (m, 2H), 3.43 – 3.13

(m, 2H), 2.01 – 1.69 (m, 2H), 1.45 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.0, 156.0, 155.5, 148.8, 141.9, 138.4, 137.2, 131.5, 131.1, 130.7, 130.6, 129.0, 121.3, 78.9, 45.7, 37.5, 28.6, 28.5(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{23}N_3NaO_3S$ $[M+Na]^+$ 408.1352, found 408.1344.

***tert*-Butyl (3-(10-oxodipyrido[3,2-*b*:3',2'-*f*][1,4]thiazepin-11(10*H*)-yl)propyl)carbamate (12e)**

Yield 108.2 mg, 40%; yellow solid; R_f (CH_2Cl_2/EtOAc = 4/1): 0.25; mp 159-161 ˚C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 – 8.38 (m, 2H), 8.02 – 7.96 (m, 2H), 7.30 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.13 (dd, *J* = 7.7, 4.7 Hz, 1H), 5.18 (d, *J* = 6.4 Hz, 1H), 4.58 – 4.32 (m, 2H), 3.40 – 3.09 (m, 2H), 1.96 – 1.67 (m, 2H), 1.41 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.0, 157.1, 155.9, 154.6, 151.1, 149.2, 142.9, 140.0, 134.3, 127.8, 123.8, 121.8, 78.9, 45.8, 41.1, 37.6, 28.4(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{19}H_{22}N_4NaO_3S$ $[M+Na]^+$ 409.1305, found 409.1301.

***tert*-Butyl (3-(9-(*N*,*N*-dimethylsulfamoyl)-5-oxobenzo[*b*]pyrido[3,2-*f*][1,4]thiazepin-6(5*H*)-yl)propyl)carbamate (12f)**

Yield 306.9 mg, 89%; yellow solid; R_f (CH_2Cl_2/EtOAc = 4/1): 0.21; mp 159-161 ˚C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.14 (d, *J* = 2.1 Hz, 1H), 8.01 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.79 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.34 (dd, *J* = 7.8, 4.8 Hz, 1H), 5.03 – 4.84 (br s, 1H), 4.79 (dt, *J* = 14.4, 7.4 Hz, 1H), 3.84 – 3.74 (m, 1H), 3.41 – 3.25 (m, 1H), 3.28 – 3.14 (m, 1H), 2.77 (s, 6H), 2.04 – 1.81 (m, 1H), 1.77 (dt, *J* = 13.6, 6.6 Hz, 1H), 1.44 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.0, 157.6, 156.0, 151.3, 146.1, 139.9, 135.0, 134.8, 133.8, 133.4, 129.3, 126.1, 123.9, 79.3, 48.7, 37.8(2C), 37.7, 28.6, 28.4(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{28}N_4NaO_5S_2$ $[M+Na]^+$ 515.1393, found 515.1393.

***tert*-Butyl (3-(5-oxo-9-(trifluoromethyl)benzo[*b*]pyrido[3,2-*f*][1,4]thiazepin-6(5*H*)-yl)propyl)carbamate (12g)**

Yield 222.2 mg, 70%; yellow solid; mp 159-161 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, J = 4.8, 1.8 Hz, 1H), 8.05 – 7.97 (m, 2H), 7.64 (dd, J = 8.4, 2.3 Hz, 1H), 7.53 (dd, J = 8.4, 1.0 Hz, 1H), 7.33 (dd, J = 7.8, 4.8 Hz, 1H), 5.07 – 4.86 (br s, 1H), 4.93 – 4.77 (m, 1H), 3.79 – 3.64 (m, 1H), 3.35 (q, J = 8.2, 7.4 Hz, 1H), 3.28 – 3.01 (m, 1H), 1.90 (dt, J = 13.9, 7.2 Hz, 1H), 1.80 – 1.67 (m, 1H), 1.43 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.1, 157.9, 155.9, 151.1, 145.4, 139.8, 134.8, 133.9, 131.5 (q, J = 3.7 Hz), 129.2, 127.1, 126.0, 123.9, 123.0 (d, J = 272.6 Hz), 79.2, 77.2, 48.4, 37.6, 28.4(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{21}H_{22}F_3N_3NaO_3S$ $[M+Na]^+$ 476.1226, found 476.1221.

***tert*-Butyl (4-(10-oxobenzo[*f*]pyrido[3,2-*b*][1,4]thiazepin-11(10*H*)-yl)butyl)carbamate (12h)**

Yield 137.0 mg, 49%; yellow solid; mp 159-161 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, J = 4.7, 1.9 Hz, 1H), 7.91 (dd, J = 7.7, 1.8 Hz, 1H), 7.75 – 7.66 (m, 1H), 7.48 – 7.40 (m, 1H), 7.47 – 7.21 (m, 2H), 7.07 (dd, J = 7.7, 4.7 Hz, 1H), 4.77 – 4.62 (br s, 1H), 4.49 (dt, J = 14.3, 7.3 Hz, 1H), 4.27 (dt, J = 13.5, 6.9 Hz, 1H), 3.14 (q, J = 6.6 Hz, 2H), 1.80 – 1.68 (m, 2H), 1.64 – 1.55 (m, 2H), 1.44 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.3, 155.9, 148.8, 141.7, 138.4, 137.2, 131.8, 131.0, 130.6, 130.3, 128.9(2C), 121.2, 48.2, 40.2, 28.4(3C), 28.0, 27.3, 25.7 ppm. HRMS (ESI), *m/z* calcd for $C_{21}H_{25}N_3NaO_3S$ $[M+Na]^+$ 422.1509, found 422.1503.

Preparation of *tert*-Butyl (2-(7-nitro-5-oxido-11-oxodibenzo[*b,f*][1,4]thiazepin-10(11*H*)-yl)ethyl)carbamate 13

To a solution of thiazepine **12a (**278.0 mg, 0.67 mmol) in CH_2Cl_2 (10 mL) *m*-CPBA (289.4 mg, 1.68 mmol) was added at 0°C. This solution was stirred for 4 hours at room temperature. After completion of the reaction, the mixture was concentrated *in vacuo*, diluted with Et_2O (3 ml). The crystals formed were filtered and dried in air afford desired product **13**.

