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General Multicomponent Strategy for the Synthesis of 2-Amino-1,4-diazaheterocycles: Scope, Limitations, and Utility

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Multicomponent reactions of primary 1,2- and 1,3-diamines with carbonyl compounds and isocyanides resulting in the formation of diverse 2-amino-1,4-diazaheterocycles are described. Lewis acids (LAs) promote the reactions effectively, and chlorotrimethylsilane (TMSCl) has been found to be a promoter of choice. The scope and limitations of the reactions with regard to each of the components are evaluated and discussed. Post-IMCR modifications of the synthesized heterocycles have been elaborated.

Introduction

The discovery and development of new scaffolds for drug discovery is a supremely important current application of heterocyclic chemistry. Medicinal chemistry as a discipline applies specific restrictions on the compounds that may be used in the field. So-called "drug-likeness" and "lead-likeness" rules have been developed to reduce the time and effort spent on discovery of new drug candidates.[1] Key requirements for newly synthesized compounds include low molecular weight, non-reactivity, water solubility, a specific number of H-bond donors and acceptors, and – of course – the potential for convenient modification of the molecular core decoration. In view of this, the development of new synthetic strategies to access scaffolds that meet these requirements is one of the top priority tasks for synthetic and medicinal chemists. Furthermore, such strategies are more valuable if they allow scaffold diversity rather than compound diversity.

During the past decade, isocyanide-based multicomponent reactions (IMCRs) have attracted significant interest within the scientific community as an efficient, convenient, time-saving, and atom-economical approach to a variety of heterocyclic molecules.[2] The best example of success in this field is the Ugi reaction.[3] The "classic" Ugi ensemble, consisting of a carbonyl compound, an amine, a carboxylic acid, and an isocyanide, is in fact able to provide only one linear, dipeptide-like scaffold with vast molecular diversity arising from easily accessible components. Obviously, the Ugi IMCR would not be so successful had multiple strategies for the synthesis of various heterocyclic scaffolds not been developed and introduced. In particular, one important application of the Ugi reaction is based on the employment of bifunctional reagents bearing two of four functionalities of the Ugi ensemble, with intramolecular IMCR assuring heterocyclic ring formation.

Another promising way to extend the utility of the IMCRs involves "nonclassical" functionalities, leading to new IMCRs.[4] One good illustration of the efficiency of this approach is the introduction of aminoazaheterocycles as bifunctional reagents into reactions with aldehydes and isocyanides, first reported simultaneously by Blackburn's[5] and Groebke's[6] groups and somewhat later by Bienaymé and co-authors[7] (Scheme 1, a). Despite the facts that only the annulated 3-aminoimidazoles **1** can be synthesized by this strategy and that only aldehydes and not ketones have been shown to be successful starting materials,[6] the vast utility of this reaction has been confirmed by the number of subsequent publications and by the multiple-thousand-member focused libraries of fused aminoimidazoles that have been successfully synthesized by use of this reaction.[2a,8]

On the other hand, introduction of the 1,2- or even 1,3-diazanucleophiles **2** (Scheme 1, b) into such IMCRs might represent a possible route to the various amino(imino)azaheterocycles **3**. Nevertheless, only limited data relating to IMCRs of 1,2- and 1,3-diazabinucleophiles had been published at the time we started our own research in this field. $InCl_3$-catalyzed IMCRs of 2-aminomethylpyridine with aldehydes and isocyanides followed by spontaneous oxidation produced the pyrido[1,2-*a*]pyrazines **4** (Scheme 1, c),[9–11] whereas recently published[12] reactions between the proline-based tetrazoles **5**, aliphatic aldehydes, and isocyanides

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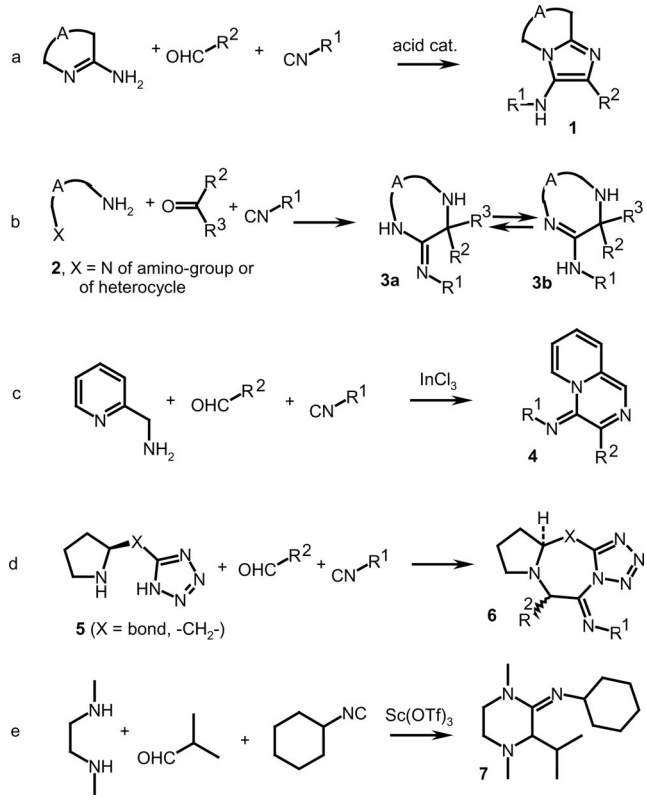


Scheme 1. Aza-dinucleophiles in IMCRs.

afforded the annulated pyrazine- and 1,4-diazepine-imines **6** (Scheme 1, d) with no catalyst required, probably due to the high N–H acidity of the tetrazole ring. Also worth mentioning is the synthesis by Keung et al.[13] of highly substituted 2-aminoamidines through $Sc(OTf)_3$-mediated "linear" four-component reactions of aldehydes, isocyanides, and two equiv. of amines. *N*,*N*′-Dimethylethylenediamine proved to be a successful starting material in place of two equiv. of amine in an intramolecular three-component variant of this reaction[14] (Scheme 1, e), but the only example reported was the piperazin-2-imine **7**. Like the Groebke–Blackburn–Bienamé reaction, the above-mentioned four-center three-component reactions (4C-3CRs) have an obvious limitation relating to their carbonyl components: only aldehydes, but not ketones, have been reported as successful starting materials. In addition, the heavily substituted pyrazin-/piperazinimines obtainable by these 4C-3CRs are unsuitable for further modifications. It was thus thought that these limitations might be overcome through the use of primary 1,2- and 1,3-diamines in IMCRs.

In our recent short communications,[15] we have reported our preliminary results relating to new IMCRs of primary diamines with carbonyl compounds and isocyanides leading to partially hydrogenated pyrazin-2-amines and 1,4-diazepin-2-amines.[16] Importantly, application of these newly discovered IMCRs to various diamino and carbonyl components might provide access to a great number of new amino-azaheterocyclic cores. Moreover, these scaffolds should be amenable to subsequent modifications, thanks to the existing secondary amino groups in the 1,4-diazaheterocycle and in the amidine moiety. It should be noted that, simultaneously with our publications, TsOH-catalyzed MCRs of 2,3-diaminomaleonitrile with ketones and isocyanides were proposed for the synthesis of 6,6-disubstituted 1,6-dihydropyrazin-2,3-dicarbonitriles.[17] In addition, two more publications[18,19] describing Brønsted-acid-catalyzed IMCRs of 1,2-phenylenediamines with carbonyl compounds appeared while this manuscript was in preparation. In view of the growing synthetic interest in IMCRs of diamines, and of the opportunities that these IMCRs might provide as a promising strategy for the synthesis of privileged heterocycles containing 2-aminopyrazine,[20–22] 2-aminoquinoxaline,[23] and other related aminoazaheterocyclic cores, we report here the scope, limitations, extensions, and some subsequent applications of the discovered IMCRs.

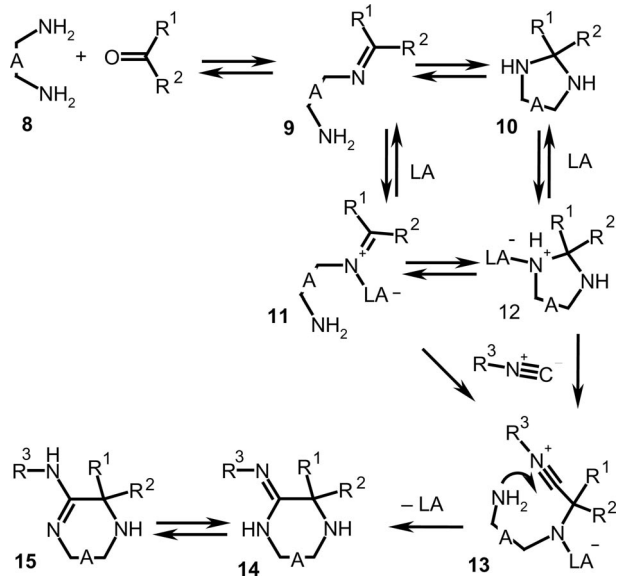
Results and Discussion

Evaluation of Promoters and Optimization of Reaction Conditions

From the mechanisms of known IMCRs, the most probable scenario for the 4C-3CR of a 1,*n*-diamine **8**, a carbonyl compound, and an isocyanide can be surmised to be a multi-step sequence as shown in Scheme 2. The azomethyne **9**, formed in the first step of the reaction, is able to exist in equilibrium with the corresponding cyclic aminal **10**.[24] Each of these ring–chain tautomeric forms is able to react with nucleophiles – in our case an isocyanide – and activation of both is required for the reaction to proceed. The activated intermediates **11** and **12** should convert into the same intermediate **13**, which upon intramolecular cyclization might yield the imine **14** or the tautomeric amine **15**. Importantly, the cation **13** could be trapped by any nucleophile existing in the reaction mixture, including the starting isocyanide[25] or available amines, which would yield a number of high-molecular-weight products. Therefore, ultimate reaction success should be highly dependent on the right choice of promoter, which should efficaciously activate intermediates **11** and **12** and stabilize cation **13**. We thus initially evaluated possible additives for the reaction performance.

