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Synthesis of Piperazinones, Piperazines, Tetrahydropyrazines, and Dihydropyrazinones from Polymer-Supported Acyclic Intermediates via *N*-Alkyl- and *N*-Acyliminiums

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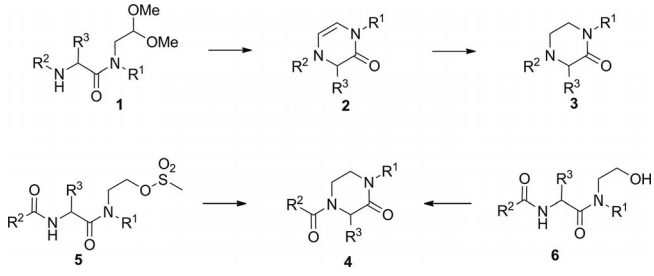
Keywords: Piperazinones / Cyclization / Piperazines / Solid-phase synthesis / Iminiums / Heterocycles

Trisubstituted piperazinones, piperazines, tetrahydropyrazines, and dihydropyrazinones were prepared in a one-step procedure from easily accessible polymer-supported acyclic precursors containing either a masked aldehyde or ketone group. Acid-mediated unmasking of the aldehyde triggered cyclic iminium formation followed by reduction with triethylsilane present in the cleavage cocktail. The effect of the substituent at the iminium-forming nitrogen was evaluated: whereas complete conversion to the target compounds was observed with *N*-alkyl, aryl, and phenylsulfonamido derivatives, the *N*-acyl compound suffered from a partial reduction of the aldehyde to an alcohol. Similarly, ketones readily provided cyclic iminiums with *N*-alkyl compounds, whereas their cyclization with *N*-acyl precursors proceeded unwillingly. Interestingly, cleavage of the resin-bound acyclic precursor at 60 °C in the presence of triethylsilane resulted in the decomposition of the amide bond and formation of a lactone. An analogous synthetic route was also successfully used for the preparation of piperazines and tested as an alternative route for the synthesis of diazepanones.

Introduction

Piperazines and piperazinones are frequently occurring pharmacophores present in numerous currently used drugs and a variety of chemical routes have been devised for their preparation in a structurally diverse form (for in depth review cf. e.g.[1]). One frequently applied route for piperazinones **3** syntheses is based on formation of 3,4-dihydropyrazin-2(1*H*)-ones **2** (Scheme 1) from 2-amino-*N*-(2,2-dimethoxyethyl)acetamides **1** through the agency of cyclic iminium intermediates, followed by hydrogenation, typically using a Pd catalyst.[2–4] Reduction of 3,4-dihydropyrazin-2(1*H*)-ones with triethylsilane (TES)[5] and $NaCNBH_3$[4] has also been reported. Iminium chemistry has been reviewed in several excellent papers.[6–9] Alternative routes from the analogous acyclic precursors by C–N bond formation include cyclization of mesylates **5** with the amide nitrogen[10] and Mitsunobu alkylation between the amide and alcohol functions of precursor **6**.[11] Amine – alcohol cyclization has also been reported.[2]



Scheme 1. Reported syntheses of piperazinones.

We developed a solid-phase synthesis of linear precursors for formation of cyclic *N*-alkyl and *N*-acyliminiums. Exposure of the acyclic resin-bound intermediates to TFA yielded trisubstituted dihydropyrazinones and tetrahydropyrazines, whereas treatment of the same intermediates with the TES-containing cleavage cocktail afforded piperazines and piperazinones. This scenario represents an example of scaffold hopping[12] as it enables the preparation of topologically different scaffolds decorated with the same R groups from identical precursors based on the selection of resin-cleaving reaction conditions.

Results and Discussion

The objective of this work was to demonstrate the ability of structurally different acyclic precursors to form cyclic iminiums and to reduce them with TES. We prepared model compounds designed to form cyclic *N*-alkyl and *N*-acyl-

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iminiums from secondary amines and amides. Cyclic iminiums were obtained by the reaction with internal carbonyl compounds, aldehydes, and ketones. This section is divided into three main parts. The first evaluates the ability of various aldehydes and ketones to form piperazinones from *N*-acyliminiums. The second part discloses the results obtained with *N*-alkyliminiums. The last part of this section briefly discusses application of the synthetic strategy to diazepanones.

Linear precursors for *N*-acyl and *N*-alkyliminiums were prepared from simple commercially available building blocks in the solid phase. Cyclic iminium intermediates were formed from an aldehyde or ketone and amide or amine. Among the various methods for iminium ion synthesis, the condensation of secondary amides/amines with aldehydes/ketones is regarded as one of the most versatile.[6,13–15] All polymer-supported acyclic precursors were synthesized using standard solid-phase chemistry[16–21] and individual synthetic steps will be portrayed for each particular reaction sequence.

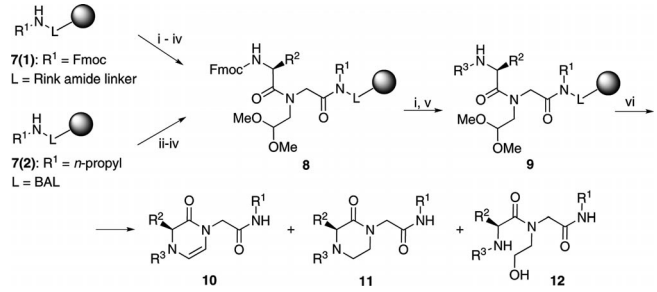
First, we focus on the construction of acyclic resin-bound intermediates that can form *N*-acyliminiums with aldehydes and ketones; secondly, we disclose our results with *N*-alkyliminium-forming intermediates.

N-Acyliminiums: Synthesis of Piperazinones

Aldehyde-Containing Precursors

In order to assess the scope and limitations of TFA cleavage and TES-mediated reduction of cyclic *N*-acyliminiums we prepared a series of model resin-bound compounds **9** attached to the Rink resin[22] (Scheme 2) using well-documented chemistry (specific protocols are included in the experimental section). Resin-bound acyclic intermediates **9** were exposed to 50% TFA in DCM. 3,4-Dihydropyrazin-2(1*H*)-ones **10** were cleanly formed in the absence of TES in the cleavage cocktail. Since this route was well documented,[23] we did not focus on the isolation and characterization of target 3,4-dihydropyrazin-2(1*H*)-ones **10**.

Resin-bound acyclic intermediates **9** were then exposed to 50% TFA in DCM containing 10% TES. Whereas all tested sulfonamides, *N*-alkyl, and *N*-aryl derivatives provided target products **11**, reactions of acyl and Fmoc derivatives afforded crude reaction mixtures containing different ratios of three components: non-reduced 3,4-dihydropyrazin-2(1*H*)-one **10**, target piperazinone **11**, and amino alcohol **12**, formed by TES-mediated reduction of the aldehyde (Table 1). Modification of the reaction conditions (reaction time, TES concentration, temperature) did not improve the purity of target *N*-acylated compounds **11**.



Scheme 2. Solid-phase synthesis of model compounds **11**. Reagents and conditions: (i) 50% piperidine/DMF (*v*/*v*), 15 min; (ii) bromoacetic acid, DIC, DIEA, DCM, room temp., 1 h; (iii) 2,2-dimethoxy-ethylamine, DIEA, DMF, room temp., 2 h; (iv) Fmoc-amino acid, DIC, THF, 16 h; (v) benzenesulfonyl chlorides, lutidine, DCM, room temp., 16 h; or 1-fluoro-2-nitrobenzenes, DIEA, DMSO, room temp. for 4,5-dichloro-1-fluoro-2-nitrobenzene, 50 °C for 1-fluoro-2-nitrobenzene, 16 h; or carboxylic acid, DIC, *N*-hydroxybenzotriazole (HOBt), DMF/DCM (1:1), 16 h; (vi) 10% TES, 50% TFA, 40% DCM, 1 h.

Table 1. Product distribution after 1 h treatment with TES/TFA cleavage cocktail.[a]

Entry	R^1	R^2	R^3	Composition of mixture [%]		
				10	**11**	**12**
1	H	H	benzoyl	30	40	30
2	H	H	Fmoc	10	68	22
3	H	CH_3	Fmoc	23	58	11
4	H	H	Fmoc-Pro	40	52	<1
5	H	H	Tos-Pro	66	24	<1
6	H	H	Fmoc-Gly	68	23	<1

[a] Distribution of components in crude preparation was estimated from LC traces with detection at λ = 220 nm.

Table 2 lists model compounds prepared for all three types of N^4-substituted target compounds. Replacement of Gly with Ala [compound **11**(**1**,**2**,**1**)] did not influence the purity, nor did synthesis on BAL linker[24] after reductive amination with *n*-propylamine. To demonstrate the versatil-

Table 2. Synthesized piperazinones **11**.