Yield 205.3 mg, 71%; yellow solid; mp 141-143 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.34 (dd, J = 8.8, 2.7 Hz, 1H), 8.27 (d, J = 2.6 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.81 – 7.67 (m, 3H), 7.60 (td, J = 7.5, 1.5 Hz, 1H), 6.97 (t, J = 5.9 Hz, 1H), 4.76 – 4.58 (m, 1H), 3.95 – 3.81 (m, 1H), 3.31

– 3.10 (m, 2H), 1.29 (s, 9H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d6*) δ 164.5, 155.9, 147.2, 146.9, 146.1, 141.3, 133.1, 131.7, 131.5, 129.3, 128.6, 128.1, 126.6, 119.5, 78.3, 49.3, 38.5, 28.5(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}N_3NaO_6S$ $[M+Na]^+$ 454.1043, found 454.1047.

Preparation of *tert*-Butyl (2-(7-nitro-5,5-dioxido-11-oxodibenzo[*b,f*][1,4]thiazepin-10(11*H*)-yl)ethyl)carbamate 14

To a stirred solution of thiazepine **12a** (299.5 mg, 0.720 mmol) in a mixture of carbon tetrachloride (4 mL), acetonitrile (4 mL), and water (8 mL), $NaIO_4$ (462 mg, 2.160 mmol) was added. Once all of the $NaIO_4$ had dissolved, $RuCl_3$ (0.4 mg, 0.036 mmol) was added, and the reaction mixture was stirred vigorously at room temperature overnight. It was extracted with CH_2Cl_2; the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by crystallization from MeOH.

Yield 203.0 mg, 63%; white solid; mp 179-125 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.59 – 8.51 (m, 2H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.98 – 7.92 (m, 1H), 7.92 – 7.84 (m, 2H), 7.83 – 7.77 (m, 1H), 6.78 (t, *J* = 5.9 Hz, 1H), 4.46 (dt, *J* = 13.8, 7.0 Hz, 1H), 4.17 – 3.95 (m, 1H), 3.37 (dd, *J* = 13.3, 7.1 Hz, 2H), 3.19 (dd, *J* = 13.7, 7.4 Hz, 1H), 1.32 (s, 9H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d6*) δ 166.2, 155.9, 144.9, 144.5, 140.0, 137.3, 135.7, 132.8, 132.6, 131.3, 130.1, 128.9, 123.9, 122.0, 78.4, 51.0, 28.5(3C) ppm. HRMS (ESI), *m/z* calcd for $C_{20}H_{21}N3NaO_7S$ $[M+Na]^+$ 470.0992, found 470.0994.

General Procedure for the Preparation of Compounds 17

Boc-protected amine **11-14** (0.20 mmol) was dissolved in 4M solution of HCl in 1,4-dioxane (2 mL) and stirred at room temperature overnight. Volatiles were removed *in vacuo* and the residue was triturated with diethyl ether (2 mL). The solid formed was filtered off and washed with diethyl ether (1 mL). The ammonium hydrochloride salt thus obtained was suspended in water (0.5 mL) and methanol (0.5 mL) was added. 10% aq. NaOH (0.60 mmol) was added and the resulting mixture was stirred at room temperature: for 3 hours (**17a-j**), 24 hours (**17k-r**) or 36

hours (**17s-u**) as the progress of the reaction was monitored by TLC analysis. Volatiles were removed *in vacuo* and the residue was treated with water (1 mL), the solid formed was filtered off and washed with diethyl ether (0.5 mL).

Products **17s-u** were purified by HPLC eluting with H_2O-MeCN with addition of 0.1% TFA (elution gradient MeCN: 15→95 %); flow rate 10mL/min, column temperature 40°C.

2-Nitro-5,6,7,8-tetrahydro-9*H*-dibenzo[*b,i*][1,4,7]oxadiazecin-9-one (17a)

Yield 40.7 mg, 68%; yellow solid; mp 173-175 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.92 (dd, J = 9.0, 2.6 Hz, 1H), 7.96 – 7.74 (br s, 1H), 7.62 – 7.46 (m, 3H), 7.32 – 7.18 (m, 3H), 5.80 – 5.67 (br s, 1H), 3.55 (t, J = 7.1 Hz, 2H), 3.39 – 3.21 (m, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 167.4, 155.2, 149.8, 148.7, 140.0, 131.4, 131.0, 129.8, 125.5, 122.8, 121.8, 119.4, 116.1, 44.8, 37.8 ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{13}N_3NaO_4$ $[M+Na]^+$ 322.0798, found 322.0810.

2-(Trifluoromethyl)-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecin-9-one (17b)

Yield 38.8 mg, 60 %; white solid; mp 167-170 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.39 – 8.26 (m, 1H), 8.16 – 7.96 (br s, 1H), 7.67 – 7.40 (m, 3H), 7.28 (d, J = 4.4 Hz, 2H), 6.18 – 6.01 (br s, 1H), 3.83 – 3.42 (m, 3H), 3.14 (s, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 169.5, 168.1, 158.8, 155.1, 143.9, 141.6, 136.0, 131.2, 129.8, 129.0, 125.6 (d, J = 223.9 Hz), 124.6 (q, J = 4.8 Hz), 123.0, 43.5, 37.8 ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{13}F_3N_3O_2$ $[M+H]^+$ 324.0954, found 324.0944.

2-Nitro-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecin-9-one (17c)

Yield 40.2 mg, 67 %; yellow solid; mp 194-196 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.87 (dd, J = 13.1, 2.4 Hz, 1H), 8.16 – 8.00 (br s, 1H), 7.91 (d, J = 11.9 Hz, 1H), 7.76 – 7.50 (m, 1H), 7.50 – 7.10 (m, 3H), 6.74 – 6.58 (br s, 1H), 3.72 (d, J = 77.5 Hz, 3H), 3.25 – 3.09 (m, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 167.3, 157.1, 150.7, 141.9 (2C), 136.8, 136.1, 131.1,

129.5, 125.4, 124.0, 118.4, 44.0, 37.8 ppm HRMS (ESI), *m/z* calcd for $C_{14}H_{13}N_4O_4$ $[M+H]^+$ 301.0931, found 301.0940.

13-Methyl-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrazino[2,3-*b*][1,4,7]oxadiazecin-9-one (17d)

Yield 22.7 mg, 42 %; white solid; mp 136-138 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.10 (t, J = 5.3 Hz, 1H), 8.00 (d, J = 2.8 Hz, 1H), 7.55 (d, J = 2.8 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 5.88 (t, J = 7.6 Hz, 1H), 3.84 – 3.00 (m, 4H), 2.46 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 167.8, 152.8, 152.1, 151.1, 139.5, 133.0, 132.2, 131.7, 131.2, 126.7, 125.1, 43.8, 37.4, 16.9 ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{14}N_4NaO_2$ $[M+Na]^+$ 293.1009, found 293.1001.