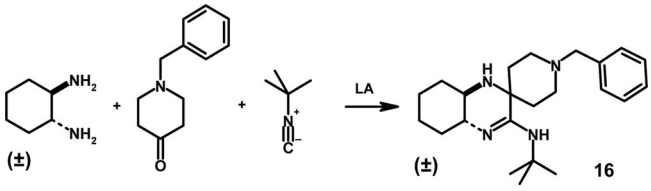
After thorough investigation of the literature precedents for catalysis of reactions of isocyanides, we created a short list of potential promoters that might be useful for our purposes. To evaluate additive activity, we used a model reaction involving *tert*-butyl isocyanide, *N*-benzylpiperidin-4-one, and *trans*-cyclohexane-1,2-diamine (Table 1). Both carbonyl and diamine components are easily detectable either by ESI-MS or by evaporative light-scattering detection (ELSD) methods, allowing the reaction to be monitored by LC-MS analysis.

$Sc(OTf)_3$ and $Yb(OTf)_3$ were examined as Lewis acids (LAs, Table 1, entries 1 and 2) because of their established activity in the amino amidine synthesis discussed above. We also paid attention to silicon LAs (SLAs), the ability of



Scheme 2. Scenario for reactions of diamines with isocyanides and carbonyl compounds.

Table 1. The MCR of *trans*-cyclohexane-1,2-diamine, *N*-benzylpiperidin-4-one, and *t*BuNC in the presence of additives.[a]



Entry	Promoter	mol-%	Yield[b] [%]
1	$Yb(OTf)_3$	20	54
2	$Sc(OTf)_3$	20	64
3	TBSOTf	20	55
4	TBSCl	20	34
5	TMSCl	20	38
6	TBSOTf/$Yb(OTf)_3$	20/20	81 (55)[c]
7	TMSCl	100	91 (78)[c]
8	TMSCl	200	89 (67)[c]
9	HCl (8 M solution in dioxane)	100	64
10	none	–	traces

[a] For details see the Exp. Sect. [b] Yields were determined by LC-MS (ELSD) of the reaction mixtures. [c] Isolated yields.

which to activate C=O and C=N bonds for catalyzed additions to C-nucleophiles,[26] including isocyanides,[27] is well documented. *tert*-Butyl(dimethyl)silyl trifluoromethanesulfonate (TBSOTf), *tert*-butyl(chloro)dimethylsilane (TBSCl), and chlorotrimethylsilane (TMSCl) were thus selected as potential promoters of this reaction (Table 1, entries 3–5). Because combinations of SLAs with $Yb(OTf)_3$ are able to promote reactions between azomethynes and π-C-nucleophiles much more effectively than these LAs by themselves,[28] we also examined the TBSOTf/$Yb(OTf)_3$ system (Table 1, entry 6). We also realized that the amidine functionality formed during the IMCR is normally a significantly stronger base than the starting diamines and can bond with the LA efficiently, therefore reducing its activity. Therefore, two experiments with 1 and 2 equiv. of TMSCl were set up (Table 1, entries 7 and 8). Finally, two more test experiments, with a Brønsted acid (HCl, Table 1, entry 9) and with no additives (Table 1, entry 10), were attempted.

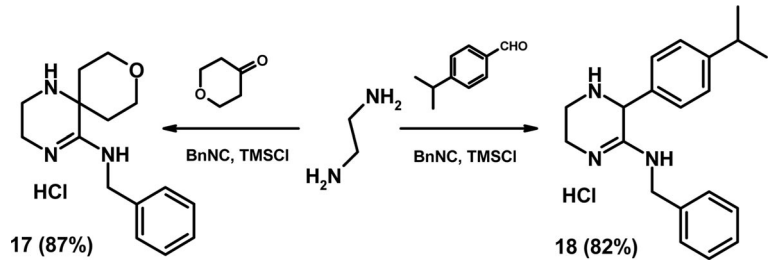
Indeed, no reaction was observed in the absence of additives (Table 1, entry 10) whereas all the evaluated additives demonstrated reactivity in the investigated IMCR to variable extents. TBSOTf and metal triflates (Table 1, entries 1–3) showed moderate activity, whereas silyl chlorides proved to be less suitable as catalysts. In contrast, the TBSOTf/$Yb(OTf)_3$ system (Table 1, entry 6) demonstrated the best catalytic activity. However, all of the reactions were accompanied by the formation of high-molecular-weight by-products when LAs were used as catalysts. To our satisfaction, side reactions were suppressed when the quantity of TMSCl was increased to 1 equiv. (Table 1, entry 7). This essentially improved the reaction outcome in terms of the yield and purity of the target compound. Interestingly, further increases in TMSCl concentration (Table 1, entry 8) somewhat reduced the yield of target material. Although a protic solvent was used for this evaluation, it seems that TMSCl itself, and not HCl (resulting from its hydrolysis), is the actual and effective promoter of the reaction. At least, the HCl-promoted reaction (Table 1, entry 9) produced a mixture of several unidentified by-products that made isolation of the target compound **16** problematic. Isolated yields for the most successful entries (entries 6–8) were in good agreement with those observed by LC-MS analysis of the reaction mixtures.

From these results, the conditions of entry 7 (Table 1) were chosen for further protocol optimization with ethylenediamine as a diamine component. For this purpose, a series of reactions with benzyl isocyanide and both tetrahydro-4*H*-pyran-4-one and 4-isopropylbenzaldehyde (Scheme 3) were carried out under various sets of reaction conditions. Aprotic solvents such as chloroform or acetonitrile, which seem to be preferable for the performance of SLA-promoted reactions, proved to be inefficient because of formation of insoluble ethylenediamine or intermediate azomethyne salts. This reduced the reaction rates and caused formation of several high-molecular-weight by-products. In contrast, alcohols and especially methanol demonstrated the best results. Furthermore, water produced during azomethyne formation did not interfere with the IMCR process, and its removal was not necessary unless required for azomethyne formation with carbonyl compounds of low reactivity. Simple chromatography-free workup procedures furnished the monohydrochlorides of the target aminopyrazines **17** and **18** in high yields and with high degrees of purity.

In summary of our observations, the following advantages of employing 1 equiv. of TMSCl as a promoter of choice are:

– highest yields of target products,

– cleanness of the IMCR allows chromatography-free isolation,



Scheme 3. IMCRs of ethylenediamine with carbonyl compounds.

– simple workup and isolation procedures,
– controlled formation of pharmacologically acceptable monohydrochlorides of target compounds,
– low cost and availability of the promoter,
– adaptability of the protocol to both parallel and scale-up synthesis,
– utilization of metal-free conditions avoids residual metal contamination in target compounds, an important consideration for medicinal chemistry.[29]

IMCRs of Ethylenediamine

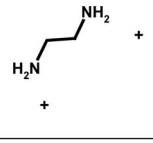
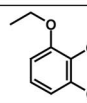
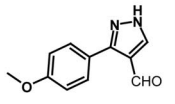
With the optimized protocol for the IMCR to hand, we further evaluated the scope of the reactions of ethylenediamine with a set of eight isocyanides and 16 carbonyl compounds, including ketones (Table 2, rows 1–6) and both aromatic (Table 2, rows 7–9) and heteroaromatic (Table 2, rows 10–16) aldehydes with a widely variable nature of substitution including highly electron-donating (Table 2, rows 7, 12–15) and electron-withdrawing (Table 2, rows 8, 10, 11) (hetero)aromatic nuclei. The experiment was designed in full-matrix parallel synthesis format, 128 reactions in total, at 0.1 mmol scale. Yields of all the reactions were determined by LC-MS analysis with use of ELSD by calculation of the peak with the expected [M + H] value for the product area versus the total peak areas. The results of this experiment are summarized in Table 2.

To our satisfaction, the majority of the reactions were successful, with either high (74 reactions furnished 80% yields or more of target compounds) or moderate (40 reactions furnished 30–79% yields of target compounds) yields. Only 11% of the reactions failed to provide reasonable amounts of target compounds (yields less than 20%), with the majority of these involving 2-tetralone and 6-methoxy-1-tetralone (Table 2, rows 5, 6). The rest of the cyclic ketones demonstrated high reactivity. Furthermore, all the aldehydes proved to be very reactive, and most often no signs of starting materials were detected in the reaction mixtures. However, somewhat lower yields of target compounds were caused by some minor formation of by-products. Oxidation products detectable in the LC-MS as their molecular ions $[M - 2 + H]^+$, where M is the molecular weight of the target product, were the most frequently occurring impurities, especially in the case of pyridine-4-carbaldehyde (Table 2, row 10). These by-products were the results of oxidation of the C(3)–N(4) bonds (see below), and this side reaction might be minimized by employing oxygen-free conditions. In addition, reduced yields in the cases of aldehydes with π-excessive heterocyclic nuclei (Table 2, rows 12–14) can be explained by partial oligomerization, which was suppressed in the cases of morpholino- and pyridino-substituted isocyanides (Table 2, columns E and F). Furthermore, these isocyanides demonstrated good results for all of the tested carbonyl compounds, including the previously mentioned poorly reactive tetralones. This observation, which is consistent with the concept of Lewis base acceleration of SLA-promoted reactions of isocyanides,[27,30] could be the subject of further investigation directed towards IMCR performance improvement.

To evaluate the preparative value of the IMCRs, some of these and a dozen more reactions were performed at 0.5 and/or 10 mmol scales (General procedures A and B, respectively; see Exp. Sect.). The results of these experiments are summarized in Table 3. The majority of the reactions furnished the target compounds in at least good isolated yields in spite of the employment of a general procedure that was not optimized for specific sets of starting components. To our satisfaction, aliphatic aldehydes proved to be suitable for the IMCRs (Table 3, entries 6–8). Interestingly, formation of side-products was usually less (by LC-MS analysis) when the same reactions were performed in a scaled-up format. No oxidation products were observed when pyridinecarbaldehydes were used, for instance, and the reaction of pyrrole-2-carbaldehyde also proceeded cleanly. Small amounts of ethylenediamine hydrochloride were only a non-critical impurity of the crude isolated products in some cases. This impurity was easily removed on transformation of the initially formed hydrochlorides into the free bases by standard procedures. Although yields of the free bases were somewhat lower, the obtained products did not require any additional purification.

In summary of the results for the tested ethylenediamine IMCRs, it is important to note that the reactions are applicable for a wide range of isocyanides and – more importantly – carbonyl compounds such as ketones and a wide variety of aldehydes. Both electron-rich and electron-poor aldehydes reacted smoothly, as did the sterically hindered pivalaldehyde or the easily enolized acetaldehyde. It appears that additional functionalities in the carbonyl component have limited or no effect. For example, the *o*-hydroxy group in 3-ethoxy-2-hydroxybenzaldehyde does not affect reaction success (Table 3, entry 9).