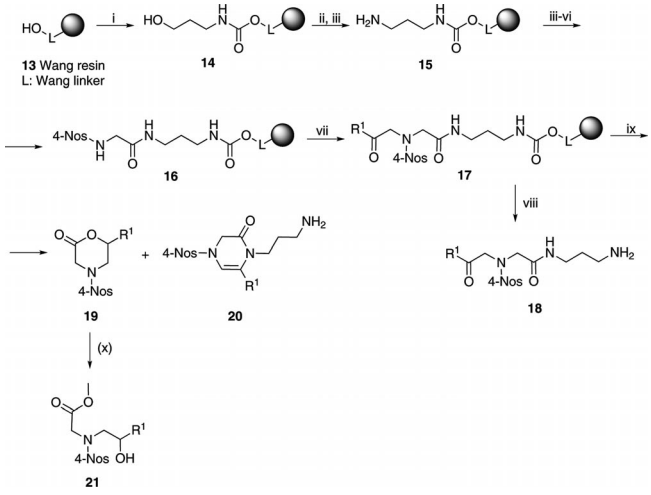
Entry	Product	R^1	R^2	R^3	Purity [%][a]	MS [M + H]$^+$	Yield [%]
1	**11**(**1**,**1**,**1**)	$-CH_2$-$CONH_2$	H	Tos	95	312	81
2	**11**(**1**,**1**,**2**)	$-CH_2$-$CONH_2$	H	$-CH_2$-CO-Ph	89	276	66
3	**11**(**1**,**1**,**3**)	$-CH_2$-$CONH_2$	H	$-(CH_2)_2$-Pht	84	331	47
4	**11**(**1**,**1**,**4**)	$-CH_2$-$CONH_2$	H	2-NO_2-4-CF_3-Ph	91	347	71
5	**11**(**1**,**1**,**5**)	$-CH_2$-$CONH_2$	H	4,5-diCl-2-NO_2-Ph	93	347, 349	67
6	**11**(**1**,**2**,**1**)	$-CH_2$-$CONH_2$	Me	Tos	87	326	76
7	**11**(**2**,**1**,**1**)	$-CH_2$-CO-βAla-Ala-NH_2	H	Tos	73	454	53
8	**11**(**3**,**1**,**4**)	$-CH_2$-CONH-*n*Pr	H	2-NO_2-4-CF_3-Ph	73	389	32
9	**11**(**3**,**1**,**6**)	$-CH_2$-CONH-*n*Pr	H	2-Nos	66	385	62
10	**11**(**3**,**1**,**7**)	$-CH_2$-CONH-*n*Pr	H	2-NO_2-Ph	77	321	29

[a] Approximate purity estimated from LC traces with detection at λ = 220 nm.

ity of the substitution pattern we prepared compound **11**(**1**,**1**,**2**) from resin **9**(**1**,**1**,**6**) by alkylation with phenacyl bromide and compound **11**(**1**,**1**,**3**) from the same resin by Mitsunobu alkylation using *N*-(2-hydroxyethyl)phthalimide.[25] The 2-Nos group was removed before cyclization.[26] To confirm the applicability of the TES-mediated reduction for the introduction of a piperazinone ring as a peptide backbone constraint we prepared compound **11**(**2**,**1**,**1**).

Ketone-Containing Precursors

The efficient formation of piperazinones by TES-mediated reduction of cyclic *N*-acyliminiums prepared from aldehydes and amides prompted us to evaluate the application of this transformation to *N*-acyliminiums prepared using ketone-based intermediates, given that ketones are known to be substantially less prone to formation of acyliminiums.[13] Accordingly, we then synthesized resin bound model compounds **17** attached to Wang resin[27] by a propylenediamine linker (Scheme 3).



Scheme 3. Synthesis of model compounds **21**. Reagents and conditions: (i) CDI, pyridine, DCM, room temp., 3 h, then 3-amino-1-propanol, DCM, room temp., 2 h; (ii) phthalimide, PPh_3, DIAD, DMF, room temp., 16 h; (iii) hydrazine monohydrate, methanol/THF (1:1), room temp., 4 h; (iv) Fmoc-Gly-OH, HOBt, DIC, DMF/DCM (1:1), room temp., 2 h; (v) 50% piperidine/DMF (*v*/*v*), room temp., 15 min; (vi) 4-nitrobenzenesulfonyl chloride (4-Nos-Cl), lutidine, DCM, room temp., 16 h; (vii) bromoketone, DIEA, DMF, room temp., 16 h; (viii) 10% TES, 50% TFA, 40% DCM, room temp., 0.5–16 h; (ix) 10% TES, 50% TFA, 40% DCM, 60 °C, 15–30 h; (x) methanol, room temp., 16 h.

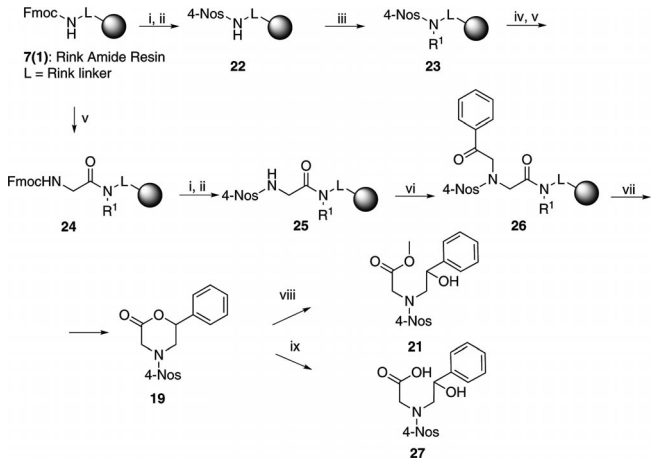
We first assessed the acid-mediated formation of cyclic *N*-alkyliminiums from **17**. The acyclic precursors **17** were treated with TFA under the standard conditions (room temp., 30 min) and yielded only the acyclic compound **18**, identified from LC/MS traces. Exposure to TFA at 60 °C yielded the expected 3,4-dihydro-1*H*-pyrazin-2-ones **20**, and compound **20**(**4**,**1**) was isolated and fully characterized. A further increase in temperature to 80 °C and extension of the reaction time from 1 h to 12 h resulted in decomposition of the compounds; LC traces revealed complex mixtures lacking a major product. The decomposition of **20** was dependent on the R^2 substituent. The ethyl precursors decomposed significantly faster than phenyl or trifluoromethylphenyl-substituted derivatives.

The TES/TFA-mediated transformation yielded unexpected results. Treatment of acyclic substrates **17** with TES-containing cleavage cocktail at 60 °C for 15–30 h afforded crude reaction mixtures composed of several components with two major products; the first corresponded to non-reduced 3,4-dihydro-1*H*-pyrazin-2-ones **20** and the second corresponded to lactones **19**, formed by TES-mediated reduction of the ketone to the alcohol and subsequent cyclization. The relative ratios of products **19** and **20** were highly dependent on the R^1 group. Although the trifluoromethylphenyl-substituted derivative afforded a crude mixture of non-reduced cyclic **20**(**1**) and acyclic product **21**(**1**) in a ratio of 2:1 (both compounds were isolated and fully characterized), the phenyl- and ethyl-modified precursors yielded a mixture with minor 3,4-dihydro-1*H*-pyrazin-2-one **20**, as determined from LC traces (Table 3). The structures of acyclic methyl esters **21** were confirmed by 2D NMR spectroscopic experiments (COSY, gHMBC, gHSQC). Analogous formation of lactone from carboxamide has been reported.[28–32] Attempts to isolate lactones **19** were unsuc-

Table 3. Synthesized acyclic compounds **21**.

Entry	Compound	R^1	Ratio **20**/**21**[a]	MS [M + Na]$^+$	Yield [%]
1	**21**(**1**)	4-CF_3-Ph	1:2	485	45
2	**21**(**2**)	Ph	1:4	417	42
3	**21**(**3**)	Et	1:4	369	52

[a] Relative ratio estimated from LC traces with detection at λ = 220 nm.



Scheme 4. Synthesis of acyclic hydroxy derivatives. Reagents and conditions: (i) 50% piperidine/DMF (*v*/*v*), room temp., 15 min; ii) 4-Nos-Cl, lutidine, DCM, room temp., 16 h; (iii) methanol or ethanol, PPh_3, DIAD, THF, room temp., 16 h; (iv) 2-mercaptoethanol, DBU, DMF, room temp., 5 min; (v) Fmoc-Gly-OH, HOBt, DIC, DMF/DCM (1:1), room temp., 16 h; (vi) bromoketone, DIEA, DMF, room temp., 16 h; (vii) 10% TES, 50% TFA, 40% DCM, 60 °C, 22 h; (viii) methanol, room temp., 16 h; (ix) acetonitrile, 10 mM aqueous ammonium acetate, room temp., 16 h.

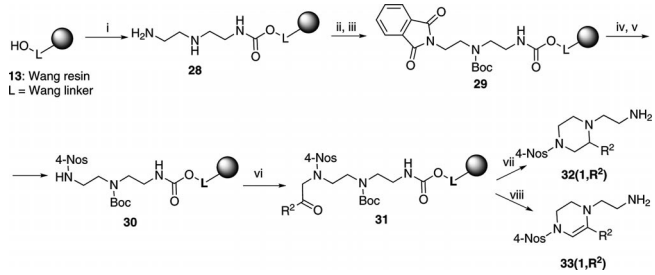
cessful due to decomposition of crude product in methanol, the solvent used for dissolving crude product leading up to purification.

Because the exposure of acyclic precursors **17** to the TFA/TES cleavage cocktail caused reduction of the ketone to the alcohol, and unexpected cleavage of the amide bond, we evaluated the potential effect of the carboxamide *N*-substituent on the reaction outcome. We synthesized acyclic precursors **26** attached to the Rink linker with *N*-methyl, *N*-ethyl, and also *N*-H substituents (Scheme 4). TES-assisted cyclization of all three precursors **26** at 60 °C afforded lactone **19** which underwent alcoholysis in methanol to give methyl ester **21**. To prevent methanolysis, we extracted the crude product after cleavage from the resin into acetonitrile, and LC/MS revealed the presence of **19**. However, attempted HPLC purification of this lactone using acetonitrile/water caused hydrolysis; following this procedure the reaction products within the mixture were distributed as 80% of hydroxy acid **27** and 20% of lactone **19** as determined by LC.