11-Chloro-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecin-9-one (17e)

Yield 38.8 mg, 67 %; yellow solid; mp 155-157 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.26 – 8.03 (br s, 1H), 7.97 (d, J = 4.7 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.32 (s, 1H), 7.09 (d, J = 7.9 Hz, 1H), 6.76 – 6.64 (m, 1H), 5.64 (t, J = 7.8 Hz, 1H), 3.72 – 3.38 (m, 2H), 3.31 – 3.04 (m, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 166.1, 154.9, 154.5, 144.7, 144.5, 132.7, 130.9, 129.1, 129.0, 127.9, 124.7, 116.7, 43.5, 37.9 ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{12}ClN_3NaO_2$ $[M+Na]^+$ 312.0510, found 312.0514.

2-Nitro-5,6,7,8-tetrahydro-9*H*-dibenzo[*b,i*][1,4,7]thiadiazecin-9-one (17f)

Yield 41.0 mg, 65%; yellow solid; mp 148-151 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.30 (d, J = 2.8 Hz, 1H), 8.22 – 8.12 (br s, 1H), 8.08 (dd, J = 9.2, 2.7 Hz, 1H), 7.90 (d, J = 7.4 Hz, 1H), 7.54 – 7.37 (m, 2H), 7.26 (dd, J = 7.0, 2.0 Hz, 1H), 7.07 (d, J = 9.2 Hz, 1H), 6.17 (t, J = 6.1 Hz, 1H), 3.79 – 3.34 (m, 4H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 169.6, 158.8, 138.4, 133.1, 133.0, 131.8, 130.3, 130.2 129.5, 127.4 (2C), 121.1, 115.8, 44.9, 37.3 ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{13}N_3NaO_3S$ $[M+Na]^+$ 338.0570, found 338.0578.

9-Oxo-6,7,8,9-tetrahydro-5*H*-dibenzo[*b,i*][1,4,7]thiadiazecine-2-carbonitrile (17g)

Yield 26.0 mg, 44 %; yellow solid; mp 159-162 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.09 (t, J = 5.7 Hz, 1H), 7.96 – 7.83 (m, 2H), 7.61 (d, J = 8.6 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.25 (d, J = 7.0 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 5.84 (t, J = 6.1 Hz, 1H), 3.66 – 3.35 (m, 4H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 169.5, 156.8, 141.3, 135.1, 132.1, 130.2, 129.4, 129.3, 127.7, 121.9, 119.5, 117.0, 100.6, 79.7, 45.3, 37.4 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{13}N_3NaOS$ $[M+Na]^+$ 318.0672, found 318.0681.

5,6,7,8-Tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecin-9-one (17h)

Yield 22.8 mg, 42 %; yellow solid; mp 159-161 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.19 – 8.09 (m, 2H), 7.90 – 7.78 (m, 2H), 7.50 – 7.37 (m, 2H), 7.23 (dd, J = 6.4, 2.5 Hz, 1H), 6.62 (dd, J = 7.5, 4.8 Hz, 1H), 5.93 (t, J = 6.0 Hz, 1H), 4.05 – 3.86 (m, 1H), 3.76 – 3.51 (m, 1H), 3.33 (s, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 169.9, 163.0, 150.2, 145.7, 132.5, 130.5, 130.1, 129.3, 127.5, 127.4, 116.6, 115.5, 43.7, 37.5 ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{14}N_3OS$ $[M+H]^+$ 272.0852, found 272.0855.

2-Nitro-5,6,7,8-tetrahydro-9*H*-dibenzo[*b,i*][1,4,7]thiadiazecin-9-one 14,14-dioxide (17j)

Yield 46.5 mg, 67%; yellow solid; mp 143-145 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.50 – 8.14 (m, 3H), 7.75 (dt, J = 15.5, 7.5 Hz, 2H), 7.55 – 7.34 (m, 1H), 7.34 – 7.10 (m, 2H), 4.02 – 3.60 (m, 2H), 3.17 – 3.00 (m, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 167.2, 156.7, 138.3, 137.8, 137.7, 134.8, 130.7, 130.5, 129.1, 128.7, 127.7, 123.9, 119.2, 40.4, 36.6 ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{13}N_3NaO_5S$ $[M+Na]^+$ 370.0468, found 370.0461.

2-Nitro-6,7,8,9-tetrahydrodibenzo[*b,j*[*1*]oxa[4,8]diazacycloundecin-10(5*H*)-one (17k)

Yield 34.5 mg, 54%; white solid; mp 189-191 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) 8.55 (t, J = 6.0 Hz, 1H), 7.89 (dd, J = 9.1, 2.6 Hz, 1H), 7.67 – 7.53 (m, 2H), 7.44 – 7.26 (m, 3H), 7.04 (d, J = 9.1 Hz, 1H), 6.63 (t, J = 7.3 Hz, 1H), 3.72 – 3.52 (m, 2H), 3.44 – 3.32 (m, 2H), 1.79 – 1.52 (m, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 164.8, 154.4, 147.9, 147.7, 137.02, 131.9,

131.5, 130.3, 130.3, 126.2, 124.1, 121.6, 114.4, 114.3, 44.8, 39.6, 25.0 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{16}N_3O_4$ $[M+H]^+$ 314.1135, found 314.1129.

2-(Trifluoromethyl)-6,7,8,9-tetrahydrobenzo[*j*]pyrido[3,2-*b*][*1*]oxa[4,8]diazacycloundecin-10(5*H*)-one (17l)

Yield 46.5 mg, 69 %; white solid; mp 143-146 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.40 (t, J = 5.7 Hz, 1H), 8.22 (s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.40 – 7.28 (m, 2H), 7.16 (s, 1H), 6.77 (t, J = 6.9 Hz, 1H), 3.84 – 3.56 (m, 2H), 3.33 – 3.22 (m, 2H), 1.77 – 1.61 (m, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 165.3, 156.2, 154.6, 143.3, 140.6 (q, J = 4.4 Hz), 131.8, 131.4, 129.9, 125.8, 125.1 (d, J = 223.9 Hz), 121.6, 114.4, 114.1, 43.1, 39.7, 25.6 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{15}F_3N_3O_2$ $[M+H]^+$ 338.1111, found 338.1127.