Table 2. Evaluation of the scope of IMCRs of ethylenediamine with various carbonyl compounds and isocyanides.[a]

			Isocyanides R–NC, R:							
			A	B	C	D	E	F	G	H
			*t*Bu	$MeO(CH_2)_2$	Cyclopentyl	$MeO(CH_2)_3$	$3\text{-}PyCH_2$	2-(4-Morpholino)-ethyl	*p*-MeOBn	*o*-MeOBn
Carbonyl compounds	1		>95	>95	>95	>95	>95	>95	89	94
	2		>95	>95	>95	>95	>95	>95	82	80
	3		>95	>95	>95	>95	>95	>95	>95	>95
	4		93	>95	>95	91	75	>95	90	94
	5		37	20	30	<5	83	>95	15	30
	6		<5	25	19	<5	>95	88	19	19
	7		>95	85	91	78	>95	>95	89	75
	8		85	77	>95	>95	50	48	>95	87
	9		>95	90	>95	61	77	>95	>95	70
	10		60	70	70	90	86	40	30	41
	11		70	>95	84	80	>95	>95	63	72
	12		40	20	48	36	>95	>95	64	43
	13		57	20	48	69	63	55	32	27
	14		>95	48	71	30	0	>95	17	>95
	15		86	60	87	84	40	60	82	70
	16		90	89	>95	>95	84	63	>95	91

[a] For details see the Exp. Sect.

IMCRs of (Hetero)aromatic 1,2-Diamines

We next examined the developed conditions with respect to 1,2-phenylenediamine as a diamine component. Its reactions with ketones and isocyanides demonstrated excellent results and furnished the target 3,4-dihydroquinoxalin-2-amine hydrochlorides **19** in high yields (Scheme 4). A representative set of spiro-quinoxaline compounds synthesized in this manner is shown in Table 4 (entries 1–5).

Table 3. Synthesis of various 3,4,5,6-tetrahydropyrazin-2-amines through IMCRs of ethylenediamine.

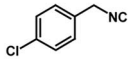
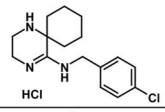
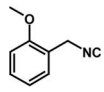
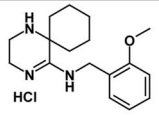
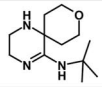
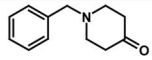
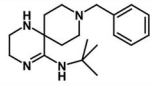
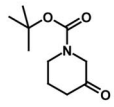
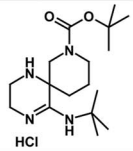
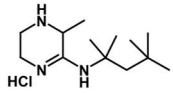
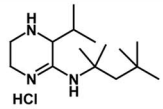
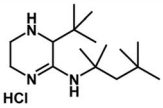
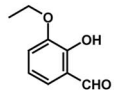
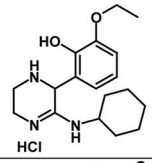
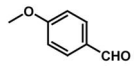
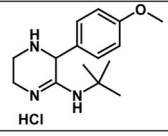
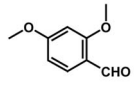
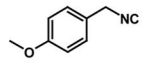
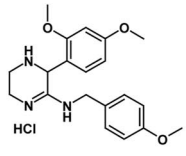
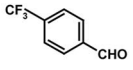
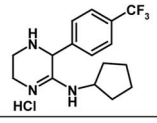
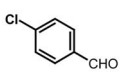
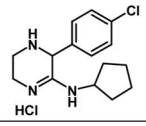
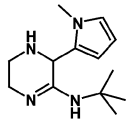
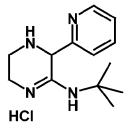
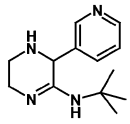
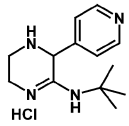
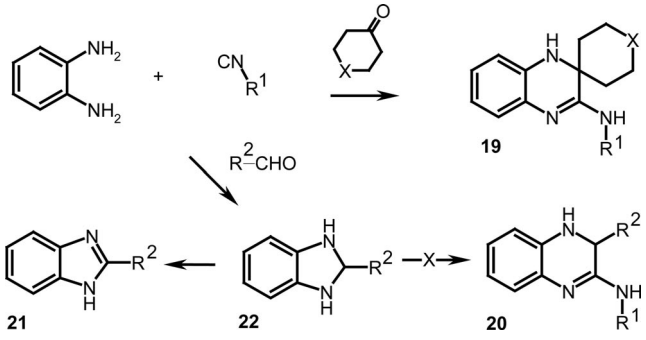
Entry	Carbonyl compound	Isocyanide	Product	General procedure	Isolated yield (%)
1				A	85
2				A	68
3				A	58
4				A	52
5				A B	60 63
6				A B	50 58
7				A B	74 80
8				A B	82 85
9				A	58
10				A	85
11				A	63
12				A	92
13				A	88

Table 3. *(Continued)*.

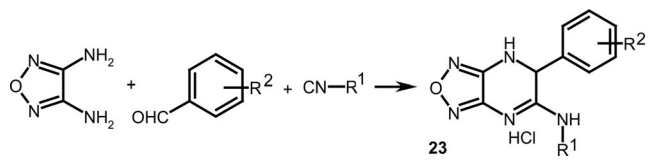
Entry	Carbonyl compound	Isocyanide	Product	General procedure	Isolated yield (%)
14				A	58
15				A	62[a]
16				A	51
17				A	45[a]

[a] These compounds were not completely characterized because of contamination with *tert*-butylamine hydrochloride [about 10–15 mol-%: 8.2 (br. s) and 1.2 (s) in 1:3 ratio in ^{1}H NMR spectra]. See the Exp. Sect. for attempted isolation in the forms of the free bases (synthesis of the 5,6-dihydropyrazine-2-amines **33** and **34**).



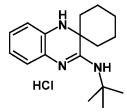
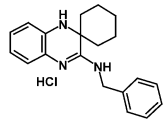
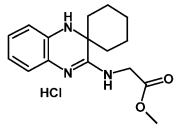
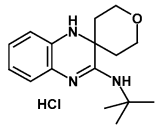
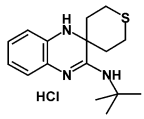
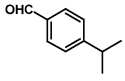
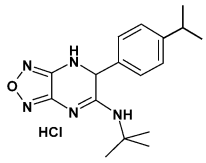
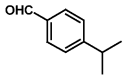
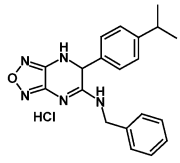
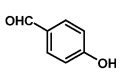
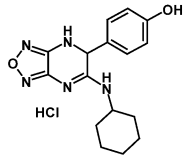
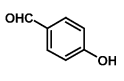
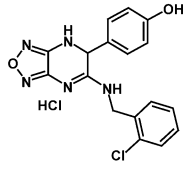
Scheme 4. Reactions of 1,2-phenylenediamine with carbonyl compounds and isocyanides.

At the same time, attempted reactions with (un)substituted benzaldehydes failed to provide the desired compounds. From the LC-MS analysis data for the reaction mixtures, the target quinoxalin-2-amines **20** proved to be minor products whereas 2-aryl-1*H*-benzimidazoles **21** were dominant. The formation of the 2-aryl-2,3-dihydro-1*H*-benzimidazolines **22** was followed by oxidation to the 2-aryl-1*H*-benzimidazoles **21** as a lower-energy process. TMSCl was able to play a role as a promoter in this reaction, as previously reported.[31] Interestingly, all of our attempts to avoid oxidative processes, which included special purification of the 1,2-phenylenediamine, employment of oxygen-free conditions, and/or use of antioxidant additives (hydroquinone, *p*-methoxyphenol, thiophenol, etc.) were also unsuccessful. It should be noted in this context that the same oxidative side reactions were observed in the HCl-promoted IMCRs of 1,2-phenylenediamine with aldehydes.[18] Nevertheless, those authors were able to isolate 3-arylquinoxalin-2-amines in moderate yields through the employment of an IMCR/2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation sequence in one-pot mode. In view of this, the most recently published results[32] appear unexpected: the same reaction in the presence of catalytic amounts (20 mol-%) of $Fe(ClO_4)_3$, which is a strong oxidizing agent, led directly to aromatic 3-arylquinoxalin-2-amines in excellent isolated yields (91–93%). On the other hand, TsOH-promoted IMCRs were shown to be effective for the synthesis of 3-aryl-3,4-dihydroquinoxalin-2-amines,[17] but only 1,2-phenylenediamines bearing strongly electron-withdrawing Ar groups were reported to be able to produce these products. This can be interpreted in terms of slow formation of the dihydroimidazole ring, so isocyanide is allowed to react with azomethyne directly, even though the corresponding 2,3-dihydro-1*H*-benzimidazoles, which should be less sensitive to oxidative processes than their unsubstituted analogues, are formed during the reaction. Therefore, less electron-rich aromatic 1,2-diamines such as some heterocyclic diamines, instead of 1,2-phenylenediamine, might be more successful candidates for IMCRs with aldehydes. Indeed, as a test case, [1,2,5]oxadiazole-3,4-di-



Scheme 5. Reactions of [1,2,5]oxadiazole-3,4-diamine with aldehydes and isocyanides.

Table 4. Synthesis of fused dihydropyrazin-2-amines through IMCRs.

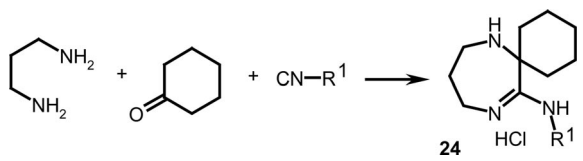
Entry	Diamine	Carbonyl compound	Isocyanide	Product	General procedure	Isolated yield (%)
1					A B	79 92
2					A	82
3					A	49
4					A	85
5					A	79
6					A	69
7					A	81
8					A	88
9					A	91

amine reacted smoothly with different aldehydes and isocyanides to provide the 6,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-amines **23** in high yields (Scheme 5). The results of these reactions are shown in Table 4 (entries 6–9).