N-Alkyliminiums: Synthesis of Piperazines and Tetrahydropyrazines

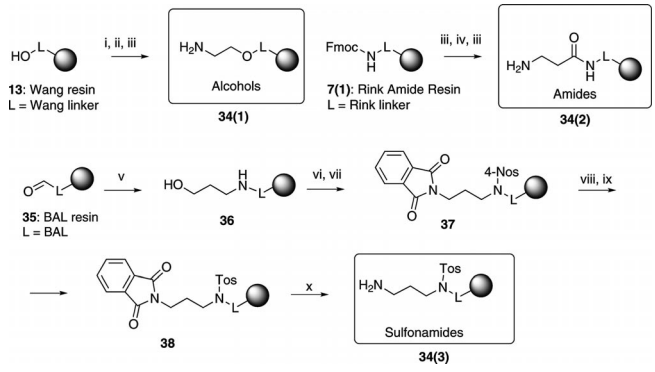
Unsuccessful synthesis of piperazinones using ketones instead of aldehydes for cyclic *N*-acyliminium formation prompted us to prepare *N*-alkyliminiums and explore their reduction to piperazines, although piperazinones can also be reduced to piperazines by DMS.[2] Since synthesis of tetrahydropyrazines through the agency of cyclic *N*-alkyliminiums has not been reported, we describe the synthesis and full characterization of 2-substituted-1,2,3,4-tetrahydropyrazines. To prepare the acyclic precursor, we applied a synthetic route used recently for the preparation of 2-(2-amino/hydroxyethyl)-1-aryl-3,4-dihydropyrazino[1,2-*b*]-?>indazol-2-iums[33] (Scheme 5). Resin-bound acyclic precursors **31** were treated with TFA to yield tetrahydropyrazines **33**. TFA cleavage in the presence of TES yielded target piperazines **32**. The cyclization and subsequent reduction proceeded smoothly although the reaction time had to be extended relative to the *N*-acyliminium case in order to achieve optimal transformation to the target compounds (Table 4).

Encouraged by these results, we expanded the chemistry to diversify substituents on the heterocycle. Previous syntheses using diethylenetriamine did not allow modification



Scheme 5. Synthesis of piperazines. Reagents and conditions: (i) CDI, pyridine, DCM, room temp., 3 h, then diethylenetriamine, DCM, room temp., 16 h; (ii) *N*-hydroxyphthalimide, DMF, room temp., 16 h; (iii) Boc_2O, pyridine, DCM, room temp., 2 h; (iv) hydrazine monohydrate, methanol/THF (1:1), room temp., 4 h; (v) 4-Nos-Cl, lutidine, DCM, room temp., 16 h; (vi) bromoketone, DIEA, DMF, room temp., 16 h; (vii) 10% TES, 50% TFA, 40% DCM, 4 h to 16 h, (viii) 50% TFA, 50% DCM, room temp., 1 h.

of this segment of the acyclic precursor. Now, we synthesized this segment by a stepwise assembly that enhanced diversification. In addition, we also varied the type of linker and attachment to resin in order to prepare compounds with various functional groups on the R^1 substituent



Scheme 6. Preparation of resin-bound amines. Reagents and conditions: (i) trichloroacetonitrile, DCM, 0 °C, 30 min, then DBU, DCM, room temp., 1 h; (ii) 2-(Fmoc-amino)ethanol, anhydrous THF, $BF_3{\cdot}Et_2O$, room temp., 30 min; (iii) 50% piperidine/DMF (*v*/*v*), room temp., 15 min; (iv) Fmoc-β-Ala-OH, HOBt, DIC, DCM/DMF (1:1), room temp., 16 h; (v) 3-amino-1-propanol, 10% AcOH in DMF, room temp., 16 h, then $NaBH(OAc)_3$, 10%AcOH in DMF, room temp., 8 h; (vi) 4-Nos-Cl, lutidine, DCM, room temp., 16 h; (vii) phthalimide, PPh_3, DIAD, anhydrous THF, room temp., 16 h; (viii) 2-mercaptoethanol, DBU, DMF, room temp., 5 min; (ix) *p*-toluenesulfonyl chloride, lutidine, DCM, room temp., 16 h; (x) hydrazine monohydrate, THF/methanol (1:1, *v*/*v*), room temp., 16 h.

Table 4. Synthesized piperazines **32**.

Entry	Product	R^1–H	R^2	Time [h]	Purity [%][a]	MS $[M + H]^+$	Yield [%]
1	**32**(**1**,**2**)	$-(CH_2)_2$-NH_2	Ph	5	89	391	73
2	**32**(**1**,**4**)	$-(CH_2)_2$-NH_2	4-Me-Ph	16	86	421	63
3	**32**(**1**,**5**)	$-(CH_2)_2$-NH_2	4-CN-Ph	4	77	416	57
4	**32**(**2**,**1**)	$-(CH_2)_2$-OH	4-CF_3-Ph	16	91	460	23
5	**32**(**2**,**3**)	$-(CH_2)_2$-OH	Et	20	81	344	56
6	**32**(**2**,**5**)	$-(CH_2)_2$-OH	4-CN-Ph	17	87	417	27
7	**32**(**3**,**5**)	$-(CH_2)_2$-$CONH_2$	4-CN-Ph	48	86	444	61

[a] Approximate purity estimated from LC traces with detection at λ = 220 nm.

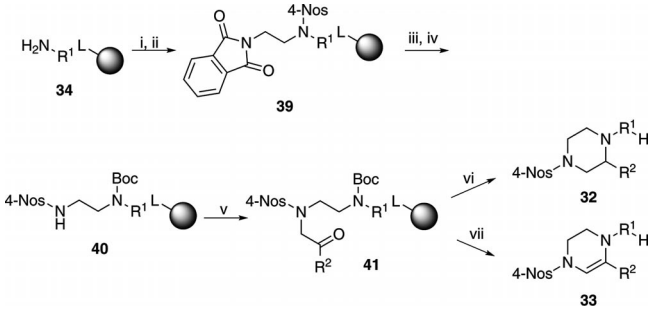
Table 5. Synthesized tetrahydropyrazines **33**.

Entry	Product	R^1–H	R^2	Purity[%][a]	MS $[M + H]^+$	Yield [%]
1	**33**(**1**,**5**)	$-(CH_2)_2$-NH_2	4-CN-Ph	88	414	79
2	**33**(**1**,**6**)	$-(CH_2)_2$-NH_2	4-Me-Ph	92	403	74
3	**33**(**1**,**7**)	$-(CH_2)_2$-NH_2	4-Cl-Ph	87	423	83
4	**33**(**2**,**6**)	$-(CH_2)_2$-OH	4-Me-Ph	84	404	67
5	**33**(**4**,**1**)	$-(CH_2)_3$-NH-Tos	4-CF_3-Ph	91	625	35
6	**33**(**4**,**2**)	$-(CH_2)_3$-NH-Tos	Ph	83	557	25

[a] Approximate purity estimated from LC traces with detection at λ = 220 nm.

(amine, amide, sulfonamide, alcohol). To obtain alcohols, we immobilized 2-(Fmoc-amino)ethanol to Wang resin [resin **34**(**1**)].[34,35] Amides were prepared by acylation of Rink amide resin with Fmoc-β-Ala-OH [resin **34**(**2**)] whereas sulfonamides were synthesized on BAL resin using 3-aminopropanol and subsequently converted to resin-bound amines **34**(**3**) (Scheme 6).

Resin bound amines **34** were subjected to a reaction sequence analogous to Scheme 7. Target piperazines **32** were obtained by TFA cleavage in the presence of TES. The model compounds' reduction capacity in the cleavage cocktail with TES relied heavily on the presence of electron withdrawing groups on the aromatic ring of the bromoketones. Specifically, we first alkylated the primary amine group with bromoacetophenone, and there was no trace of reduction even after 48 h [unlike the *N*-aminopropyl compound **32**(**1**,**2**)]. However, when electron withdrawing groups, in this case trifluoromethyl or cyano groups, were present on bromoketones with an aromatic ring, the compound was reduced successfully after 17 h. Although such was the case for both model compound sets with –OH and $-CONH_2$ end groups, compound **32**(**3**,**5**) with its carboxamide took 48 h to be reduced. Finally, we prepared model compound **32**(**2**,**3**) with an aliphatic bromoketone, 1-bromobutan-2-one, and the reduction proceeded successfully in 20 h. Although no electron withdrawing group was present on the aliphatic bromoketone, the lack of an electron donating group (in this case the benzene ring) in the aliphatic bromoketone potentially aided such a process.

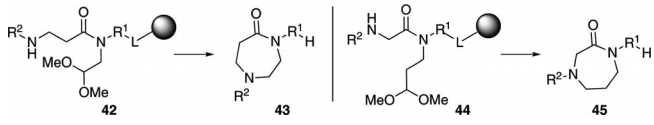


Scheme 7. Stepwise assembly of the acyclic precursors. Reagents and conditions: (i) 4-Nos-Cl, lutidine, DCM, room temp., 16 h; (ii) *N*-(2-hydroxyethyl)phthalimide, PPh_3, DIAD, anhydrous THF, room temp., 16 h; (iii) 2-mercaptoethanol, DBU, DMF, room temp., 5 min, then Boc_2O, DCM, room temp., 2 h; (iv) hydrazine monohydrate, methanol/THF (1:1) room temp., 16 h, then 4-Nos-Cl, lutidine, DCM, room temp., 16 h; (v) bromoketones, DIEA, DMF, room temp., 16 h; (vi) 10% TES, 50% TFA, 40% DCM, 16 h to 48 h; (vii) 50% TFA, 50% DCM, 1 h.

The cleavage of acyclic derivatives **41** using TFA afforded cyclic tetrahydropyrazines **33** (Table 5). Surprisingly, these pyrazines **33** substituted with *p*-toluenesulfonyl moiety (R^1) exhibited significantly lower stability when compared to derivatives with amine, amide or alcohol modification. Furthermore, the fast decomposition of all prepared tetrahydropyrazines substituted with the 2-Nos moiety (R^3) was observed during any attempt to isolate the pure product without any dependence on the R^2 substituent (specifically derivatives with R^2 = trifluoromethylphenyl, phenyl, and ethyl groups). On the other hand, 4-Nos crude target products displayed noticeably improved stability. Therefore, we isolated and fully characterized derivatives **33**(**4**,**2**) and **33**(**4**,**1**).

Ring Expansion – Synthesis of Diazepanones

The synthetic route described in Scheme 2 can also be applied to the synthesis of seven-membered ring diazepanones. The use of Fmoc-β-Ala-OH instead of α-amino acids yielded resin-bound compound **42**, replacing 2,2-dimethoxy-ethylamine with 3,3-diethoxypropylamine yielded compound **43** (Scheme 8). Resin-bound acyclic precursors **42** and **44** were treated with the TES-containing cleavage cocktail to afford 1,4-diazepan-5-ones **43** and 1,4-diazepan-2-ones **45** (Table 6). The purity and yield of target compounds was expectedly lower relative to those of the six-membered ring forming reactions. The major impurity corresponded to the non-reduced olefin, analogous to compound **10**; we have not tried to optimize the reaction conditions. Despite the presence of olefin, these synthetic routes are still useful for practical syntheses, and optimized protocols will be reported in due time.