2-Nitro-6,7,8,9-tetrahydrobenzo[*j*]pyrido[3,2-*b*][*1*]oxa[4,8]diazacycloundecin-10(5*H*)-one (17m)

Yield 33.9 mg, 54 %; yellow solid; mp 148-150 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.82 (d, J = 2.4 Hz, 1H), 8.41 (t, J = 5.4 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.46 (t, J = 6.6 Hz, 1H), 7.40 – 7.30 (m, 2H), 3.96 – 3.52 (m, 2H), 3.43 – 3.23 (m, 9H), 1.81 – 1.70 (m, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 165.5, 157.5, 154.6, 142.5, 141.5, 135.2, 132.0, 131.3, 129.9, 126.3, 123.7, 119.5, 43.1, 39.6, 26.0 ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{15}N_4O_4$ $[M+H]^+$ 315.1088, found 315.1090.

10-Oxo-5,6,7,8,9,10-hexahydrodibenzo[*b,j*][*1*]oxa[4,8]diazacycloundecine-4-carbonitrile (17n)

Yield 41.1 mg, 70 % (0.14 mmol); white solid; mp 159-161 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.51 (t, J = 6.3 Hz, 1H), 7.58 (td, J = 7.7, 1.8 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.45 (dd, J = 7.6, 1.8 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.27 (dd, J = 5.4, 3.9 Hz, 1H), 6.74 – 6.68 (m, 2H), 6.19 (t, J = 7.6 Hz, 1H), 3.81 – 3.70 (m, 2H), 3.30 (q, J = 5.7 Hz, 2H), 1.57 (p, J = 5.1 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 164.2, 153.7, 150.7, 143.6, 131.6, 131.4, 130.6,

129.0, 126.3, 124.4, 122.2, 119.7, 119.0, 99.6, 45.9, 39.9, 25.7 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{16}N_3O_2$ $[M+H]^+$ 294.1237, found 294.1232.

6,7,8,9-Tetrahydrobenzo[*j*]pyrido[3,2-*b*][*1*]thia[4,8]diazacycloundecin-10(5*H*)-one (17o)

Yield 21.7 mg, 38 %; yellow solid; mp 132-134 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.38 (t, J = 6.1 Hz, 1H), 8.02 (d, J = 4.9 Hz, 1H), 7.84 (d, J = 4.6 Hz, 1H), 7.67 (d, J = 7.4 Hz, 1H), 7.49 – 7.38 (m, 2H), 7.27 (d, J = 4.9 Hz, 1H), 6.83 (t, J = 7.0 Hz, 1H), 6.46 (t, J = 6.1 Hz, 1H), 4.14 – 3.68 (m, 2H), 3.26 – 2.88 (m, 2H), 2.05 – 1.35 (m, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 169.1, 159.8, 149.6, 145.3, 142.8, 136.6, 133.5, 130.4, 129.7, 128.2, 115.2, 113.2, 42.0, 39.0, 25.9 ppm. HRMS (ESI), *m/z* calcd for $C_{15}H_{16}N_3OS$ $[M+H]^+$ 286.1009, found 286.1014.

7,8,9,10-Tetrahydrodipyrido[3,2-*b*:3',2'-*j*][*1*]thia[4,8]diazacycloundecin-5(6*H*)-one (17p)

Yield 14.9 mg, 26 %; yellow solid; mp 123-125 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.53 (dd, J = 4.8, 1.9 Hz, 1H), 8.32 (t, J = 5.6 Hz, 1H), 8.07 (dd, J = 4.8, 1.9 Hz, 1H), 7.65 (dd, J = 7.6, 1.9 Hz, 1H), 7.54 (dd, J = 7.6, 1.9 Hz, 1H), 7.39 (dd, J = 7.6, 4.7 Hz), 6.54 – 6.44 (m, 2H), 4.25 – 4.02 (m, 1H), 3.55 – 3.37 (m, 1H), 3.26 – 3.04 (m, 2H), 2.05 – 1.85 (m, 1H), 1.66 – 1.46 (m, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 166.4, 160.1, 155.2, 150.1, 150.0, 145.5, 137.6, 137.1, 123.3, 113.9, 112.7, 42.0, 39.2, 25.8 ppm. HRMS (ESI), *m/z* calcd for $C_{14}H_{15}N_4OS$ $[M+H]^+$ 287.0961, found 287.0974.

***N,N*-Dimethyl-5-oxo-5,6,7,8,9,10-hexahydrobenzo[*b*]pyrido[3,2-*j*][*1*]thia[4,8]diazacycloundecine-13-sulfonamide (17q)**

Yield 49.5 mg, 63 %; yellow solid; mp 140-143 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.56 (dd, J = 4.8, 1.9 Hz, 1H), 8.31 (t, J = 5.5 Hz, 1H), 7.68 (dd, J = 7.6, 1.9 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.41 (dd, J = 7.6, 4.8 Hz, 1H), 7.01 – 6.94 (m, 1H), 6.45 (dd, J = 9.0, 4.8 Hz, 1H), 3.82 – 3.68 (m, 1H), 3.51 – 3.37 (m, 2H), 3.19 (dt, J = 12.4, 5.4 Hz, 1H), 2.42 (s, 6H), 2.01 (q, J = 11.4, 10.7 Hz, 1H), 1.55 (d, J = 14.4 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 166.3, 155.1,

153.5, 150.3, 137.7, 137.3, 136.7, 130.7, 123.5, 121.5, 117.6, 113.0, 43.5, 39.3, 37.9(2C), 24.8 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{20}N_4NaO_3S_2$ $[M+Na]^+$ 415.0869, found 415.0872.

13-(Trifluoromethyl)-7,8,9,10-tetrahydrobenzo[*b*]pyrido[3,2-*j*][*1*]thia[4,8]diazacycloundecin-5(6*H*)-one (17r)

Yield 48.8 mg, 69 %; yellow solid; mp 144-147 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.57 (dd, J = 4.8, 1.9 Hz, 1H), 8.23 (t, J = 5.6 Hz, 1H), 7.67 (dd, J = 7.6, 1.9 Hz, 1H), 7.55 (d, J = 2.3 Hz, 1H), 7.47 – 7.38 (m, 2H), 6.90 (d, J = 8.7 Hz, 1H), 6.39 (t, J = 6.9 Hz, 1H), 3.73 – 3.22 (m, 4H), 2.03 – 1.56 (m, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 166.8, 154.3, 152.7, 150.3, 138.1, 137.1, 133.9 (q, J = 3.7 Hz), 128.03 (q, J = 3.7 Hz), 126.3, 123.6, 117.5, 117.1 (d, J = 32.1 Hz), 112.8, 43.5, 39.4, 24.9 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{15}F_3N_3OS$ $[M+H]^+$ 354.0882, found 354.0881.