IMCRs of Propane-1,3-diamine and Carbonyl Compounds

Inspired by the success of the IMCRs of 1,2-diamines, we further extended our studies to propane-1,3-diamine. Its re-

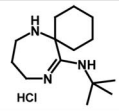
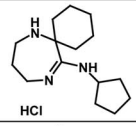
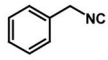
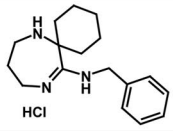
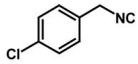
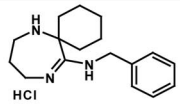
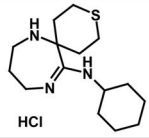
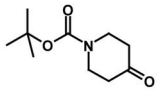
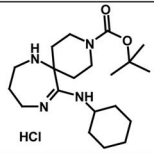
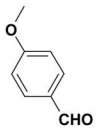
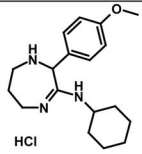
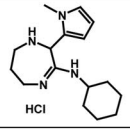
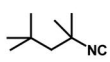
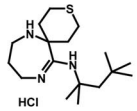
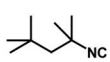
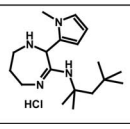
actions might provide tetrahydro-1,4-diazepine-2-amines, the core of which is undoubtedly a privileged structure, particularly useful in the design of peptide secondary structure mimetics.[33] With this hope in mind, we examined the reaction between propane-1,3-diamine and cyclohexanone (Scheme 6; Table 5, entries 1–4). In comparison with the IMCRs of 1,2-diamines, propane-1,3-diamine required somewhat elevated temperatures and increased reaction time for the reactions to go to completion.

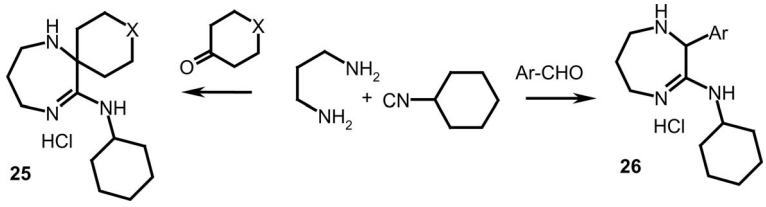


Scheme 6. IMCRs of propane-1,3-diamine with cyclohexanone and various isocyanides.

To verify the applicability of the carbonyl compounds, two more ketones (tetrahydro-4*H*-thiopyran-4-one and *N*-Boc-piperidin-4-one) and two aldehydes (*p*-methoxybenzal-

Table 5. Synthesis of 1,4-diazepine-2-amines through IMCRs of propane-1,3-diamine.

Entry	Carbonyl compound	Isocyanide	Product	General procedure	Yield (%)
1				A B	63 75
2				A	81
3				A	79
4				A	91
5				A	72
6				A B	62 71
7				A	64
8				A	59
9				A	56
10				A	43



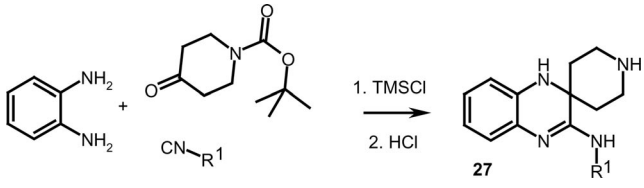
Scheme 7. IMCRs of propane-1,3-diamine with cyclohexyl isocyanide and various carbonyl compounds.

dehyde and 1-methylpyrrole-2-carbaldehyde) were allowed to react with propane-1,3-diamine and cyclohexyl isocyanide (Scheme 7). We were pleased to find that all of these reactions proceeded cleanly, providing the target 1,4-diazepine-2-amines **25** and **26** in good yields (Table 5, entries 5–10).

Although sterically hindered 1,1,3,3-tetramethylbutyl (TMB) isocyanide reacted smoothly and cleanly with propane-1,3-diamine and both tetrahydro-4*H*-thiopyran-4-one and 1-methylpyrrole-2-carbaldehyde, providing almost quantitative formation (LC-MS monitoring results) of the target diazepine-2-amines, the isolated yields subsequently proved to be only moderate (Table 5, entries 9 and 10), probably because of high solubilities of their hydrochlorides in organic solvents, resulting in losses during water-free isolation.

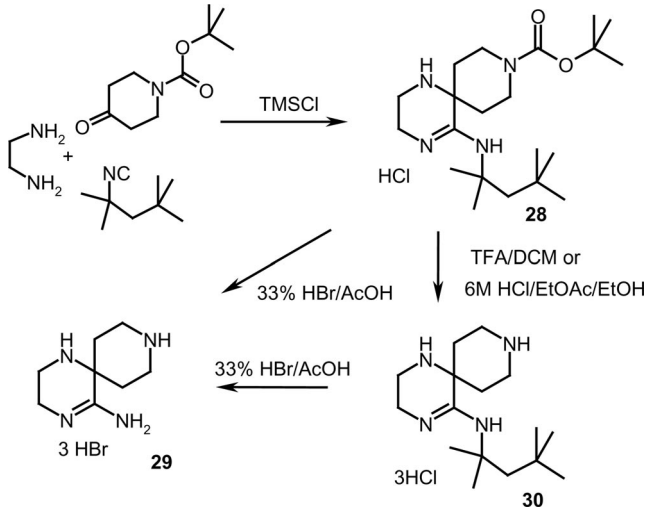
Subsequent Modifications of the Synthesized Scaffolds

The high variability of the components potentially utilizable in these IMCRs paves the way for the successful synthesis of highly diverse and unique aminoheterocyclic scaffolds, including fused and spirocyclic systems. Furthermore, each of the synthesized scaffolds contains a secondary amino group – a potential site for introduction of one more point of diversity. Scaffold diversity can be significantly broadened by employment of IMCR components bearing additional functionalities such as phenolic hydroxy (Table 3, entry 9; Table 4, entries 8, 9) or methoxycarbonyl (Table 4, entry 3) groups. Obviously, the Boc/de-Boc strategy can also serve this purpose. For instance, three spiro-piperidines each with a secondary amino group in the piperidine moiety were synthesized at 0.2 mol scale by a one-pot procedure (Scheme 8).



Scheme 8. Large-scale synthesis of deprotected spiro-piperidines.

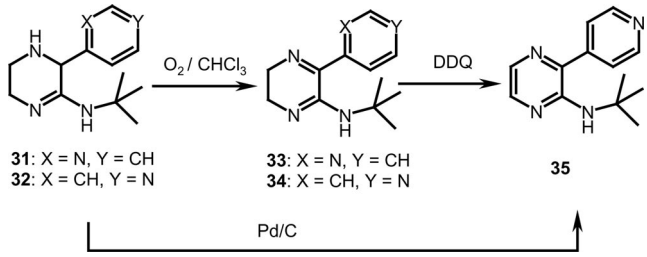
Frequent use of TMB isocyanide as an isocyanide component has been fruitful in our work. Besides being the most sterically hindered of the isocyanides used during the evaluation of the scope of the IMCRs, this isocyanide was also able to serve as a synthetic equivalent of cyanide anion (or hypothetical isocyanide HNC) in this type of IMCR. The spiro compound **28** (Scheme 9), synthesized from ethylenediamine, *N*-Boc-piperidin-4-one, and TMB-NC, for instance, underwent cleavage of both Boc and TMB groups when it was treated with HBr/AcOH at elevated temperatures with the formation of spiro compound **29** in almost quantitative yield. Furthermore, we were able to carry out step-by-step selective cleavage of the Boc group by standard protocols (either TFA/CH_2Cl_2 or HCl/EtOH/EtOAc), which provided compound **30** in high yield, with subsequent cleavage of the TMB group furnishing compound **29**. A remarkably similar mode has been used for the synthesis of 3-aminoimidazo[1,2-*a*]pyri(mi)dines containing primary amino groups, derived from N-TMB derivatives obtainable from the Groebke–Blackburn–Bienamé reaction.[34] Clearly, such a synthetic approach to tetrahydropyrazin-2-amines containing primary amino groups in their amidine moieties could open a window of opportunity for promising modifications of these scaffolds by annulation of other azaheterocycles.



Scheme 9. Selective and nonselective cleavage of Boc and TMB groups.

Partial dehydrogenation and full aromatization of the dihydropyrazine ring could represent another route for post-IMCR modifications of obtainable scaffolds. Thus, the crude products obtained when we tried to isolate the free bases of the 2- and 4-pyridyl-substituted tetrahydropyrazines **31** and **32** from their HCl salts (Table 3, entries 15 and 17) proved to be mixtures of the target materials and the oxidized products **33** and **34** (Scheme 10), respectively, as was confirmed by LC-MS and ^{1}H NMR analyses. Com-

plete oxidation was achieved by simply stirring their solutions in $CHCl_3$ overnight in open vials, thus providing the dihydropyrazines **33** and **34**.



Scheme 10. Partial dehydrogenation and aromatization of the dihydropyrazine ring.

As was shown in the case of the 4-pyridyl derivative **34**, further oxidation of the dihydropyrazine ring to form the aminopyrazine **35** can be achieved by employing DDQ. Moreover, this compound can be synthesized directly from the tetrahydro derivative **32** when heated under reflux in 2-methoxyethanol in the presence of Pd/C. Therefore, an IMCR/aromatization sequence can serve as a convenient route to a variety of synthetically challenging 3-(het)arylpyrazin-2-amines.

Conclusions

MCRs of 1,2- and 1,3-diamines with carbonyl compounds and isocyanides have been developed as direct and convenient routes to a variety of heterocycles containing 2-aminopyrazine and 2-amino-1,4-diazepine cores, including related benzo-, hetareno-, and spiro-fused systems. In its scope, this IMCR approach has been shown to be acceptable for a wide range of carbonyl compounds including ketones and aliphatic, aromatic, and heterocyclic aldehydes with both electron-donating and electron-withdrawing substituents. The scaffold diversity obtainable by this IMCR approach is demonstrated by the structural variability of the components capable of participating in these developed IMCRs. Amino derivatives of fourteen heterocyclic systems (pyrazine, 1,4-diazaspiro[5.5]undec-4-ene, 9-oxa-1,4-diazaspiro[5.5]undec-4-ene, 1,4,9-triazaspiro[5.5]undec-4-ene, 1,4,8-triazaspiro[5.5]undec-4-ene, spiro[cyclohexane-1,2′-quinoxaline], spiro[piperidine-4,2′-quinoxaline], spiro[pyran-4,2′-quinoxaline], spiro[quinoxaline-2,4′-thiopyran], [1,2,5]oxadiazolo[3,4-*b*]pyrazine, 1,4-diazepine, 7,11-diazaspiro[5.6]dodec-11-ene, 3-thia-7,11-diazaspiro[5.6]dodec-11-ene, and 3,7,11-triazaspiro[5.6]dodec-11-ene) have been synthesized and characterized during the course of this work. Furthermore, the scope of the reactions could be significantly extended to the synthesis of spiro- and (het)arenofused 1,4-diazaheterocycles through the involvement of readily available carbonyl and, more importantly, (hetero)cyclic 1,2- and 1,3-diamines. Importantly, the compounds obtainable by this IMCR approach meet all requirements of both lead- and drug-likeness.