Scheme 8. Access to diazepanones. For reagents and conditions cf. Scheme 2.

Table 6. 1,4-Diazepan-5-ones **43** and 1,4-diazepan-2-ones **45**.

Entry	Product	R^1–H	R^2	Purity [%][a]	MS $[M + H]^+$	Yield [%]
1	**43(1,1)**	$-CH_2$-$CONH_2$	Tos	61	326	44
2	**43(1,8)**	$-CH_2$-$CONH_2$	Fmoc-	64	394	NI
3	**45(3,6)**	$-CH_2$-CONH-*n*Pr	2-Nos	47	399	14
4	**45(3,7)**	$-CH_2$-CONH-*n*Pr	2-NO_2-Ph	57	335	35

[a] Relative amount in crude product based on LC traces with detection at λ = 220 nm; NI, not isolated.

Conclusions

Straightforward solid-phase synthesis afforded linear precursors for the formation of cyclic *N*-alkyl and *N*-acyliminiums. Exposure of acyclic resin-bound intermediates to TFA yielded trisubstituted dihydropyrazinones and tetrahydropyrazines, whereas treatment of the same intermediates with the TES-containing cleavage cocktail afforded piperazines and piperazinones. *N*-Alkyl, *N*-aryl, and *N*-benzenesulfonyl derivatives were obtained in high purity, but *N*-acyl derivatives suffered from incomplete reduction of dihydropyrazinones and partial reduction of the aldehyde to the alcohol. The TES-mediated approach is also amenable to synthesis of diazepanones.

Experimental Section

Synthesis of Acetals: Acylation with Bromoacetic Acid, Reaction with 2,2-Dimethoxyethylamine or 3,3-Diethoxypropylamine and Acylation with Fmoc-Amino Acids (Resins 8)

Rink amide resin **7(1)** (ca. 1 g, loading 0.66 mmol/g) was washed 3× with DCM. The Fmoc protecting group was removed by 15 min exposure to 50% piperidine in DMF and then the resin was washed 3× with DMF and 3× with DCM.

Resins **7** were washed 3× with DCM. A solution of bromoacetic acid (0.5 M, 5 mmol, 700 mg) in DCM (10 mL) was prepared in a polypropylene reaction vessels and DIC (2.5 mmol, 387 μL) was added. After 5 min *N*,*N*′-diisopropylurea (DIU) was filtered off, DIEA (2.5 mmol, 436 μL) was added and solution was added to resin and reacted for 1 h. The resin was washed 5× with DCM and 3× with DMF.

A solution of 2,2-dimethoxy-ethylamine (10 mmol, 1.09 mL) or 3,3-diethoxy-propylamine (10 mmol, 1.62 mL) and DIEA (10 mmol, 1.74 mL) in DMF (10 mL) were added to the resin, and the reaction slurry was then agitated for 2 h. The resin was washed 3× with DMF, 3× with DCM, and then 3× with THF.

A solution of Fmoc-amino acid (Fmoc-Gly-OH: 10 mmol, 2.97 g or Fmoc-Ala-OH: 10 mmol, 3.11 g) and DIC (5 mmol, 774 μL) in THF (10 mL) were added to resin, and the reaction slurry was agitated at room temp. for 16 h. The resin was washed 3× with THF and 3× with DCM.

Sulfonylation with Benzenesulfonyl Chlorides (Resins 9–1, 16, 22, 30, 37, 39): Resins **8**, **15**, **7(1)**, **29**, **36**, **34** (ca. 250 mg) were washed 3× with DCM and 3× with DMF. The Fmoc protecting group was removed by 15 min exposure to 50% piperidine in DMF and then the resin was washed 3× with DMF and 3× with DCM. A 0.5 M solution of benzenesulfonyl chlorides (1 mmol) and 0.5 M lutidine (1 mmol, 116 μL) in DCM (2 mL) was added to the resin and the reaction slurry was agitated at room temp. for 16 h. The resin was washed 5× with DCM.

Arylation with 1-Fluoro-2-nitrobenzenes (Resins 9–2): The Fmoc protecting group of resin **8** (ca. 250 mg) was removed as described above. The resin was washed 3× with DMSO. A solution of 1-fluoro-2-nitrobenzenes (0.5 M, 1 mmol) and DIEA (1 mmol, 174 μL) in DMSO (2 mL) was added to the resin and the resin slurry was agitated at 50 °C (for unsubstituted *o*-fluoronitrobenzene) or room temp. (for 4,5-dichloro-1-fluoro-2-nitrobenzenes) for 16 h. The resin was washed 3× with DMSO and 5× with DCM.

Acylation with Fmoc-Amino Acids or Carboxylic Acids [Resins 9–3, 16, 24, 34(2)]: The Fmoc protecting group of resins **8**, **15**, **23**, **7(1)** (ca. 250 mg) was removed as described above. The resin was washed 3× with DCM. Fmoc-amino acids (0.4 mmol) were dissolved in DMF (1 mL) and HOBt (0.4 mmol, 61 mg), DIC (0.4 mmol, 63 μL) and DCM (1 mL) were added and the solution was added to the resin. After 16 h reaction at room temp., the resin was washed 3× with DMF and 3× with DCM.

Reaction of Wang Resin with CDI and 3-Amino-1-propanol (Resins 14) or Diethylenetriamine (Resins 28): Wang resin (Advanced ChemTech, 1 mmol/g, 1 g) was washed 3× with DCM. A solution of CDI (810 mg, 5 mmol) and pyridine (400 μL, 5 mmol) in DCM (10 mL) was added and the resin slurry was agitated at room temp. for 2 h. The resin was washed 3× with DCM and a solution of 3-amino-1-propanol or diethylenetriamine (5 mmol) in DCM (10 mL) was added. Resin slurry was agitated at room temp. for 16, washed 5× with DCM.

Mitsunobu Reaction with Phthalimide (Resins 15,37) or *N*-(2-Hydroxyethyl)phthalimide (Resins 29, 39): Resins **14**, **36**, **28**, **24** (ca. 1 g) were washed 3× with anhydrous THF. Solutions of phthalimide (2.5 mmol, 368 mg) or *N*-(2-hydroxyethyl)phthalimide (2.5 mmol, 478 mg) and PPh_3 (2.5 mmol, 655 mg) in anhydrous THF (10 mL) were added. The resin was kept in a freezer for 30 min and then reacted with DIAD (2.5 mmol, 480 μL) at room temp. for 16 h. The resin was washed 3× with THF and 5× with DCM.

Mitsunobu Reaction with Methanol or Ethanol (Resins 23): Resins **22** (ca. 250 mg) were washed 3× with anhydrous THF. A solution of methanol (0.625 mmol, 25 μL) or ethanol (0.625 mmol, 37 μL) and PPh_3 (0.625 mmol, 164 mg) in anhydrous THF (2.5 mL) was added. The resin was kept in a freezer for 30 min and then reacted with DIAD (0.625 mmol, 123 μL) at room temp. for 16 h. The resin was washed 3× with THF and 5× with DCM.

Removal of Pht Group [Resins 15, 30, 34(3), 40]: Resin **14**, **29**, **38**, **39** (ca. 1 g) was washed 3× with THF and reacted with a solution of hydrazine hydrate (2 mL) in methanol/THF (10 mL, 1:1) at room temp. for 16 h. The resin was washed 3× with methanol, 5× with DCM.

Alkylation with Bromoketones (Resins 17, 26, 31, 41): Resin **16**, **25**, **30**, **40** (ca. 250 mg) was washed 3× with DMF. A solution (0.5 M) of bromoketones (1.25 mmol) and DIEA (1.25 mmol, 218 μL) in DMF (2.5 mL) was added to the resin, and the reaction slurry was

agitated at room temp. for 16 h. The resin was washed 3× with DMF and 5× with DCM.

Removal of Nos Group (Resins 24, 30, 38): Resin **23**, **29**, **37** (ca. 1 g) was washed 3× with DMF and was treated with a solution of 2-mercaptoethanol (0.6 M, 6 mmol, 420 μL) and DBU (0.2 M, 2 mmol, 300 μL) in DMF (10 mL) for 5 min.

Reaction with Boc_2O (Resins 29, 40): Resin **28**, **39** (ca. 1 g) was washed with 3× with DCM and was treated with a solution of Boc_2O (5 mmol, 1.1 g) in DCM (10 mL) at room temp. for 2 h. The resin was then washed 5× with DCM.

Reaction of Wang Resin with Trichloroacetonitrile and 2-(Fmoc-amino)ethanol [Resins 34(1)]: Wang resin (1 g) was suspended in solution of trichloroacetonitrile (1.5 mL) in anhydrous DCM (10 mL) and kept for 30 min in freezer. Then, a solution of DBU (100 μL) in anhydrous DCM (2 mL) was added and the resin slurry was kept at room temp. for 1 h. The resin was washed 3× with anhydrous DCM and 3× with anhydrous THF. A solution of 2-(Fmoc-amino)ethanol (3 mmol, 849 mg) in anhydrous THF (10 mL) was added to the resin, followed by dropwise addition of a solution of $BF_3{\cdot}Et_2O$ (63 μL). The resin was reacted at room temp. for 30 min and washed 3× with THF, 3× with methanol then 5× with DCM.