2-Nitro-5,6,7,8,9,10-hexahydro-11*H*-dibenzo[*b,k*][*1*]oxa[4,9]diazacyclododecin-11-one (17s)

Yield 32.0 mg, 49 %; yellow solid; mp 112-115 ˚C. ^{1}H NMR (400 MHz, D_2O) δ) 8.01 (dd, J = 9.1, 2.6 Hz, 1H), 7.61 – 7.48 (m, 2H), 7.44 – 7.25 (m, 3H), 7.08 (d, J = 9.1 Hz, 1H), 4.53 – 4.42 (m, 1H), 4.04 – 3.92 (m, 1H), 2.87 – 2.79 (m, 2H), 1.73 – 1.52 (m, 4H) ppm. ^{13}C{^{1}H} NMR (101 MHz, D_2O) δ 166.2, 158.7, 152.3, 151.0, 147.5, 144.2, 142.8, 140.2, 133.9, 131.5, 125.0, 121.3, 119.1, 49.5, 38.8, 24.6, 23.9 ppm. HRMS (ESI), *m/z* calcd for $C_{17}H_{17}N_3NaO_4$ $[M+H]^+$ 350.1111, found 350.1119.

2-Nitro-5,6,7,8,9,10-hexahydro-11*H*-benzo[*k*]pyrido[3,2-*b*][*1*]oxa[4,9]diazacyclododecin-11-one (17t)

Yield 14.4 mg, 22 %; yellow solid; mp 111-113 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.74 (d, J = 2.4 Hz, 1H), 8.19 (t, J = 5.9 Hz, 1H), 7.96 (dd, J = 7.8, 1.7 Hz, 1H), 7.87 – 7.75 (br s, 2H), 7.70 (td, J = 7.8, 1.8 Hz, 1H), 7.44 (td, J = 7.6, 1.1 Hz, 1H), 7.29 (dd, J = 8.1, 1.1 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 3.55 (q, J = 6.4 Hz, 2H), 2.95 – 2.75 (m, 2H), 1.73 – 1.55 (m, 4H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 166.4, 154.3, 153.2, 140.6, 140.4, 134.7, 134.0, 132.4,

126.4, 125.1, 122.8, 112.9, 40.4, 39.1, 26.2, 24.9 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{17}N_4O_4$ $[M\text{-}Cl]^+$ 329.1244, found 329.1247.

5,6,7,8,9,10-Hexahydro-11*H*-benzo[*k*]pyrido[3,2-*b*][*1*]thia[4,9]diazacyclododecin-11-one (17u)

Yield 13.8 mg, 23 %; yellow solid; mp 112-115 ˚C. ^{1}H NMR (400 MHz, D_2O) δ 8.34 (dd, J = 4.8, 1.7 Hz, 1H), 8.05 (dd, J = 7.9, 1.7 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.52 – 7.47 (m, 1H), 7.40 – 7.32 (m, 2H), 7.22 (dd, J = 7.8, 4.8 Hz, 1H), 4.52 (dt, J = 12.7, 6.2 Hz, 1H), 4.08 – 3.97 (m, 1H), 2.91 (q, J = 6.3 Hz, 2H), 1.75 – 1.54 (m, 4H) ppm. ^{13}C{^{1}H} NMR (101 MHz, D_2O) δ 170.9, 153.7, 148.8, 143.2, 137.5, 136.4, 132.4, 132.0, 131.2, 130.9, 129.4, 123.0, 48.2, 39.1, 24.5, 24.3 ppm. HRMS (ESI), *m/z* calcd for $C_{16}H_{18}N_3OS$ $[M+H]^+$ 300.1165, found 300.1173.

General Procedure for the Preparation of Compounds 18a-f

Boc-protected amine **11a**, **11g**, **11i** or **12d** (0.20 mmol) was dissolved in 4M solution of HCl in 1,4-dioxane (2 mL) and the mixture was stirred at room temperature overnight. Volatiles were removed *in vacuo* and the residue was triturated with diethyl ether (2 mL). The solid formed was filtered off and washed with diethyl ether (1 mL). The ammonium hydrochloride salt was suspended in biphasic mixture of water (10 ml) and CH_2Cl_2 (10 ml). A solution of Na_2CO_3 (0.20 mmol) in water (5 mL) was added at 0 ºC. The organic phase was separated and concentrated *in vacuo*. The residue was immediately dissolved in anhydrous toluene (10 mL), aldehyde (0.20 mmol) was added followed by a catalytic amount (2 mg) of *p*-TsOH. The solution was heated at reflux for 48 h. Toluene was removed *in vacuo*. The residue was dissolved in anhydrous THF (2 mL), the solution was cooled to 0 ºC. $NaBH_4$ (0.40 mmol) was added followed by a dropwise addition of methanol (0.5 mL). The resulting solution was stirred at 0 ºC for 3 h and concentrated in vacuo. The residue was dissolved in DCM (5 mL) and washed with water (5 mL). Organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was suspended in water (0.5 mL) and methanol (0.5 mL) was added. 10 % aq. of K_2CO_3 (0.60 mmol) was added

and the resulting mixture was stirred at room temperature for 2 h (**18a**) or 24 h (**18b-f**). Volatiles were removed *in vacuo* and the residue was treated with water (1 mL). The solids formed were filtered off and washed with diethyl ether (0.5 mL). Compound **18a** was obtained in analytically pure form. Compounds **18b-f** were purified by preparative HPLC eluting with H_2O-MeCN with addition of 0.1% TFA (elution gradient MeCN: 15→95 %); flow rate 10mL/min, column temperature 40°C.