Although the IMCR can be promoted by various LAs including metal triflates and SLAs, TMSCl has been identified as a promoter of choice.[35] Originally developed for a limited set of components, the protocol for the performance of the IMCRs and isolation of the target materials has been successfully applied to a great variety of diamines, carbonyl compounds, and isocyanides. Therefore, the isolated yields listed could be significantly improved by protocol optimization for specific sets of the components. The developed IMCRs can be performed over a wide range of scales starting from 0.1 mmol (in parallel synthesis format) up to multimol loading. Some synthetically useful post-IMCR modifications of the generated scaffolds such as Boc and TMB removal, partial dehydrogenation, and full aromatization have been outlined.

Experimental Section

General: Commercially available reagents (ethylenediamine, *trans*-cyclohexane-1,2-diamine, 1,2-phenylenediamine, 1,2,5-oxadiazole-3,4-diamine, isocyanides, carbonyl compounds, LAs listed in the article) and solvents were employed without purification. ^1H and ^{13}C NMR spectra, including Attached Proton Test (APT) NMR spectra, at 400 and 100 MHz, respectively, were recorded with a Varian Unity+ spectrometer; chemical shifts are reported in ppm with use of TMS as internal standard in $CDCl_3$ or [D_6]DMSO. The following abbreviations are used in NMR spectra descriptions: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, Ar = aryl, Py = pyridyl, Pyr = pyrrolyl, *i*Pr = isopropyl, and exch. D_2O = exchange with D_2O. IUPAC nomenclature is used for atom numbering; see compound names to refer to position numbers. HR mass spectra (ESI-TOF, positive) were obtained with an Agilent ESI-TOF 6210 mass spectrometer.

Purities of all synthesized compounds (more than 98% unless otherwise specified) were confirmed by LC-MS analysis performed with a Shimadzu HPLC instrument with PE SCIEX API 150EX mass-, Alltech 2056 ELS-, and Shimadzu UV- (254 and 215 nm) detectors. Separation was achieved with a Phenomenex Luna 3μ C18 (4.6 × 150 mm) column with use of a gradient (5–95%) of acetonitrile in water both with 0.05% TFA over 12 min at 0.8 mL min^{-1}.

General Procedures for the MCRs of Diamines, Carbonyl Compounds, and Isocyanides

Evaluation of Promoters' Activities – Synthesis of (4a′*S*,8a′*S*)-/(4a′*R*,8a′*R*)-1-Benzyl-*N*-*tert*-butyl-4a′,5′,6′,7′,8′,8a′-hexahydro-1′*H*-spiro[piperidine-4,2′-quinoxalin]-3′-amine (16): A mixture of *trans*-cyclohexanediamine (1.14 g, 10 mmol) and *N*-benzylpiperidin-4-one (1.89 g, 10 mmol) in $CHCl_3$ (15 mL) was heated under reflux for 2 h, volatile components were evaporated, a fresh portion of $CHCl_3$ (10 mL) was added, the solvent was evaporated to dryness, and the residue was diluted with methanol up to a volume of 20 mL to afford a solution (0.5 M) of the intermediate azomethyne. In each entry, a mixture of this solution (1000 μL), a solution of *tert*-butyl isocyanide in CH_3CN (1 M, 500 μL), and the appropriate amount of LA was stirred for 24 h at ambient temperature in a closed tube. Yields were determined by LC-MS (ELSD) analysis of the reaction mixtures. To isolate the reaction product, each of the entries 6, 7, and 8 was worked up by the following procedure. The reaction mixture was evaporated to dryness under reduced pressure, the residue was dissolved in water and treated with aq. NaOH solution (10%), and this was extracted with $CHCl_3$. The organic layer was washed with water and brine and dried (Na_2SO_4), and the

solvents were evaporated. The oily residue crystallized slowly to afford a colorless solid consisting of the individual compound **16**. Isolated yields: 55% (entry 6), 78% (entry 7), 67% (entry 8).

Data for Compound 16: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.36 (m, 5 H, 5 × Ar-H), 3.61 (br. s, 1 H, 3′-NH, exch. D_2O), 3.51 (s, 2 H, 1-CH_2), 2.60–2.77 (m, 3 H, 2-H, 6-H, 4a′-H), 2.23–2.47 (m, 2 H, 2-H, 6-H), 1.95–2.11 (m, 3 H, 3-H, 5-H, 8a′-H), 1.69–1.79 (m, 5 H, 3-H, 5-H, 2 × 5′-H, 4′-H), 1.46–1.54 (m, 1 H, 4′-H), 1.31 (s, 9 H, *t*Bu), 0.97–1.40 (m, 4 H, 2 × 6′-H, 2 × 7′-H), 0.84 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, 1′-H, exch. D_2O) ppm. ^{13}C NMR APT (100 MHz, $CDCl_3$): δ = 159.2 (C), 138.3 (C), 129.6 (CH), 128.5 (CH), 127.3 (CH), 63.7 (CH_2), 62.0 (CH), 53.9 (C), 53.5 (CH), 51.0 (CH_2), 48.8 (CH_2), 41.5 (C), 37.4 (CH_2), 35.1 (CH_2), 33.2 (CH_2), 32.7 (CH_2), 29.4 (CH_3), 26.0 (CH_2), 25.8 (CH_2) ppm. HRMS: calcd. for $C_{23}H_{36}N_4$ [M + H]$^+$ 369.3013; found 369.3015.

Evaluation of the Scope of the IMCR Approach with Ethylenediamine, Various Carbonyl Compounds, and Isocyanides (Designed as a Full-Matrix Parallel Synthesis at 0.1 mmol Scale, Table 2): A mixture of equimolar amounts (5 mmol) of the ethylenediamine and the carbonyl compound in MeOH (5 mL) was heated at 50 °C for 3 h in a closed vessel, allowed to cool, and diluted with MeOH to afford a solution of the intermediate azomethyne (0.5 M). For each entry, a mixture of this solution (200 μL), a solution of TMSCl in acetonitrile (2 M, 50 μL), and a solution of isocyanide in MeOH (1 M, 100 μL) was shaken at 40 °C for 24 h (capped 96 deep well vials). Yields were determined by LC-MS (ELSD) of diluted aliquots of the reaction mixtures.

General Procedure A for MCRs of Diamines, Carbonyl Compounds, and Isocyanides (Designed for Parallel Synthesis at 0.5 mmol Scale): The syntheses were performed in 10 mL capped tubes in a one-pot fashion without employment of any protective procedures such as inert or anhydrous atmosphere. A mixture of MeOH solutions (1 M, 500 μL) of the carbonyl compound (0.5 mmol) and of the diamine (0.5 mmol) was stirred for 3 h at 45–50 °C. Solutions of TMSCl in acetonitrile (1 M, 500 μL, 0.5 mmol) and isocyanide in MeOH (1 M, 500 μL, 0.5 mmol) were added, and the resulting mixture was stirred at 50–60 °C for 4 h and then at ambient temperature until completion of the reaction (LC-MS-ELSD monitoring). Reactions of ethylenediamine usually required stirring overnight, whereas reactions of (hetero)aromatic diamines and propane-1,3-diamine required stirring for 20–24 h at 40–50 °C. The reaction mixture was evaporated under reduced pressure, treated with dry EtOAc, kept in an ultrasonic bath until completion of precipitate formation, and then centrifuged. The precipitate was washed twice with EtOAc, acetonitrile, and Et_2O with centrifugation each time, and dried under reduced pressure. The procedure usually provided pure monohydrochlorides of the target materials (compounds **17**, **18**, and compounds represented in Table 3, Table 4, and Table 5). In some cases, in which ethylenediamine was used as a starting diamine, however, crude products were contaminated by ethylenediamine hydrochloride, which could not be removed by simple procedures such as recrystallization. In these cases, the crude products were dissolved in water, treated with aq. NaOH (10%), and extracted with $CHCl_3$. The organic layers were washed with water and brine and dried (Na_2SO_4), and the solvents were evaporated. Residues after evaporation were the pure products (Table 3, entries 3, 4, 14, 16) in the form of their free bases.

General Procedure B for MCRs of Diamines, Carbonyl Compounds, and Isocyanides (Designed for 10 mmol Scale Synthesis): A mixture of a carbonyl compound (10 mmol), the diamine (10 mmol), and MeOH (15 mL) was stirred for 1 h at 45–50 °C. An isocyanide (10 mmol) and a solution of TMSCl (10 mmol) in acetonitrile were added, and the resulting mixture was stirred at 50–60 °C until completion of the reaction (LC-MS-ELSD monitoring). The reaction mixture was evaporated under reduced pressure, treated with dry EtOAc, and kept in an ultrasonic bath until completion of precipitate formation. The precipitate was filtered off, washed carefully with EtOAc, acetonitrile, and Et_2O, and dried under reduced pressure. This protocol was employed for the scale-up synthesis of compounds **17**, **18**, and **28**, as well as those of Table 3 entries 5–8, Table 4 entry 1, and Table 5 entry 6, side by side with Procedure A.

Data for the Aminoheterocycles Synthesized by the IMCR

***N*-Benzyl-9-oxa-1,4-diazaspiro[5.5]undec-4-en-5-amine Hydrochloride (17):** This compound was produced through the MCR of ethylenediamine, tetrahydro-4*H*-pyran-4-one, and benzyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.94 (br. s, 1 H, 1-H, exch. D_2O), 9.74 (br. m, 1 H, 5-NH, exch. D_2O), 7.24–7.40 (m, 5 H, 5 × Ar-H), 4.59 (d, $^3J_{H,H}$ = 3.3 Hz, 2 H, NCH_2Ph; with D_2O: s, 2 H), 3.59–3.78 (m, 4 H, 2 × 8-H, 2 × 10-H), 3.18–3.25 (m, 2 H, 2 × 3-H; with D_2O: t, $^3J_{H,H}$ = 4.8 Hz, 2 H), 2.84–2.92 (m, 2 H, 2 × 2-H; with D_2O: t, $^3J_{H,H}$ = 4.8 Hz, 2 H), 2.65 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, 1-H, exch. D_2O), 2.11–2.21 (m, 2 H, 7-H, 11-H), 1.65–1.73 (m, 2 H, 7-H, 11-H) ppm. ^{13}C NMR APT (100 MHz, [D$_6$]DMSO): δ = 167.1 (C), 136.3 (C), 129.2 (CH), 128.2 (CH), 127.9 (CH), 62.1 (CH_2), 53.9 (C), 44.5 (CH_2), 41.6 (CH_2), 36.2 (CH_2), 33.3 (CH_2) ppm. HRMS: calcd. for $C_{15}H_{21}N_3O$ [M + H]$^+$ 260.1757; found 260.1755.