Reductive Amination with 3-Amino-1-propanol (Resins 36): BAL resin **35** (ca. 1 g) was washed 3× with DCM and 3× with dry DMF. A solution of dry DMF (9 mL), AcOH (1 mL), and 3-amino-1-propanol (380 μL, 5 mmol) was added. The resin slurry was agitated at room temp. 17 h. Then sodium triacetoxyborohydride (1.056 g, 5 mmol) was added, agitated for 5 h, a second portion of sodium triacetoxyborohydride (1.056 g, 5 mmol) was added and agitated for 3 h. The resin was washed 3× with AcOH (5%) in DMF then 3× with DMF neutralized with piperidine (5%) in DMF, then 5× with DMF and finally 3× with DCM.

Reaction with *p*-Toluenesulfonyl Chloride (Resins 38): Resin **37** (ca. 1 g) was washed 3× with DCM. A solution of *p*-toluenesulfonyl chloride (572 mg, 3.0 mmol) and lutidine (382 μL, 3.3 mmol) in DCM (10 mL) was added. The resin slurry was agitated at room temp. for 22 h. The resin was washed 5× with DCM.

Cleavage from Resin and Reduction (Compounds 11, 21, 32, 43, and 45): Resin **9**, **41**, **42**, or **44** (ca. 200 mg) was treated with a solution of TFA, TES, and DCM (2 mL, 5:1:4) for 1–48 h. Resin **17** (ca. 250 mg) was treated with a solution of TFA, TES, and DCM (2 mL, 5:1:4) for 15–30 h at 60 °C. The cleavage cocktail was collected, and the resin was washed 3× with TFA (50%) in DCM. The combined extracts were concentrated by a stream of nitrogen, and the crude products were purified by reverse phase HPLC.

Cleavage from Resin with TFA (Compounds 33): Resin **31** (ca. 250 mg) was treated with a solution of TFA/DCM (2 mL, 1:1) for 1 h. The cleavage cocktail was collected, and the resin was washed 3× with TFA (50%) in DCM. The combined extracts were concentrated by a stream of nitrogen, and the crude products were purified by reverse phase HPLC.

Analytical Data of Individual Compounds: Piperazinones

9*H*-Fluoren-9-yl-methyl [2-(4-Carbamoylmethyl-3-oxo-3,4-dihydro-2*H*-pyrazin-1-yl)-2-oxoethyl]-carbamate 10(1,1,8): Yield 3.7 mg (14%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.90 (m, 2 H), 7.73 (m, 2 H), 7.58 (t, J = 6.2 Hz, 1 H), 7.47 (s, 1 H), 7.42 (t, J = 7.5 Hz, 2 H), 7.31–7.36 (m, 2 H), 7.14 (s, 1 H), 6.46–6.50 (m, 1 H), 5.86–5.91 (m, 1 H), 4.28–4.32 (m, 3 H), 4.20 (s, 2 H), 4.05 (s, 2 H), 3.96 (d, J = 6.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 168.9, 165.0, 163.0, 156.6, 143.8, 140.7, 127.6, 125.2, 120.1, 115.2, 107.5, 65.7, 47.6, 46.6, 45.4, 42.0 ppm. HRMS (ESI): calcd. for $C_{2.3}H_{23}N_4O_5$ [M + H]$^+$ 435.1654; found 435.1663.

2-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-yl]-acetamide 11(1,1,1): Yield 24 mg (81%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.70 (m, 2 H), 7.48 (m, 2 H), 7.36 (br. s., 1 H), 7.10 (br. s., 1 H), 3.81 (s, 2 H), 3.52 (s, 2 H), 3.35–3.38 (m, 2 H), 3.21–3.27 (m, 2 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]-DMSO): δ = 169.3, 163.4, 144.2, 131.3, 130.1, 127.8, 48.6, 48.6, 46.9, 42.7, 21.1 ppm. HRMS (ESI): calcd. for $C_{13}H_{18}N_3O_4S$ [M + H]$^+$ 312.1013; found 312.1037.

2-[2-Oxo-4-(2-oxo-2-phenyl-ethyl)-piperazin-1-yl]-acetamide 11(1,1,2): Yield 13.7 mg (66%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.97 (dd, J = 8.4, 1.3 Hz, 2 H), 7.60–7.68 (m, 1 H), 7.53 (t, J = 7.8 Hz, 2 H), 7.38 (br. s., 1 H), 7.05 (br. s., 1 H), 4.04 (s, 2 H), 3.87 (s, 2 H), 3.27–3.33 (m, 2 H), 3.22 (s, 2 H), 2.81–2.88 (m, 2 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 196.6, 169.7, 166.3, 135.7, 133.4, 128.7, 128.0, 61.8, 56.4, 48.9, 48.1, 47.1 ppm. HRMS (FAB): calcd. for $C_{14}H_{18}N_3O_3$ [M + H]$^+$ 276.1339; found 276.1343.

2-{4-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-2-oxo-piperazin-1-yl}acetamide 11(1,1,3): Yield 6.9 mg (47%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.86–7.90 (m, 2 H), 7.82–7.86 (m, 2 H), 7.33 (br. s., 1 H), 7.02 (br. s., 1 H), 3.82 (s, 2 H), 3.72 (t, J = 6.3 Hz, 2 H), 3.20–3.25 (m, 2 H), 3.08 (s, 2 H), 2.69–2.75 (m, 2 H), 2.61 (t, J = 6.3 Hz, 2 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 169.6, 167.8, 166.2, 134.5, 131.6, 123.1, 56.7, 54.1, 48.6, 48.0, 47.1, 39.8, 34.7 ppm. HRMS (FAB): calcd. for $C_{16}H_{19}N_4O_4$ 331.1379; found 331.1401.

2-(4-(2-Nitro-4-(trifluoromethyl)phenyl)-2-oxopiperazin-1-yl)-acetamide 11(1,1,4): Yield 37.3 mg (71%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 8.18 (d, J = 2.0 Hz, 1 H), 7.86 (dd, J = 9.1, 2.0 Hz, 1 H), 7.48 (d, J = 9.1 Hz, 1 H), 7.45 (s, 1 H), 7.13 (s, 1 H), 3.96 (s, 2 H), 3.81 (s, 2 H), 3.51–3.56 (m, 2 H), 3.46–3.50 (m, 2 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 169.5, 165.0, 145.6, 138.4, 130.1, 123.8–124.2 (m), 123.6 (q, J = 270.9 Hz), 120.3, 119.2 (q, J = 33.7 Hz), 52.9, 48.7, 47.4, 46.2 ppm. HRMS (FAB): calcd. for $C_{13}H_{14}F_3N_4O_4$ 347.0967; found 347.0962.

2-(4-(4,5-Dichloro-2-nitrophenyl)-2-oxopiperazin-1-yl)acetamide 11(1,1,5): Yield 34.6 mg (67%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 8.19 (s, 1 H), 7.62 (s, 1 H), 7.44 (s, 1 H), 7.12 (s, 1 H), 3.94 (s, 2 H), 3.76 (s, 2 H), 3.42–3.46 (m, 2 H), 3.38–3.42 (m, 2 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 169.5, 165.1, 142.7, 139.4, 136.6, 127.4, 122.3, 122.1, 53.2, 48.5, 48.1, 46.5 ppm. HRMS (FAB): calcd. for $C_{12}H_{13}Cl_2N_4O_4$ 347.0327; found 347.0308.

2-[3-Methyl-2-oxo-4-(toluene-4-sulfonyl)-piperazin-1-yl]-acetamide 11(1,2,1): Yield 23.4 mg (76%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.73 (m, 2 H), 7.42 (m, 2 H), 7.31 (br. s., 1 H), 7.05 (br. s., 1 H), 4.13–4.22 (m, 1 H), 3.80 (d, J = 16.5 Hz, 1 H), 3.70 (d, J = 16.5 Hz, 1 H), 3.64 (dt, J = 13.9, 3.2 Hz, 1 H), 3.49 (ddd, J = 13.9, 9.6, 4.4 Hz, 1 H), 3.17–3.28 (m, 2 H), 2.39 (s, 3 H), 1.31 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]-DMSO): δ = 169.2, 167.3, 143.7, 136.4, 130.1, 126.9, 53.7, 48.8, 46.8, 38.8, 21.0, 18.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{20}N_3O_4S$ [M + H]$^+$ 326.1169; found 326.1191.

2-(3-{2-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-yl]-acetyl-amino}-propionylamino)propionamide 11(2,1,1): Yield 18.1 mg (53%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.97 (d, J = 7.6 Hz, 1 H), 7.93 (t, J = 5.7 Hz, 1 H), 7.70 (m, 2 H), 7.49 (m, 2 H), 7.28 (br. s., 1 H), 6.95 (br. s., 1 H), 4.17 (quin,

J = 7.3 Hz, 1 H), 3.84–3.90 (m, 1 H), 3.79–3.84 (m, 1 H), 3.52 (s, 2 H), 3.33–3.37 (m, 2 H), 3.17–3.27 (m, 4 H), 2.42 (s, 3 H), 2.18–2.33 (m, 2 H), 1.16 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 174.4, 170.0, 167.1, 163.5, 144.3, 131.4, 130.1, 127.8, 48.7, 48.6, 47.9, 46.9, 42.8, 35.3, 35.1, 21.1, 18.3 ppm. HRMS (ESI): calcd. for $C_{1.9}H_{28}N_5O_6S$ [M + H]$^+$ 454.1755; found 454.1732.

2-[4-(2-Nitro-4-trifluoromethyl-phenyl)-2-oxo-piperazin-1-yl]-*N*-propyl-acetamide 11(3,1,4): Yield 8.0 mg (32%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 8.19 (d, J = 1.8 Hz, 1 H), 7.96 (t, J = 5.4 Hz, 1 H), 7.88 (dd, J = 9.0, 1.8 Hz, 1 H), 7.47 (d, J = 9.0 Hz, 1 H), 3.98 (s, 2 H), 3.82 (s, 2 H), 3.50 (bd, J = 5.3 Hz, 4 H), 3.02 (q, J = 6.7 Hz, 2 H), 1.41 (sxt, J = 7.3 Hz, 2 H), 0.83 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 167.3, 165.0, 145.5, 138.5, 130.1, 124.0–124.4 (m), 123.7 (q, J = 270.9 Hz), 120.3, 119.2, (q, J = 33.7 Hz), 52.8, 48.7, 47.5, 46.3, 40.3, 22.4, 11.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{19}F_3N_4O_4$ [M + H]$^+$ 389.1416; found 389.1431.