8-Benzyl-2-(trifluoromethyl)-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecin-9-one (18a)

Yield 22.3 mg, 27%; white solid; mp 133-135 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.33 (d, J = 2.0 Hz, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.56 – 7.31 (m, 1H), 7.40 – 7.33 (m, 2H), 7.33 – 7.25 (m, 3H), 7.23 – 7.13 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.44 (t, J = 6.1 Hz, 1H), 4.76 (d, J = 15.1 Hz, 1H), 3.96 (d, J = 15.1 Hz, 1H), 3.88 – 3.81 (m, 1H), 3.44 – 3.35 (m, 2H), 3.27 – 3.17 (m, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 168.0, 157.1, 152.0, 142.4 (q, J = 4.4 Hz), 137.9, 136.5, 131.2, 129.7, 129.0, 128.3, 128.1, 127.6, 124.6, 124.4 (d, J = 270.8 Hz), 123.5, 120.4, 117.9, 115.5, 115.2, 50.9, 47.5, 43.7 ppm. **HRMS** (ESI), *m/z* calcd for $C_{22}H_{18}F_3N_3NaO_2$ $[M+Na]^+$ 436.1243, found 436.1250.

9-(4-Methylbenzyl)-2-(trifluoromethyl)-6,7,8,9-tetrahydrobenzo[*j*]pyrido[3,2-*b*][*1*]oxa[4,8]diazacycloundecin-10(5*H*)-one (18b)

Yield 34.4 mg, 39 %; white solid; mp 148-150 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.7, 1.8 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.57 – 7.39 (m, 1H), 7.32 – 7.24 (m, 2H), 7.18 (dd, J = 8.1, 1.1 Hz, 1H), 7.13 (d, J = 8.5 Hz, 2H), 6.84 – 6.78 (m, 2H), 5.07 – 4.87 (m, 1H), 4.01 – 3.92 (m, 1H), 3.80 (s, 3H), 3.62 (d, J = 3.4 Hz, 2H), 2.75 – 2.58 (m, 2H), 2.00 – 1.85 (m, J = 6.8 Hz, 1H), 1.80 (dt, J = 14.0, 6.9 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.0, 160.8, 158.5, 157.4, 138.2 (q, J = 4.5 Hz), 133.6, 132.4, 132.3, 131.3, 129.1, 127.4, 126.3(2C), 126.0, 125.1 (d, J = 235.5 Hz), 119.56 116.2, 113.7, 109.8, 55.2, 53.2, 48.3, 45.7, 28.4 ppm. HRMS (ESI), *m/z* calcd for $C_{24}H_{23}F_3N_3O_2$ $[M+H]^+$ 442.1737, found 442.1740.

9-(Pyridin-4-ylmethyl)-2-(trifluoromethyl)-6,7,8,9-tetrahydrobenzo[*j*]pyrido[3,2-*b*][*1*]oxa[4,8]diazacycloundecin-10(5*H*)-one (18c)

Yield 36.0 mg, 42 %; white solid; mp 102-105 ˚C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.83 – 8.77 (m, 2H), 8.09 (dt, *J* = 2.2, 1.2 Hz, 1H), 7.92 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.76 – 7.71 (m, 2H), 7.69 – 7.62 (m, 1H), 7.46 (t, *J* = 5.8 Hz, 1H), 7.38 (td, *J* = 7.6, 1.1 Hz, 1H), 7.16 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.80 (d, *J* = 2.1 Hz, 1H), 4.35 (s, 2H), 3.54 (q, *J* = 6.3 Hz, 2H), 3.07 (t, *J* = 7.7 Hz, 2H), 2.11 – 1.95 (m, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d6*) δ 166.6, 159.4, 159.1, 158.7, 158.4, 153.8, 153.2, 147.6, 145.2, 140.8 (q, *J* = 4.4 Hz), 139.0, 134.5, 132.25 125.7, 124.91 (d, *J* = 265.3 Hz), 121.9, 117.7, 116.3, 49.1, 45.6, 37.8, 25.9 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{19}F_3N_4NaO_2$ $[M+Na]^+$ 451.1352, found 451.1354.

9-(4-Methoxybenzyl)-10-oxo-5,6,7,8,9,10-hexahydrodibenzo[*b,j*][*1*]oxa[4,8]diazacycloundecine-4-carbonitrile (18d)

Yield 24.0 mg, 29 %; white solid; mp 153-156 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.56 – 7.44 (m, 4H), 7.32 – 7.24 (m, 2H), 7.18 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.15 – 7.10 (m, 1H), 6.83 – 6.78 (m, 2H), 4.92 (dt, *J* = 13.7, 6.7 Hz, 1H), 3.95 (dt, *J* = 13.8, 6.9 Hz, 1H), 3.80 (s, 3H), 3.62 (d, *J* = 3.4 Hz, 2H), 2.75 – 2.59 (m, 2H), 1.92 (dt, *J* = 14.0, 6.9 Hz, 1H), 1.80 (dt, *J* = 14.0, 6.9 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.0, 160.8, 158.5, 157.4, 138.2, 133.7, 133.6, 132.5, 132.3, 131.4, 129.2, 128.3, 127.5, 126.3(2C), 126.0, 119.6, 116.3, 113.7, 109.8, 55.3, 53.2, 48.3, 45.7, 28.5 ppm. HRMS (ESI), *m/z* calcd for $C_{25}H_{24}N_3O_3$ $[M+H]^+$ 414.1812, found 414.1808.

10-Oxo-9-(thiophen-2-ylmethyl)-5,6,7,8,9,10-hexahydrodibenzo[*b,j*][*1*]oxa[4,8]diazacycloundecine-4-carbonitrile (18e)

Yield 25.7 mg, 33 %; brown solid; mp 147-149 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.62 – 7.48 (m, 2H), 7.47 (td, *J* = 7.8, 1.8 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.21 – 7.13 (m, 2H), 6.90 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.84 (d, *J* = 3.4 Hz, 1H), 4.91 (dt, *J* = 13.6, 6.5 Hz, 1H), 4.02 – 3.90 (m, 1H), 3.87 (d, *J* = 12.5 Hz, 2H), 2.78 – 2.63 (m, 2H), 1.94 (dt, *J* = 13.5, 6.8

Hz, 1H), 1.81 (dt, *J* = 13.7, 6.8 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.0, 160.8, 157.4, 144.1, 138.2, 133.6, 132.3, 131.4, 127.5, 126.5, 126.3(2C), 126.0, 124.7, 124.2, 119.6, 116.3, 109.8, 48.3(2C), 45.6, 28.4 ppm. HRMS (ESI), *m/z* calcd for $C_{22}H_{20}N_3O_2S$ $[M+H]^+$ 390.1271, found 390.1280.