***N*-Benzyl-3-(4-isopropylphenyl)-3,4,5,6-tetrahydropyrazin-2-amine Hydrochloride (18):** This compound was produced through the MCR of ethylenediamine, 4-isopropylbenzaldehyde, and benzyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.43 (br. s, 1 H, 1-H, exch. D_2O), 9.63 (br. m, 1 H, 2-NH, exch. D_2O), 7.28–7.40 (m, 5 H, 5 × Ar-H), 7.24 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2 × Ar-H), 7.21 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2 × Ar-H), 4.91 (s, 1 H, 3-H), 4.68 (dd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 5.9 Hz, 1 H, PhCHN; with D_2O: d, $^2J_{H,H}$ = 15.0 Hz, 1 H), 4.55 (dd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 5.1 Hz, 1 H, PhCHN; with D_2O: d, $^2J_{H,H}$ = 15.0 Hz, 1 H), 3.23–3.39 (m, 2 H, 2 × 6-H), 2.79–2.94 (m, 2 H, 5-H, Ar-CH), 2.67–2.78 (m, 1 H, 5-H), 1.18 (d, $^3J_{H,H}$ = 7.0 Hz, 6 H, 2 × Me) ppm. ^{13}C NMR APT (100 MHz, [D$_6$]-DMSO): δ = 163.0 (C), 148.8 (C), 136.5 (C), 136.2 (C), 129.1 (CH), 128.9 (CH), 128.7 (CH), 127.0 (CH), 57.1 (CH), 45.3 (CH_2), 41.0 (CH_2), 37.1 (CH_2), 33.8 (CH), 24.5 (CH_3) ppm. HRMS: calcd. for $C_{20}H_{25}N_3$ [M + H]$^+$ 308.2121; found 308.2123.

***N*-(4-Chlorobenzyl)-1,4-diazaspiro[5.5]undec-4-en-5-amine Hydrochloride (Table 3, entry 1):** This compound was produced through the MCR of ethylenediamine, cyclohexanone, and *p*-chlorobenzyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.81 (br. m, 2 H, 4-H, 5-NH, exch. D_2O), 7.42 (s, 4 H, 4 × Ar-H), 4.56 (d, $^3J_{H,H}$ = 6.2 Hz, 2 H, $ArCH_2N$, with D_2O: s, 2 H), 3.15–3.23 (m, 2 H, 2 × 3-H), 2.78–2.86 (m, 2 H, 2 × 2-H), 2.43 (br. m, 1 H, 1-H, exch. D_2O), 1.87–2.00 (m, 2 H), 1.52–1.78 (m, 5 H), 1.22–1.47 (m, 3 H) (5 × CH_2) ppm. ^{13}C NMR APT (100 MHz, [D$_6$]DMSO): δ = 168.4 (C), 135.8 (C), 132.8 (C), 130.0 (CH), 129.0 (CH), 56.0 (C), 43.6 (CH_2), 41.9 (CH_2), 36.4 (CH_2), 33.1 (CH_2), 24.9 (CH_2), 20.7 (CH_2) ppm. HRMS: calcd. for $C_{16}H_{22}ClN_3$ [M + H]$^+$ 292.1575; found 292.1578.

***N*-(2-Methoxybenzyl)-1,4-diazaspiro[5.5]undec-4-en-5-amine Hydrochloride (Table 3, entry 2):** This compound was produced through the MCR of ethylenediamine, cyclohexanone, and 2-methoxybenzyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.51 (br. s, 1 H, 4-H, exch. D_2O), 9.38 (br. t, $^3J_{H,H}$ = 5.1 Hz, exch. D_2O, 1 H, 5-NH), 7.27–7.35 (m, 1 H, Ar-H), 7.09 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, Ar-H), 7.04 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ar-H), 6.91–6.97 (m, 1 H, Ar-H), 4.41 (d, $^3J_{H,H}$ = 5.1 Hz, 2 H; $ArCH_2N$, with D_2O: s, 2 H), 3.81

(s, 3 H, OMe), 3.22 (t, $^3J_{H,H}$ = 4.8 Hz, 2 H, 2×3-H), 2.86 (t, $^3J_{H,H}$ = 4.8 Hz, 2 H, 2×2-H), 2.48 (br. m, 1 H, 1-H, shoulder of DMSO, exch. D_2O), 1.86–1.98 (m, 2 H), 1.74–1.83 (m, 2 H), 1.51–1.72 (m, 3 H), 1.37–1.47 (m, 2 H), 1.19–1.34 (m, 1 H) (5×CH_2) ppm. ^{13}C NMR APT (100 MHz, [D$_6$]DMSO): δ = 168.6 (C), 157.7 (C), 129.7 (CH), 128.2 (CH), 123.6 (C), 120.9 (CH), 111.5 (CH), 56.1 (CH_3), 42.0 (CH_2), 41.3 (CH_2), 36.5 (CH_2), 33.0 (CH_2), 24.9 (CH_2), 20.7 (CH_2) ppm. HRMS: calcd. for $C_{17}H_{25}N_3O$ [M + H]$^+$ 288.2070; found 288.2063.

***N*-*tert*-Butyl-9-oxa-1,4-diazaspiro[5.5]undec-4-en-5-amine (Table 3, entry 3):** This compound was produced through the MCR of ethylenediamine, tetrahydro-4*H*-pyran-4-one, and *tert*-butyl isocyanide. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.79–3.89 (m, 2 H, 8-H, 10-H), 3.69–3.76 (m, 2 H, 8-H, 10-H), 3.66 (br. s, 1 H, 5-NH, exch. D_2O), 3.43 (t, $^3J_{H,H}$ = 5.1 Hz, 2 H, 2×3-H), 2.79 (t, $^3J_{H,H}$ = 5.1 Hz, 2 H, 2×2-H), 1.90–2.00 (m, 2 H, 7-H, 11-H), 1.53–1.61 (m, 2 H, 7-H, 11-H), 1.32 (s, 10 H, *t*Bu, 1-H, with D_2O: s, 9 H) ppm. ^{13}C NMR APT (100 MHz, $CDCl_3$): δ = 159.3 (C), 63.1 (CH_2), 51.4 (C), 50.8 (C), 47.2 (CH_2), 38.5 (CH_2), 35.0 (CH_2), 29.3 (CH_3) ppm. HRMS: calcd. for $C_{12}H_{23}N_3O$ [M + H]$^+$ 226.1914; found 226.1910.

9-Benzyl-*N*-*tert*-butyl-1,4,9-triazaspiro[5.5]undec-4-en-5-amine (Table 3, entry 4): This compound was produced through the MCR of ethylenediamine, *N*-benzylpiperidin-4-one, and *tert*-butyl isocyanide. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.34 (m, 5 H, 5×Ar-H), 3.74 (br. s, 1 H, 5-NH, exch. D_2O), 3.52 (s, 2 H, 9-CH_2Ph), 3.43 (t, $^3J_{H,H}$ = 5.5 Hz, 2 H, 2×3-H), 2.77 (t, $^3J_{H,H}$ = 5.5 Hz, 2 H, 2×2-H), 2.62–2.69 (m, 2 H, 8-H, 10-H), 2.30–2.40 (m, 2 H, 8-H, 10-H), 1.83–1.93 (m, 2 H, 7-H, 11-H), 1.64–1.71 (m, 2 H, 7-H, 11-H), 1.30–1.60 (br. s, 1 H, 1-H, exch. D_2O), 1.31 (s, 9 H, *t*Bu) ppm. ^{13}C NMR APT (100 MHz, $CDCl_3$): δ = 159.9 (C), 138.3 (C), 129.5 (CH), 128.4 (CH), 127.3 (CH), 63.6 (CH_2), 52.0 (C), 50.8 (C), 48.6 (CH_2), 47.2 (CH_2), 38.3 (CH_2), 34.7 (CH_2), 29.3 (CH_3) ppm. HRMS: calcd. for $C_{19}H_{30}N_4$ [M + H]$^+$ 315.2543; found 315.2541.

***tert*-Butyl 5-(*tert*-Butylamino)-1,4,8-triazaspiro[5.5]undec-4-ene-8-carboxylate Hydrochloride (Table 3, entry 5):** This compound was produced through the MCR of ethylenediamine, *N*-Boc-3-piperidone, and *tert*-butyl isocyanide. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.68 (br. s, 1 H, 4-H, exch. D_2O), 8.15 (br. s, 1 H, 5-NH, exch. D_2O), 3.94 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H, 7-H), 3.84 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H, 7-H), 3.19–3.44 (m, 3 H, 2×3-H, 9-H), 2.84–3.02 (m, 3 H, 2×2-H, 9-H), 2.30–2.42 (m, 2 H, 1-H, 11-H; with D_2O: m, 1 H), 1.64–1.77 (m, 2 H, 10-H, 11-H), 1.41 (s, 9 H, *t*Bu), 1.38 (s, 9 H, *t*Bu), 1.25–1.38 (m, 1 H, 10-H) ppm. ^{13}C NMR APT (100 MHz, [D$_6$]DMSO): δ = 165.1 (C), 155.4 (C), 79.2 (C), 56.2 (C), 54.1 (C), 47.4 (CH_2), 42.9 (CH_2), 42.7,[36] 36.7 (CH_2), 32.4,[36] 28.7 (CH_3), 28.6 (CH_3), 19.6 (CH_2) ppm. HRMS: calcd. for $C_{17}H_{32}N_4O_2$ [M + H]$^+$ 325.2598; found 325.2596.