2-[4-(2-Nitro-benzenesulfonyl)-2-oxo-piperazin-1-yl]-*N*-propyl-acetamide 11(3,1,6): Yield 21 mg (62%) of amorphous powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.10 (d, J = 7.5 Hz, 1 H), 8.00–8.07 (m, 1 H), 7.84–7.99 (m, 3 H), 3.91 (s,2 H) 3.86 (s,2 H), 3.52–3.60 (m, 2 H), 3.41 (t, J = 5.2 Hz, 2 H), 3.00 (q, J = 6.6 Hz, 2 H), 1.38 (sxt, J = 7.2 Hz, 2 H), 0.82 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 167.0, 163.4, 147.9, 135.3, 132.7, 130.7, 128.8, 124.5, 48.9, 48.1, 47.3, 42.6, 40.3, 22.4, 11.4 ppm. HRMS (ESI): calcd. for $C_{15}H_{20}N_4O_6S$ [M + H]$^+$ 385.1155; found 385.1176.

2-[4-(2-Nitro-phenyl)-2-oxo-piperazin-1-yl]-*N*-propyl-acetamide 11(3,1,7): Yield 6 mg (29%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.96 (t, J = 5.4 Hz, 1 H), 7.85 (dd, J = 8.2, 1.5 Hz, 1 H), 7.59–7.64 (m, 1 H), 7.38 (d, J = 7.6 Hz, 1 H), 7.14–7.18 (m, 1 H), 3.97 (s, 2 H), 3.71 (s, 2 H), 3.40–3.45 (m, 2 H), 3.29–3.36 (m, 2 H), 3.02 (q, J = 6.6 Hz, 2 H), 1.41 (sxt, J = 7.3 Hz, 2 H), 0.84 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]-DMSO): δ = 167.4, 165.6, 143.2, 142.3, 134.0, 125.7, 122.2, 121.2, 53.9, 48.8, 48.6, 46.9, 40.4, 22.4, 11.4 ppm. HRMS (ESI): calcd. for $C_{15}H_{20}N_4O_4$ [M + H]$^+$ 321.1557; found 321.1557.

1-(3-Aminopropyl)-4-(4-nitrobenzenesulfonyl)-6-(4-trifluoromethyl-phenyl)-3,4-dihydro-1*H*-pyrazin-2-one 20(4,1): Yield 6.3 mg (22%) of amorphous powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.41–8.47 (m, 2 H), 8.19–8.29 (m, 2 H), 7.83 (m, 2 H), 7.63 (m, 2 H), 7.56 (br. s., 2 H), 6.61 (s, 1 H), 4.17 (s, 2 H), 3.26 (t, J = 7.3 Hz, 2 H), 2.33–2.47 (m, 2 H), 1.11–1.28 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 162.6, 150.6, 141.1, 135.8, 130.6, 129.4, 128.9, 128.0, 125.66–125.70 (m), 125.0, 112.1, 48.4, 36.3, 25.6 ppm. HRMS (ESI): calcd. for $C_{20}H_{20}F_3N_4O_4S$ [M + H]$^+$ 485.1101; found 485.1090.

Methyl-[[2-Hydroxy-2-(4-trifluoromethylphenyl)-ethyl]-(4-nitrobenzenesulfonyl)-amino]acetate 21(1): Yield 12.4 mg (45%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 8.30–8.34 (m, 2 H), 8.01–8.06 (m, 2 H), 7.64 (d, J = 8.1 Hz, 2 H), 7.52 (d, J = 8.1 Hz, 2 H), 5.79 (br. s., 1 H), 4.80–4.91 (m, 1 H), 4.37 (d, J = 18.2 Hz, 1 H), 4.27 (d, J = 18.2 Hz, 1 H), 3.56 (s, 3 H), 3.50 (dd, J = 14.7, 3.8 Hz, 1 H), 3.39–3.44 (m, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 169.1, 149.6, 147.2, 145.0, 128.6, 126.9, 125.00–125.03 (m), 124.9, 124.3, 124.3 (q, J = 271.6 Hz), 71.0, 54.8, 51.9, 49.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}F_3N_3O_7S$ [M + NH$_4$]$^+$ 480.1047; found 480.1027.

Methyl-[(2-Hydroxy-2-phenylethyl)-(4-nitrobenzenesulfonyl)-amino]-acetate 21(2): Yield 8.0 mg (42%) of amorphous powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.32–8.37 (m, 2 H), 8.03–8.08 (m, 2 H), 7.21–7.36 (m, 6 H), 5.60 (br. s., 1 H), 4.72 (dd, J = 8.6, 3.9 Hz, 1 H), 4.36 (d, J = 18.5 Hz, 1 H), 4.19 (d, J = 18.5 Hz, 1 H), 3.54 (s, 3 H) ppm, one proton overlapped with water. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 169.2, 149.7, 145.1, 142.6, 128.6, 128.2, 127.4, 126.0, 124.4, 71.8, 55.1, 51.9, 49.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{18}N_2O_7SNa$ [M + Na]$^+$ 417.0727; found 417.0731.

Methyl-[(2-Hydroxybutyl)-(4-nitrobenzenesulfonyl)-amino]acetate 21(3): Yield 12.3 mg (52%) of amorphous powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.35–8.42 (m, 2 H), 8.05–8.12 (m, 2 H), 4.75 (d, J = 4.7 Hz, 1 H), 4.31 (d, J = 18.2 Hz, 1 H), 4.22 (d, J = 18.2 Hz, 1 H), 3.54 (s, 3 H), 3.47 (br. s., 1 H), 3.28 (d, J = 3.6 Hz, 1 H), 3.05 (dd, J = 14.5, 7.9 Hz, 1 H), 1.15–1.46 (m, 2 H), 0.79–0.87 (m, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 169.2, 149.7, 145.0, 128.7, 124.4, 70.5, 53.4, 51.9, 49.3, 27.3, 9.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{18}N_2O_7SNa$ [M + Na]$^+$ 369.0727; found 369.0717.

Analytical Data of Individual Compounds: Piperazines

2-[4-(4-Nitro-benzenesulfonyl)-2-phenyl-piperazin-1-yl]-ethylamine 32(1,2): Yield 34.2 mg (73%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 8.42 (m, 2 H), 8.00 (m, 2 H), 7.32–7.36 (m, 5 H), 7.28–7.31 (m, 1 H), 3.68 (dd, J = 11.4, 2.3 Hz, 1 H), 3.45 (ddd, J = 11.3, 2.8, 2.6 Hz, 1 H), 3.39 (dd, J = 10.3, 3.2 Hz, 1 H), 3.12–3.19 (m, 1 H), 2.58–2.67 (m, 1 H), 2.51–2.57 (m, 2 H), 2.22–2.33 (m, 2 H), 1.94–2.04 (m, 1 H), 1.76 (s, 3 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 150.2, 140.4, 139.5, 129.2, 128.7, 128.0, 127.9, 124.8, 65.5, 53.3, 52.6, 50.3, 46.0, 36.9 ppm. HRMS (ESI): calcd. for $C_{18}H_{23}N_4O_4S$ [M + H]$^+$ 391.1435; found 391.1442.

2-(2-(4-Methoxyphenyl)-4-(4-nitrophenylsulfonyl)piperazin-1-yl)-ethanaminium Acetate 32(1,4): Yield 21.1 mg (63%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 8.42 (m, 2 H), 7.99 (m, 2 H), 7.23 (d, J = 8.8 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 3.73 (s, 3 H), 3.67 (dd, J = 11.2, 2.3 Hz, 1 H), 3.41 (ddd, J = 11.2, 2.9, 2.6 Hz, 1 H), 3.32 (dd, J = 10.3, 3.2 Hz, 1 H), 3.09–3.14 (m, 1 H), 2.55–2.62 (m, 1 H), 2.47–2.53 (m, 2 H), 2.41 (dt, J = 12.8, 7.8 Hz, 1 H), 2.19–2.31 (m, 2 H), 1.92–1.99 (m, 1 H), 1.83 (s, 3 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 158.9, 150.2, 140.3, 131.4, 129.2, 129.0, 124.8, 114.1, 64.8, 55.1, 53.5, 52.7, 50.4, 46.0, 37.2 ppm. HRMS (FAB): calcd. for $C_{19}H_{25}N_4O_5S$ [M + H]$^+$ 421.1534; found 421.1540.

2-(4-(4-Nitrophenylsulfonyl)-2-(4-(trifluoromethyl)phenyl)piperazin-1-yl)ethanaminium acetate 32(1,5): Yield 20.7 mg (57%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 8.42 (m, 2 H), 8.01 (m, 2 H), 7.81 (d, J = 8.5 Hz, 2 H), 7.57 (d, J = 8.5 Hz, 2 H), 3.68 (dd, J = 11.4, 2.3 Hz, 1 H), 3.54 (dd, J = 10.1, 3.1 Hz, 1 H), 3.48 (ddd, J = 11.1, 2.9, 2.7 Hz, 1 H), 3.10–3.21 (m, 1 H), 2.64 (dt, J = 12.4, 6.3 Hz, 1 H), 2.54 (dd, J = 11.4, 2.6 Hz, 2 H), 2.23–2.35 (m, 4 H), 1.99–2.05 (m, 1 H), 1.83 (s, 3 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 150.2, 145.3, 140.3, 132.7, 129.3, 129.2, 124.8, 118.7, 110.8, 64.8, 51.9, 50.0, 50.0, 45.8, 36.8 ppm. HRMS (FAB): calcd. for $C_{19}H_{22}N_5O_4S$ [M + H]$^+$ 416.1387; found 416.1390.