9-(3,4-Dimethoxybenzyl)-6,7,8,9-tetrahydrobenzo[*j*]pyrido[3,2-*b*][*1*]thia[4,8]diazacycloundecin-10(5*H*)-one (18f)

Yield 33.1 mg, 38 %; yellow solid; mp 139-141 ˚C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 4.7, 1.8 Hz, 1H), 7.87 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.71 – 7.64 (m, 1H), 7.45 – 7.39 (m, 1H), 7.36 – 7.28 (m, 2H), 7.04 (dd, *J* = 7.7, 4.7 Hz, 1H), 6.88 – 6.76 (m, 4H), 4.70 – 4.54 (m, 3H), 4.42 – 4.28 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 2.82 – 2.60 (m, 2H), 1.99 – 1.73 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.4, 155.7, 148.6, 141.7, 138.3, 137.2, 133.0, 131.7, 130.9, 130.6, 128.8 (2C), 121.1, 120.3, 119.3, 111.4, 111.0, 110.4, 65.1, 55.7, 53.7, 46.2, 46.1, 28.5 ppm. HRMS (ESI), *m/z* calcd for $C_{24}H_{26}N_3O_3S$ $[M+H]^+$ 436.1689, found 436.1672.

General Procedure for Preparation of Compounds 19a-b

To a suspension of compound **11a** (**12a**) (0.20 mmol) in biphasic mixture of water (10 mL) and CH_2Cl_2 (10 mL) a solution of Na_2CO_3 (0.20 mmol) in water (5 mL) was added at 0 ºC. The organic phase was separated and CH_2Cl_2 was evaporated *in vacuo*. The residue was dissolved in anhydrous toluene (10 mL). The solution was heated at reflux for 48 h. Toluene was removed *in vacuo* and the residue was triturated with diethyl ether (1 mL). The solids formed were filtered off and washed with diethyl ether (0.5 mL).

7-Nitro-2,3-dihydrodibenzo[*b*,*f*]imidazo[1,2-*d*][1,4]oxazepine (19a)[6]

Yield 33.7 mg, 60 %; brown solid; mp 190-193 ˚C. ^1H NMR (400 MHz, DMSO-*d6*) δ 8.22 (d, *J* = 2.7 Hz, 1H), 8.10 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.85 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.55 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 4.11 (dd, *J* = 9.9, 6.5 Hz, 2H), 4.02 (dd, *J* = 9.9, 6.5 Hz, 2H) ppm.

7-Nitro-2,3-dihydrodibenzo[*b*,*f*]imidazo[1,2-*d*][1,4]thiazepine (19b)[7]

Yield 32.7 mg, 54 %; yellow solid; mp 214-216 °C. ^{1}H 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), 4.35 – 4.14 (br s, 2H), 3.98 (t, J = 9.1 Hz, 2H) ppm.

Spectrophotometric monitoring of the conversion rates in the HIRE reaction

The conversion was monitored using UV-1800 Shimadzu double beam spectrophotometer using 10.00 mm quartz cells. Measurements were performed at 30˚C. The solutions of ammonium hydrochloride salts obtained by deprotection of **11a**, **11f**, **11j**, **12a** and **14** were prepared by dissolving 0.01 mmol of the respective compound in 1:1 MeOH-H_2O (10 mL) and making up the total volume to 100 mL. The calibration curves were generated at four concentrations: 0.1 mM, 0.05 mM, 0.025 mM, and 0.01 mM. To start the measurements, the starting solution prepared as described above (3 mL) was placed in a 10.00 mm quartz cell and equilibrated at 30˚C. 10% aq. NaOH solution (100 µl) was added and the monitoring was started. The UV spectra were run at equal time intervals for 150 minutes. The conversion of the starting materials was evaluated using calibration curves.

Theoretical calculations

The full geometry optimization of all model structures in water solution has been carried out at the DFT level of theory using the M06-2X[18] and B3LYP[19] functionals with the help of Gaussian-09 program package.[20] The standard 6-31G* basis sets were used for all atoms. The solvent effects were taken into account using the SMD (Solvation Model based on Density) continuum solvation model.[21] No symmetry restrictions have been applied during the geometry optimization procedure. The Hessian matrices were calculated analytically for all optimized model structures to prove the location of correct minima on the potential energy surface (no imaginary frequencies) and to estimate the thermodynamic parameters, the latter being calculated at 25 °C

(Tables S1-S2). The Cartesian atomic coordinates for all optimized equilibrium model structures in water solution are presented in Table S3.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxxxxx.

X-ray crystallographic information for compounds **17a, 17b, 17d, 17e, 17k, 17n**; copies of ^{1}H and ^{13}C NMR spectra (PDF). Details of theoretical calculations (calculated total energies, enthalpies, Gibbs free energies, and entropies for optimized equilibrium model structures; calculated values of ΔE, ΔH, and ΔG; Cartesian atomic coordinates for optimized equilibrium model structures).

AUTHOR INFORMATION

Corresponding Author

* E-mail: m.krasavin@spbu.ru.

ORCID

Mikhail Krasavin: 0000-0002-0200-4772

Alexander Sapegin: 0000-0002-6364-1126

Alexander S. Novikov: 0000-0001-9913-5324

Notes

The authors declare no competing financial interest.

§ Current address: Groningen Research Institute of Pharmacy, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands.

ACKNOWLEDGEMENTS

This research was supported by the Russian Foundation for Basic Research (grant no. 18-03-01081).

REFERENCES

1. Marcaurelle, L. A.; Comer, E.; Danpani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D.; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Alkella, L. B.; Ross, N. T.; Zhang, Y. L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. An Aldol-Based Build/Couple/Pair Strategy for the Synthesis of Medium- and Large-Sized Rings: Discovery of Macrocyclic Histone Deacetylase Inhibitors. *J. Am. Chem. Soc.* **2010**, *132*, 16962-16976.

2. Kim, J.; Jung, J.; Koo, J.; Cho, W.; Lee, W. S.; Kim, C.; Park, W.; Park, S. B. Diversity-Oriented Synthetic Strategy for Developing a Chemical Modulator of Protein–Protein Interaction. *Nat. Commun.* **2016**, *7*, 13196.

3. Shiina, I. Total Synthesis of Natural 8- and 9-Membered Lactones: Recent Advancements in Medium-Sized Ring Formation. *Chem. Rev.* **2007**, *107*, 239-273.