3-Methyl-*N*-(1,1,3,3-tetramethylbutyl)-3,4,5,6-tetrahydropyrazin-2-amine Hydrochloride (Table 3, entry 6): This compound was produced through the MCR of ethylenediamine, acetaldehyde, and 1,1,3,3-tetramethylbutyl isocyanide. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.06 (br. s, 1 H, 1-H, exch. D_2O), 9.02 (br. s, 1 H, 2-NH, exch. D_2O), 4.50 (q, $^3J_{H,H}$ = 6.7 Hz, 1 H, 3-H), 3.53–3.66 (m, 2 H, 2×6-H), 3.11–3.22 (m, 1 H, 5-H), 2.93–3.03 (m, 1 H, 5-H), 2.08 (d, $^2J_{H,H}$ = 15.4 Hz, 1 H, 2-H of TMB), 1.84 (d, $^2J_{H,H}$ = 15.4 Hz, 1 H, 2-H of TMB), 1.75 (very br s, 1 H, 4-H, exch. D_2O), 1.65 (s, 3 H, 1-Me of TMB), 1.60 (s, 3 H, 1-Me of TMB), 1.57 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, 3-Me), 1.04 (s, 9 H, 3×3-Me of TMB) ppm. ^{13}C NMR APT (100 MHz, $CDCl_3$): δ = 163.5 (C), 57.9 (CH_2), 50.5 (C), 49.1 (CH), 42.3 (CH_2), 37.3 (C), 32.0 (CH_2), 31.5 (CH_3), 29.9 (CH_3), 29.5 (CH_3), 21.2 (CH_3) ppm. HRMS: calcd. for $C_{13}H_{27}N_3$ [M + H]$^+$ 226.2278; found 226.2280.

3-Isopropyl-*N*-(1,1,3,3-tetramethylbutyl)-3,4,5,6-tetrahydropyrazin-2-amine Hydrochloride (Table 3, entry 7): This compound was produced through the MCR of ethylenediamine, 2-methylpropanal, and 1,1,3,3-tetramethylbutyl isocyanide. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.28 (br. s, 1 H, 1-H, exch. D_2O), 8.84 (br. s, 1 H, 2-NH, exch. D_2O), 4.20 (d, $^3J_{H,H}$ = 4 Hz, 1 H, 3-H), 3.85–3.94 (m, 1 H, 6-H), 3.28–3.39 (m, 1 H, 6-H), 3.10–3.18 (m, 1 H, 5-H), 2.83–2.94 (m, 1 H, 5-H), 2.34–2.47 (m, 2 H, 2-H of TMB, 3-CH), 1.68 (s, 3 H, 1-Me of TMB), 1.61 (s, 3 H, 1-Me of TMB), 1.53–1.60 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, 2-H of TMB), 1.47 (br. s, 1 H, 4-H, exch. D_2O), 1.05 (s, 9 H + d, 3 H, 3×3-Me of TMB, Me of *i*Pr), 0.94 (d, $^3J_{H,H}$ = 6 Hz, 3 H, Me of *i*Pr) ppm. ^{13}C NMR APT (100 MHz, $CDCl_3$): δ = 163.2 (C), 58.3 (C), 58.1 (CH_2), 50.8 (CH_2), 42.3 (CH_2), 40.4 (CH_2), 33.1 (CH or CH_3), 32.1 (CH_2), 31.7 (CH or CH_3), 31.6 (CH or CH_3), 29.6 (CH or CH_3), 29.4 (CH or CH_3), 19.6 (CH or CH_3), 16.7 (CH or CH_3) ppm. HRMS: calcd. for $C_{15}H_{31}N_3$ [M + H]$^+$ 254.2591; found 254.2590.

3-*tert*-Butyl-*N*-(1,1,3,3-tetramethylbutyl)-3,4,5,6-tetrahydropyrazin-2-amine Hydrochloride (Table 3, entry 8): This compound was produced through the MCR of ethylenediamine, pivalaldehyde, and 1,1,3,3-tetramethylbutyl isocyanide. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.38 (br. s, 1 H, 1-H, exch. D_2O), 8.55 (br. s, 1 H, 2-NH, exch. D_2O), 4.28 (s, 1 H, 3-H), 3.97–4.08 (m, 1 H, 6-H), 3.24–3.35 (m, 1 H, 6-H), 3.08–3.16 (m, 1 H, 5-H), 2.85–2.96 (m, 1 H, 5-H), 2.53 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, 2-H of TMB), 1.68 (br. s, 1 H, 4-H, appears as a shoulder of s 1.67), 1.67 (s, 3 H, 1-Me of TMB), 1.64 (s, 3 H, 1-Me of TMB), 1.53 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, 2-H of TMB), 1.08, 1.07 (2×s, 18 H, 2×*t*Bu) ppm. ^{13}C NMR APT (100 MHz, $CDCl_3$): δ = 161.8 (C), 61.1 (CH), 58.5 (CH_2), 50.2 (C), 42.7 (C), 41.8 (CH_2 or C), 38.6 (C or CH_2), 32.2 (C or CH_2), 31.6 (CH_3), 30.4 (CH_3), 29.0 (CH_3), 27.3 (CH_3) ppm. HRMS: calcd. for $C_{16}H_{33}N_3$ [M + H]$^+$ 268.2747; found 268.2746.

2-[3-(Cyclohexylamino)-1,2,5,6-tetrahydropyrazin-2-yl]-6-ethoxyphenol Hydrochloride (Table 3, entry 9): This compound was produced through the MCR of ethylenediamine, 3-ethoxy-2-hydroxybenzaldehyde, and cyclohexyl isocyanide. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 9.95 (br. s, 1 H, 1-H, exch. D_2O), 9.15 (br. s, 1 H, OH, exch. D_2O), 8.90 (br. d, $^3J_{H,H}$ = 6.6 Hz, 1 H, 2-NH, exch. D_2O), 6.94 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 6.72–6.78 (m, 1 H, Ar-H), 6.55 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, Ar-H), 5.04 (s, 1 H, 3-H), 4.04 (q, $^3J_{H,H}$ = 6.7 Hz, 2 H, OCH_2), 3.65–3.74 (m, 1 H, CH of cyclohexyl), 3.26–3.37 (m, 2 H, 2×6-H, superposition with H_2O, intensity was determined from spectra with D_2O), 3.02 (br. s, 1 H, 4-H, exch. D_2O), 2.70–3.10 (m, 2 H, 2×5-H), 1.75–1.85 (m, 2 H), 1.61–1.73 (m, 2 H), 1.51–1.60 (m, 1 H), 1.16–1.38 (m, 6 H), 1.00–1.15 (m, 2 H) (5×CH_2, Me) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.1 (C), 147.5 (C), 145.2 (C), 125.2 (C), 121.1 (CH), 119.2 (CH), 113.7 (CH), 64.8 (CH_2), 53.3, (CH) 50.7 (CH), 41.0 (CH_2), 36.9 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 25.3 (CH_2), 24.8 (CH_2), 24.7 (CH_2), 15.3 (CH_3) ppm. HRMS: calcd. for $C_{18}H_{27}N_3O_2$ [M + H]$^+$ 318.2176; found 318.2176.

***N*-*tert*-Butyl-3-(4-methoxyphenyl)-3,4,5,6-tetrahydropyrazin-2-amine Hydrochloride (Table 3, entry 10):** This compound was produced through the MCR of ethylenediamine, 4-methoxybenzaldehyde, and *tert*-butyl isocyanide. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 9.03 (br. s, 1 H, 1-H, exch. D_2O), 9.01 (br. s, 1 H, 2-NH, exch. D_2O), 7.19 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 2×Ar-H), 6.96 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 2×Ar-H), 4.88 (s, 1 H, 3-H), 3.75 (s, 3 H, OMe), 3.34–3.41 (m, 1 H, 6-H), 3.12–3.23 (m, 1 H, 6-H), 2.78–2.86 (m, 1 H, 5-H), 2.60–2.70 (m, 1 H, 5-H), 1.40 (s, 9 H, *t*Bu) ppm. ^{13}C NMR APT (100 MHz, [D$_6$]DMSO): δ = 162.0 (C), 159.4 (C), 131.0 (C), 129.4 (CH), 114.5 (CH), 56.3 (CH_3), 55.8 (CH), 53.3 (C), 36.1

(CH_2), 28.3 (CH_3) ppm. HRMS: calcd. for $C_{15}H_{23}N_3O$ [M + H]$^+$ 262.1914; found 262.1914.

3-(2,4-Dimethoxyphenyl)-*N*-(4-methoxybenzyl)-3,4,5,6-tetrahydropyrazin-2-amine Hydrochloride (Table 3, entry 11): This compound was produced through the MCR of ethylenediamine, 2,4-dimethoxybenzaldehyde, and 4-methoxybenzyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.0 (br. s, 1 H, 1-H, exch. D_2O), 9.58 (br. m, 1 H, 2-NH, exch. D_2O), 7.27 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, Ar-H), 7.21 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2 × Ar-H), 6.89 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2 × Ar-H), 6.64 (d, $^4J_{H,H}$ = 2.2 Hz, 1 H, Ar-H), 6.60 (dd, $^3J_{H,H}$ = 8.8, $^4J_{H,H}$ = 2.2 Hz, 1 H, Ar-H), 5.60 (s, 1 H, 3-H), 4.65 (dd, $^2J_{H,H}$ = 15.4, $^3J_{H,H}$ = 6.6 Hz, 1 H, ArCHN; with D_2O: d, $^2J_{H,H}$ = 15.4 Hz, 1 H), 4.38 (dd, $^2J_{H,H}$ = 15.4, $^3J_{H,H}$ = 5.5 Hz, 1 H, ArCHN; with D_2O: d, $^2J_{H,H}$ = 15.4 Hz, 1 H), 3.80 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 3.71 (s, 3 H, OMe), 3.59–3.68 (m, 1 H, 6-H), 3.33–3.50 (m, 3 H, 4-H, 5-H, 6-H; with D_2O: m, 2 H), 3.20–3.30 (m, 1 H, 5-H) ppm. ^{13}C NMR APT (100 MHz, [D$_6$]DMSO): δ = 163.4 (C), 159.5 (C), 159.3 (C), 158.6 (C), 134.0 (CH), 129.8 (CH), 127.7 (C), 114.5 (CH), 111.9 (C), 105.8 (CH), 99.3 (CH), 56.5 (CH_3), 56.3 (CH_3), 55.8 (CH_3), 51.9 (CH), 45.1 (CH_2), 38.3 (CH_2), 38.1 (CH_2) ppm. HRMS: calcd. for $C_{20}H_{25}N_3O_3$ [M + H]$^+$ 356.1969; found 356.1960.