2-(4-(4-Nitrophenylsulfonyl)-2-(4-(trifluoromethyl)phenyl)piperazin-1-yl)ethanol 32(2,1): Yield 6.7 mg (23%) of amorphous powder. ^{1}H NMR (500 MHz,[D$_6$]DMSO): δ = 8.41 (m, 2 H), 7.99 (m, 2 H), 7.81 (d, J = 8.4 Hz, 2 H), 7.56 (d, J = 8.4 Hz, 2 H), 4.36 (t, J = 5.4 Hz, 1 H), 3.67 (dd, J = 2.2, 11.2 Hz, 1 H), 3.55 (dd, J = 3.0, 10.2 Hz, 1 H), 3.48 (dt, J = 2.6, 11.4 Hz, 1 H), 3.33–3.29 (m, 2 H), 3.22–3.14 (m, 1 H), 2.47 (d, J = 2.0 Hz, 1 H), 2.39 (td, J = 2.7, 11.6 Hz, 1 H), 2.35–2.27 (m, 1 H), 2.22 (t, J = 10.9 Hz, 1 H), 2.02

(dt, J = 5.7, 12.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 150.2, 144.7, 140.4, 129.2, 128.9, 125.42–125.48 (m), 124.7, 64.7, 58.1, 55.6, 52.3, 50.9, 46.0 ppm. HRMS (FAB): calcd. for $C_{19}H_{21}F_3N_3O_5S$ [M + H]$^+$ 460.1149; found 460.1163.

2-(2-Ethyl-4-(4-nitrophenylsulfonyl)piperazin-1-yl)ethanol 32(2,3): Yield 3.4 mg (56%) of amorphous powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.44 (m, 2 H), 8.01 (m, 2 H), 3.38 (t, J = 6.2 Hz, 2 H), 3.10–2.95 (m, 2 H), 2.89–2.75 (m, 2 H), 2.69–2.52 (m, 2 H), 2.45 (d, J = 3.6 Hz, 2 H), 2.37–2.26 (m, 1 H), 1.57–1.37 (m, 2 H), 0.81 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 150.1, 140.6, 129.1, 124.7, 59.0, 58.7, 54.3, 48.6, 48.2, 45.3, 19.4, 9.8 ppm. HRMS (FAB): calcd. for $C_{14}H_{22}N_3O_5S$ [M + H]$^+$ 344.1275; found 344.1300.

4-[1-(2-Hydroxyethy)-4-(4-nitrobenzenesulfonyl)-piperazin-2-yl]benzonitrile 32(2,5): Yield 1.8 mg (27%) of amorphous powder. ^{1}H NMR (500 MHz,[D$_6$]DMSO): δ = 8.41 (m, 2 H), 7.99 (m, 2 H), 7.81 (m, 2 H), 7.56 (m, 2 H), 4.36 (t, J = 5.4 Hz, 1 H), 3.67 (dd, J = 2.2, 11.2 Hz, 1 H), 3.55 (dd, J = 3.0, 10.2 Hz, 1 H), 3.48 (dt, J = 2.6, 11.4 Hz, 1 H), 3.33–3.29 (m, 2 H), 3.22–3.14 (m, 1 H), 2.47 (d, J = 2.0 Hz, 0 H), 2.39 (td, J = 2.7, 11.6 Hz, 1 H), 2.35–2.27 (m, 1 H), 2.22 (t, J = 10.9 Hz, 1 H), 2.02 (dt, J = 5.7, 12.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 150.2, 145.6, 140.4, 132.5, 129.2, 129.1, 124.8, 118.7, 110.7, 64.7, 58.1, 55.6, 52.0, 50.8, 46.0 ppm. HRMS (FAB): calcd. for $C_{19}H_{21}N_4O_5S$ [M + H]$^+$ 417.1227; found 417.1242.

3-[2-(4-Cyanophenyl)-4-(4-nitrobenzenesulfonyl)-piperazine-1-yl]-propionamide 32(3,5): Yield 15 mg (61%) of amorphous powder. ^{1}H NMR (500 MHz,[D$_6$]DMSO): δ = 8.41 (d, J = 9.0 Hz, 2 H), 7.99 (d, J = 9.0 Hz, 2 H), 7.80 (d, J = 8.4 Hz, 2 H), 7.54 (d, J = 8.4 Hz, 2 H), 7.21 (br. s., 1 H), 6.68 (br. s., 1 H), 3.70 (dd, J = 2.0, 11.2 Hz, 1 H), 3.53–3.45 (m, 2 H), 3.15–3.10 (m, 1 H), 2.57–2.51 (m, 1 H), 2.48–2.44 (m, 1 H), 2.35–2.25 (m, 1 H), 2.21 (t, J = 10.7 Hz, 1 H), 2.09 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 172.7, 150.2, 145.2, 140.4, 132.5, 129.2, 129.0, 124.8, 118.6, 110.7, 64.5, 51.9, 49.8, 45.9, 32.0 ppm. HRMS (FAB): calcd. for $C_{20}H_{22}N_5O_5S$ [M + H]$^+$ 444.1336; found 444.1360.

4-(1-(2-Aminoethyl)-4-(4-nitrophenylsulfonyl)-1,4,5,6-tetrahydropyrazin-2-yl)benzonitrile 33(1,5): Yield 39.3 mg (79%) of amorphous powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.42 (d, J = 8.8 Hz, 2 H), 8.12 (d, J = 8.8 Hz, 2 H), 7.81 (d, J = 8.3 Hz, 2 H), 7.73 (br. s., 2 H), 7.59 (d, J = 8.3 Hz, 2 H), 6.54 (s, 1 H), 3.43–3.54 (m, 2 H), 2.78–2.92 (m, 2 H), 2.56–2.70 (m, 4 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 150.2, 141.7, 140.7, 132.7, 132.5, 128.7, 127.4, 124.9, 118.8, 110.2, 109.1, 49.1, 44.2, 39.9, 36.5 ppm. HRMS (FAB): calcd. for $C_{19}H_{20}N_5O_4S$ [M + H]$^+$ 414.1231; found 414.1208.

2-[6-(4-Methylphenyl)-4-(4-nitrobenzenesulfonyl)-3,4-dihydro-2*H*-pyrazin-1-yl]ethylamine 33(1,6): Yield 13.6 mg (74%) of amorphous powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.42 (d, J = 8.9 Hz, 2 H), 8.10 (d, J = 8.9 Hz, 2 H), 7.67 (br. s., 2 H), 7.42 (s, 4 H), 6.33 (s, 1 H), 3.44–3.51 (m, 2 H), 3.38 (br. s., 4 H), 2.64 (br. s., 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 173.2, 150.8, 142.4, 140.5, 138.2, 136.0, 133.9, 129.9, 129.3, 127.6, 125.5, 104.5, 53.8, 45.7, 41.5, 22.4, 21.4 ppm, TFA salt peak at 39.6 overlapped with DMSO. HRMS (FAB): calcd. for $C_{19}H_{23}N_4O_4S$ [M + H]$^+$ 403.1440; found 403.1375.

2-[6-(4-Chlorophenyl)-4-(4-nitrobenzenesulfonyl)-3,4-dihydro-2*H*-pyrazin-1-yl]ethylamine 33(1,7): Yield 42.7 mg (83%) of amorphous powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.42 (d, J = 8.9 Hz, 2 H), 8.10 (d, J = 8.9 Hz, 2 H), 7.67 (d, J = 6.9 Hz, 2 H), 7.42 (s, 4 H), 6.33 (s, 1 H), 3.46 (br. s., 2 H), 3.38 (br. s., 4 H), 2.64 (br. s., 2 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 150.8, 142.4, 135.4, 133.9, 133.3, 129.4, 129.4, 129.3, 125.6, 107.4, 49.6, 45.1, 40.5, 37.2 ppm. HRMS (FAB): calcd. for $C_{18}H_{20}N_4O_4SCl$ [M + H]$^+$ 423.0888; found 423.0864.

2-(4-(4-Nitrophenylsulfonyl)-6-*p*-tolyl-3,4-dihydropyrazin-1(2*H*)-yl)ethanol 33(2,6): Yield 22.5 mg (67%) of amorphous powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.41 (d, J = 8.8 Hz, 2 H), 8.03 (d, J = 8.8 Hz, 2 H), 7.3 (m, 2 H), 7.15 (m, 2 H), 6.10 (s, 1 H), 3.45–3.50 (m, 2 H), 3.30 (t, J = 6.0 Hz, 2 H), 2.65–2.71 (m, 2 H), 2.60 (t, J = 6.1 Hz, 2 H), 2.29 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 150.1, 141.7, 137.4, 135.3, 133.2, 129.1, 128.6, 127.0, 124.8, 103.2, 59.3, 54.0, 45.8, 41.2, 20.8 ppm. HRMS (FAB): calcd. for $C_{19}H_{22}N_3O_5S$ [M + H]$^+$ 404.1275; found 404.1248.

4-Methyl-*N*-{3-[4-(4-nitrobenzenesulfonyl)-6-(4-trifluoromethylphenyl)-3,4-dihydro-2*H*-pyrazin-1-yl]-propyl}benzenesulfonamide 33(4,1): Yield 11.0 mg (35%) of amorphous powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.37–8.44 (m, 2 H), 8.03–8.11 (m, 2 H), 7.67 (d, J = 8.3 Hz, 2 H), 7.53 (d, J = 8.3 Hz, 2 H), 7.58 (d, J = 8.3 Hz, 2 H), 7.32–7.39 (m, 3 H), 6.39 (s, 1 H), 3.43 (br. s., 2 H), 2.51–2.61 (m, 4 H), 2.42 (t, J = 7.3 Hz, 2 H), 2.36 (s, 3 H), 1.38–1.53 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 150.9, 143.3, 142.4, 141.0, 138.0, 134.2, 130.3, 129.3, 127.9, 127.2, 126.05–126.10 (m), 125.6, 107.7, 50.2, 45.0, 41.2, 41.0, 28.0, 21.6 ppm. HRMS (ESI): calcd. for $C_{27}H_{28}F_3N_4O_6S_2$ [M + H]$^+$ 625.1397; found 625.1405.