4. Yudin, A. K. Macrocycles: Lessons from the Distant Past, Recent Developments, and Future Directions. *Chem. Sci.* **2015**, *6*, 30-49.

5. (a) M. Hesse, Ring Enlargement in Organic Chemistry, Wiley-VCH, Weinheim, 1991; (b) Donald, J. R.; Unsworth, W. P. Ring-Expansion Reactions in the Synthesis of Macrocycles and Medium-Sized Rings. *Chem. Eur. J.* **2017**, *23*, 8780-8799.

6. Sapegin, A.; Osipyan, A.; Krasavin, M. Structurally Diverse Arene-Fused Ten-Membered Lactams Accessed via Hydrolytic Imidazoline Ring Expansion. *Org. Biomol. Chem.* **2017**, *15*, 2906-2909.

7. Osipyan, A.; Sapegin, A.; Novikov, A.; Krasavin, M. Rare Medium-Sized Rings Prepared via Hydrolytic Imidazoline Ring Expansion (HIRE). *J. Org. Chem.* **2018**, *83*, 9707-9717.

8. Grintsevich, S.; Sapegin, A.; Reutskaya, E.; Krasavin, M. Antiviral drug nevirapine as a template for hydrated imidazoline ring expansion (HIRE): Rapid access to the diarene-fused 1,4,7-triazecine ring system. *Tetrahedron Lett.* **2019**, *60*, 20-22.

9. (a) Wasserman, H. H.; Berger, G. D.; Cho, K. R. Transamidation Reactions Using β-Lactams. The Synthesis of Homaline. *Tetrahedron Lett.* **1982**, *23*, 465-468; (b) Crombie, L.; Jones, R. C. F.; Haigh, D. Synthesis of Unsymmetrical Spermine Alkaloids of the Homalium Group. *Tetrahedron Lett.* **1986**, *27*, 5147-5150; (c) Crombie, L.; Jones, R. C. F.; Haigh, D. Transamidation Reactions of β-Lactams: A Synthesis of (±)-Dihydroperiphylline. *Tetrahedron Lett.* **1986**, *27*, 5151-5154.

10. Kramer, U.; Guggisberg, A.; Hesse, M.; Schmid, H. Use of the "Zip" Reaction for the Synthesis of a 53-Membered Polyaminolactam. *Angew. Chem. Int. Ed.* **1978**, *17*, 200-202.

11. (a) Wächli, R.; Guggisberg, A.; Hesse, M. Ring Expansion Reactions in the Formation of Macrocyclic Lactams. A Synthesis of Desoxo-Inandenine. *Tetrahedron Lett.* **1984**, *25*, 2205-2208; (b) Shemyakin, M. M.; Antonov, V. K.; Shkrob, A. M.; Shchelokov, V. I.; Agadzhanyan, Z. E. Activation of the Amide Group by Acylation: Hydroxy- and Aminoacyl Incorporation In Peprtide Systems. *Tetrahedron* **1965**, *21*, 3537-3572.

12. Stephanou, E.; Guggisberg, A.; Hesse, M. Ringerweiterungsreaktionen von *N*-(2-Aminoäthyl)-, *N*-(4-Aminobutyl)-, *N*-(6-Amino-4-aza-hexyl)- und *N*-(8-Amino-4-aza-octyl)-lactamen. 7. Mitteilung über Umamidierungsreaktionen. *Helv. Chim. Acta* **1979**, *62*, 1932-1943.

13. Grate, J. W.; Mo, K.-F.; Daily, M. D. Triazine-Based Sequence-Defined Polymers with Side-Chain Diversity and Backbone-Backbone Interaction Motifs. *Angew. Chem. Int. Ed.* **2016**, *55*, 3925 –3930.

14. (a) Sapegin, A. V.; Sakharov, V. N.; Kalandadze, L. S.; Smirnov, A. V.; Khristolyubova, T. A.; Plakhtinsky, V. V.; Ivashchenko, A. V. Synthesis of dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-one and pyrido[2,3-*b*][1,4]benzoxazepin-10(11*H*)-one compounds based on *o*-nitrochloro derivatives of benzene and pyridine. *Mendeleev Commun.* **2008**, *18*, 281-283; (b) Sapegin, A. V.; Kalinin, S. A.; Smirnov, A. V.; Dorogov, M. V.; Krasavin, M. Efficient Use of 1,2-Dihaloazine Synthons in Transition Metal-Free Preparation of Diverse Heterocycle-Fused 1,4-Oxazepines. *Eur. J. Org. Chem.* **2015**, 1333-1340.

15. R. Mendoza-Sanchez, V. B. Corless, Q. N. N. Nguyen, M. Bergeron-Brlek, J. Frost, S. Adachi, D. J. Tantillo, A. K. Yudin. Cyclols Revisited: Facile Synthesis of Medium-Sized Cyclic Peptides. *Chem. Eur. J.* **2017**, *23*, 13319-13322.

16. T. C. Stephens; A. Lawer; T. French; W. P. Unsworth. Iterative Assembly of Macrocyclic Lactones using Successive Ring Expansion Reactions. *Chem. Eur. J.* **2018**, *24*, 13947-13953.

17. (a) Baud, L. G.; Manning, M. A.; Arkless, H. L.; Stephens, T. C.; Unsworth, W. P. Ring-Expansion Approach to Medium-Sized Lactams and Analysis of Their Medicinal Lead-Like Properties. *Chem. Eur. J.* **2017**, *23*, 2225-2230; (b) Kitsiou, C.; Hindes, J. J.; I'Anson, P.; Jackson, P.; Wilson, T. C.; Daly, E. K.; Felstead, H. R.; Hearnshaw, P.; Unsworth, W. P. The Synthesis of Structurally Diverse Macrocycles By Successive Ring Expansion. *Angew. Chem. Int. Ed.* **2015**, *54*, 15794-15798; (c) Stephens, T. C.; Lodi, M.; Steer, A. M.; Lin, Y.; Gill, M. T.; Unsworth, W. P. Synthesis of Cyclic Peptide Mimetics by the Successive Ring Expansion of Lactams. *Chem. Eur. J.* **2017**, *23*, 13314-13318.

18. Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2007**, *120*, 215-241.

19. (a) Becke, A. D. Density-functional thermochemistry. iii. the role of exact exchange. *J. Chem. Phys.* **1993**, *98*, 5648–5652; (b) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785-789.

20. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision C.01, Gaussian, Inc., Wallingford, CT, 2010.

21. Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378-6396.