4-Methyl-*N*-{3-[4-(4-nitrobenzenesulfonyl)-6-phenyl-3,4-dihydro-2*H*-pyrazin-1-yl]-propyl}benzenesulfonamide 33(4,2): Yield 9.6 mg (25%) of amorphous powder. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.41 (d, J = 8.8 Hz, 2 H), 8.05 (d, J = 8.8 Hz, 2 H), 7.57 (d, J = 8.3 Hz, 2 H) 7.25–7.40 (m, 8 H), 6.16 (s, 1 H), 3.44–3.31 (m, 4 H, overlapped with water), 2.53–2.59 (m, 2 H), 2.39–2.47 (m, 2 H), 2.37 (s, 3 H), 1.41 (quin, J = 7.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 150.8, 143.3, 142.4, 138.0, 137.0, 135.9, 130.3, 129.3, 128.8, 127.5, 127.2, 125.6, 105.2, 50.1, 45.2, 41.5, 28.2, 21.7, 12.5 ppm. HRMS (ESI): calcd. for $C_{26}H_{29}N_4O_6S_2$ [M + H]$^+$ 557.1523; found 557.1519.

Analytical Data of Individual Compounds: Diazepanones

2-[7-Oxo-4-(toluene-4-sulfonyl)-[1,4]diazepan-1-yl]-acetamide 43(1,1): Yield 13.7 mg (44%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.63 (d, J = 8.2 Hz, 2 H), 7.44 (d, J = 7.9 Hz, 2 H), 7.30 (s, 1 H), 6.98 (s, 1 H), 3.82 (s, 2 H), 3.48–3.55 (m, 2 H), 3.23 (ddd, J = 4.8, 2.3, 2.1 Hz, 2 H), 3.12–3.17 (m, 2 H), 2.62–2.69 (m, 2 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]-DMSO): δ = 172.9, 170.3, 143.6, 133.8, 130.0, 127.2, 50.8, 49.5, 48.4, 43.3, 37.1, 21.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{20}N_3O_4S$ [M + H]$^+$ 326.1169; found 326.1173.

2-[4-(2-Nitro-benzenesulfonyl)-2-oxo-[1,4]diazepan-1-yl]-*N*-propyl-acetamide 45(3,6): Yield 3.6 mg (14%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 8.00 (dd, J = 7.9, 1.2 Hz, 1 H), 7.98 (dd, J = 7.9, 1.2 Hz, 1 H), 7.91 (td, J = 7.6, 1.2 Hz, 1 H), 7.85 (dt, J = 7.9, 1.2 Hz, 1 H), 7.81 (t, J = 5.6 Hz, 1 H), 4.15 (s, 2 H), 3.85 (s, 2 H), 3.45–3.52 (m, 4 H), 3.00 (q, J = 6.7 Hz, 2 H), 1.80–1.87 (m, 2 H), 1.39 (sxt, J = 7.3 Hz, 2 H), 0.83 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 169.51, 167.7, 147.6, 134.8, 132.6, 130.9, 130.0, 124.4, 52.1, 51.0, 49.0, 48.4, 40.3, 28.1, 22.4, 11.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{23}N_4O_6S$ [M + H]$^+$ 399.1336; found 399.1333.

2-[4-(2-Nitrophenyl)-2-oxo-[1,4]diazepan-1-yl]-*N*-propyl-acetamide 45(3,7): Yield 7.4 mg (35%) of amorphous powder. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.80 (t, J = 5.6 Hz, 1 H), 7.76 (dd, J = 8.1, 1.5 Hz, 1 H), 7.51 (t, J = 8.5 Hz, 1 H), 7.18 (d, J = 8.1 Hz,

1 H), 6.97 (m, 1 H), 4.02 (s, 2 H), 3.92 (s, 2 H), 3.37–3.42 (s, 2 H), 3.16 (t, J = 5.9 Hz, 2 H), 3.01 (q, J = 6.7 Hz, 2 H), 1.99 (m, 2 H), 1.39 (sxt, J = 7.3 Hz, 2 H), 0.83 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 171.2, 167.8, 144.5, 133.9, 126.1, 120.3, 119.5, 56.6, 55.7, 53.0, 51.1, 48.3, 40.3, 27.8, 22.4, 11.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{23}N_4O_4$ $[M + H]^+$ 335.1699; found 335.1714.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra for all key intermediates and final products.

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[1] C. J. Dinsmore, D. C. Beshore, *Org. Prep. Proced.* **2002**, *34*, 367–404.
[2] D. C. Horwell, R. A. Lewthwaite, M. C. Pritchard, G. S. Ratcliffe, J. R. Rubin, *Tetrahedron* **1998**, *54*, 4591–4606.
[3] S. Kitamura, H. Fukushi, T. Miyawaki, M. Kawamura, N. Konishi, Z. Terashita, T. Naka, *J. Med. Chem.* **2001**, *44*, 2438–2450.
[4] J. DiMaio, B. Belleau, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1687–1689.
[5] H. Peng, D. Carrico, V. Thai, M. Blaskovich, C. Bucher, E. E. Pusateri, S. M. Sebti, A. D. Hamilton, *Org. Biomol. Chem.* **2006**, *4*, 1768–1784.
[6] W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817–3856.
[7] B. E. Maryanoff, H. C. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104*, 1431–1628.
[8] A. Yazici, S. G. Pyne, *Synthesis* **2009**, 513–541.
[9] A. Yazici, S. G. Pyne, *Synthesis* **2009**, 339–368.
[10] P. A. Procopiou, R. A. Ancliff, M. J. Bamford, C. Browning, H. Connor, S. Davies, Y. C. Fogden, S. T. Hodgson, D. S. Holmes, B. E. Looker, K. M. L. Morriss, C. A. Parr, E. A. Pickup, S. S. Sehmi, G. V. White, C. J. Watts, D. M. Wilson, M. D. Woodrow, *J. Med. Chem.* **2007**, *50*, 6706–6717.
[11] P. E. Maligres, M. S. Waters, S. A. Weissman, J. C. McWilliams, S. Lewis, J. Cowen, R. A. Reamer, R. P. Volante, P. J. Reider, D. Askin, *J. Heterocycl. Chem.* **2003**, *40*, 229–241.
[12] H. J. Bohm, A. Flohr, M. Stahl, *Drug Discovery Today Technol.* **2004**, *1*, 217–224.
[13] J. Royer, M. Bonin, L. Micouin, *Chem. Rev.* **2004**, *104*, 2311–2352.
[14] R. Remuson, Y. Gelas-Mialhe, *Mini-Rev. Org. Chem.* **2008**, *5*, 193–208.
[15] L. E. Overman, *Acc. Chem. Res.* **1992**, *25*, 352–359.
[16] B. Vankova, V. Krchnak, M. Soural, J. Hlavac, *ACS Comb. Sci.* **2011**, *13*, 496–500.
[17] J. Koci, A. G. Oliver, V. Krchnak, *J. Org. Chem.* **2010**, *75*, 502–505.
[18] J. Koci, V. Krchnak, *J. Comb. Chem.* **2010**, *12*, 168–175.
[19] N. Pudelova, V. Krchnak, *J. Comb. Chem.* **2009**, *11*, 851–859.
[20] J. Koci, N. Pudelova, V. Krchnak, *J. Comb. Chem.* **2009**, *11*, 397–402.
[21] N. Pudelova, V. Krchnak, *J. Comb. Chem.* **2009**, *11*, 370–374.
[22] H. Rink, *Tetrahedron Lett.* **1987**, *28*, 3787–3790.
[23] S. C. Lee, S. B. Park, *J. Comb. Chem.* **2007**, *9*, 828–835.
[24] K. J. Jensen, J. Alsina, M. F. Songster, J. Vagner, F. Albericio, G. Barany, *J. Am. Chem. Soc.* **1998**, *120*, 5441–5452.
[25] T. Fukuyama, C. K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6377–6374.
[26] T. Vojkovsky, *Peptide Res.* **1995**, *8*, 236–237.
[27] S.-S. Wang, *J. Am. Chem. Soc.* **1973**, *95*, 1328–1333.
[28] H. Ito, T. Momose, M. Konishi, E. Yamada, K. Watanabe, K. Iguchi, *Tetrahedron* **2006**, *62*, 10425–10433.
[29] T. Tsunoda, S. Tatsuki, Y. Shiraishi, M. Akasaka, S. Ito, *Tetrahedron Lett.* **1993**, *34*, 3297–3000.
[30] R. N. Burgin, S. Jones, B. Tarbit, *Tetrahedron Lett.* **2009**, *50*, 6772–6774.
[31] M. Govoni, H. D. Lim, D. El-Atmioui, W. M. P. B. Menge, H. Timmerman, R. A. Bakker, R. Leurs, I. J. P. De Esch, *J. Med. Chem.* **2006**, *49*, 2549–2557.
[32] M. Casey, R. McCarthy, *Synlett* **2011**, 801–804.
[33] J. Koci, V. Krchnak, *J. Comb. Chem.* **2010**, *12*, 168–175.
[34] S. Hanessian, F. Xie, *Tetrahedron Lett.* **1998**, *39*, 733–736.
[35] L. Z. Yan, J. P. Mayer, *J. Org. Chem.* **2003**, *68*, 1161–1162.

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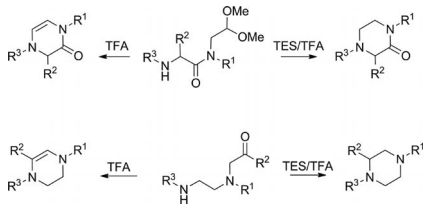
Solid-Phase Heterocycle Synthesis

Straightforward solid-phase synthesis afforded linear precursors for formation of cyclic *N*-alkyl and *N*-acyliminiums. Exposure of acyclic resin-bound intermediates to TFA yielded trisubstituted dihydropyrazinones and tetrahydropyrazines, whereas treatment of the same intermediates with a TES-containing cleavage cocktail afforded piperazines and piperazinones.



Keywords: Piperazinones / Cyclization / Piperazines / Solid-phase synthesis / Iminiums / Heterocycles