***N*-Cyclopentyl-3-[4-(trifluoromethyl)phenyl]-3,4,5,6-tetrahydropyrazin-2-amine Hydrochloride (Table 3, entry 12):** This compound was produced through the MCR of ethylenediamine, 4-trifluoromethylbenzaldehyde, and cyclopentyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.14 (br. s, 1 H, 1-H, exch. D_2O), 9.64 (br. d, $^3J_{H,H}$ = 6.6 Hz, 1 H, 2-NH, exch. D_2O), 7.77 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 2 × Ar-H), 7.52 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 2 × Ar-H), 5.06 (s, 1 H, 3-H), 4.15–4.22 (m, 1 H, CH of cyclopentyl; with D_2O: multiplicity changes, 1 H), 3.45 (m, 1 H, 4-H, exch. D_2O), 3.28–3.39 (m, 1 H, 6-H), 3.15–3.25 (m, 1 H, 6-H), 2.79–2.89 (m, 1 H, 5-H), 2.54–2.68 (m, 1 H, 5-H), 1.90–2.05 (m, 2 H), 1.42–1.70 (m, 6 H) (4 CH_2) ppm. ^{13}C NMR APT[37] (100 MHz, [D$_6$]DMSO): δ = 166.1 (C), 148.8 (C), 134.2 (CH), 133.9 (C), 133.6 (C), 130.7 (CH), 60.8 (CH), 58.3 (CH), 41.3 (CH_2), 36.9 (CH_2), 36.6 (CH_2), 28.90 (CH_2), 28.81 (CH_2) ppm. HRMS: calcd. for $C_{16}H_{20}F_3N_3$ [M + H]$^+$ 312.1682; found 312.1685.

3-(4-Chlorophenyl)-*N*-cyclopentyl-3,4,5,6-tetrahydropyrazin-2-amine Hydrochloride (Table 3, entry 13): This compound was produced through the MCR of ethylenediamine, 4-chlorobenzaldehyde, and cyclopentyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.00 (br. s, 1 H, 1-H, exch. D_2O), 9.49 (br. d, approx. $^3J_{H,H}$ = 7 Hz, 1 H, 2-NH, exch. D_2O), 7.46 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 2 × Ar-H), 7.30 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 2 × Ar-H), 4.92 (s, 1 H, 3-H), 4.06–4.18 (m, 1 H, CH of cyclopentyl), 3.16–3.40 (m, 2 H, 2 × 6-H), 2.77–2.87 (m, 1 H, 5-H), 2.57–2.69 (m, 1 H, 5-H), 1.89–2.03 (m, 2 H), 1.39–1.71 (m, 6 H) (4 × CH_2) ppm. ^{13}C NMR APT (100 MHz, [D$_6$]DMSO): δ = 161.6 (C), 138.3 (C), 133.1 (C), 130.5 (CH), 129.0 (CH), 55.9 (C), 53.5 (C), 36.5 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 24.1 (CH_2) ppm. HRMS: calcd. for $C_{15}H_{20}ClN_3$ [M + H]$^+$ 278.1418; found 278.1423.

***N*-*tert*-Butyl-3-(1-methyl-1*H*-pyrrol-2-yl)-3,4,5,6-tetrahydropyrazin-2-amine (Table 3, entry 14):** This compound was produced through the MCR of ethylenediamine, 1-methyl-1*H*-pyrrole-2-carbaldehyde, and *tert*-butyl isocyanide. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (m, 1 H, Pyr-H), 6.01 (m, 1 H, Pyr-H), 5.97 (m, 1 H, Pyr-H), 4.35 (s, 1 H, 3-H), 3.62 (s, 3 H, N-Me), 3.40–3.59 (m, 3 H, 2-NH, 2 × 6-H; with D_2O: m, 2 H), 2.87–2.96 (m, 1 H, 5-H), 2.75–2.88 (m, 1 H, 5-H), 1.60 (br. s, 1 H, 4-H, exch. D_2O), 1.21 (s, 9 H, *t*Bu) ppm. ^{13}C NMR APT (100 MHz, $CDCl_3$): δ = 153.8 (C), 130.1 (C), 124.1 (CH), 110.6 (CH), 106.6 (CH), 54.0 (CH), 50.6 (C), 46.9 (CH_2), 42.7 (CH_2), 34.4 (CH_3), 29.1 (CH_3) ppm. HRMS: calcd. for $C_{13}H_{22}N_4$ [M + H]$^+$ 235.1917; found 235.1906.

***N*-*tert*-Butyl-3-pyridin-2-yl-3,4,5,6-tetrahydropyrazin-2-amine Hydrochloride (Table 3, entry 15):** This compound was produced through the MCR of ethylenediamine, pyridine-2-carbaldehyde, and *tert*-butyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.09 (br. s, 1 H, 1-H), 9.00 (br. s, 1 H, 2-NH), 8.45–8.51 (m, 1 H, Py-H), 8.22 (br. s, 0.65 H, impurity), 7.80–7.88 (m, 1 H, Py-H), 7.52–7.58 (m, 1 H, Py-H), 7.30–7.36 (m, 1 H, Py-H), 5.09 (s, 1 H, 3-H), 3.53 (br. s, 1 H, 4-H), 3.24–3.41 (m, 1 H, 6-H), 3.08–3.18 (m, 1 H, 6-H), 2.75–2.86 (m, 1 H, 5-H), 2.56–2.66 (m, 1 H, 5-H), 1.39 (s, 9 H, *t*Bu), 1.25 (s, 1.60 H, impurity) ppm. HRMS: calcd. for $C_{13}H_{20}N_4$ [M + H]$^+$ 233.1761; found 233.1763.

***N*-*tert*-Butyl-3-pyridin-3-yl-3,4,5,6-tetrahydropyrazin-2-amine (Table 3, entry 16):** This compound was produced through the MCR of ethylenediamine, pyridine-3-carbaldehyde, and *tert*-butyl isocyanide. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54–8.61 (m, 2 H, 2 × Py-H), 7.71 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, Py-H), 7.28–7.34 (m, 1 H, Py-H), 4.27 (s, 1 H, 3-H), 3.53–3.67 (m, 2 H, 2 × 6-H), 3.22 (br. s, 1 H, 2-NH, exch. D_2O), 2.77–2.90 (m, 2 H, 2 × 5-H), 1.89 (br. s, 1 H, 4-H, exch. D_2O), 1.27 (s, 9 H, *t*Bu) ppm. ^{13}C NMR APT (100 MHz, $CDCl_3$): δ = 153.5 (C), 150.3 (CH), 149.5 (CH), 136.9 (C), 136.3 (CH), 123.8 (CH), 57.0 (CH), 51.1 (C), 46.5 (CH_2), 40.3 (CH_2), 29.1 (CH_3) ppm. HRMS: calcd. for $C_{13}H_{20}N_4$ [M + H]$^+$ 233.1761; found 233.1759.

***N*-*tert*-Butyl-3-pyridin-4-yl-3,4,5,6-tetrahydropyrazin-2-amine Hydrochloride (Table 3, entry 17):** This compound was produced through the MCR of ethylenediamine, pyridine-4-carbaldehyde, and *tert*-butyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.47 (br. s, 1 H, 1-H), 9.31 (br. s, 1 H, 2-NH), 8.56 (m, 2 H, 2 × Py-H), 8.22 (br. s, 0.57 H, impurity), 7.28 (m, 2 H, 2 × Py-H), 5.11 (s, 1 H, 3-H), 3.25–3.39 (m, 1 H, 6-H), 3.00–3.11 (m, 1 H, 6-H), 2.76–2.90 (m, 1 H, 5-H), 2.50–2.62 (m, 1 H, 5-H), 1.40 (s, 9 H, *t*Bu), 1.21 (s, 1.67 H, impurity) ppm. HRMS: calcd. for $C_{13}H_{20}N_4$ [M + H]$^+$ 233.1761; found 233.1761.

***N*-*tert*-Butyl-1′*H*-spiro[cyclohexane-1,2′-quinoxalin]-3′-amine Hydrochloride (Table 4, entry 1):** This compound was produced through the MCR of 1,2-phenylenediamine, cyclohexanone, and *tert*-butyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.54 (br. s, 1 H, 4-H), 8.14 (br. s, 1 H, 3-NH), 7.78 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ar-H), 7.15 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ar-H), 7.05 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ar-H), 6.79 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ar-H), 6.46 (br. s, 1 H, 1-H), 1.86–1.98 (m, 2 H, 2′-H, 6′-H), 1.50–1.78 (m, 7 H, 2′-H, 2 × 3′-H, 4′-H, 2 × 5′-H, 6′-H), 1.56 (s, 9 H, *t*Bu), 1.18–1.32 (m, 1 H, 4′-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 158.4, 133.6, 126.6, 123.8, 119.0, 118.8, 116.0, 55.7, 54.7, 29.7, 28.1, 24.5, 19.9 ppm. HRMS: calcd. for $C_{17}H_{25}N_3$ [M + H]$^+$ 272.2121; found 272.2125.

***N*-Benzyl-1′*H*-spiro[cyclohexane-1,2′-quinoxalin]-3′-amine Hydrochloride (Table 4, entry 2):** This compound was produced through the MCR of 1,2-phenylenediamine, cyclohexanone, and benzyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.04 (br. s, 1 H, 4-H), 10.06 (br. t, $^3J_{H,H}$ = 5.9 Hz, 1 H, 3-NH), 7.49 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar-H), 7.30–7.46 (m, 5 H, 5 × Ar-H), 7.12 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 7.02 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 6.76 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 6.48 (br. s, 1 H, 1-H), 4. 97 (d, $^3J_{H,H}$ = 5.9 Hz, 2 H, $PhCH_2N$), 1.80–1.92 (m, 2 H, 2′-H, 6′-H), 1.62–1.79 (m, 5 H, 2 × 3′-H, 4′-H, 2 × 5′-H), 1.50–1.60 (m, 2 H, 2′-H, 6′-H), 1.12–1.28 (m, 1 H, 4′-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 160.7, 135.9, 133.8, 129.1, 128.2, 127.8, 126.5, 123.8, 119.1, 117.9, 115.8, 54.9, 45.7, 30.8, 24.8, 19.6 ppm. HRMS: calcd. for $C_{20}H_{23}N_3$ [M + H]$^+$ 306.1965; found 306.1967.

Methyl *N*-1′*H*-Spiro[cyclohexane-1,2′-quinoxalin]-3′-ylglycinate Hydrochloride (Table 4, entry 3): This compound was produced through the MCR of 1,2-phenylenediamine, cyclohexanone, and methyl isocyanoacetate. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.14 (br. s, 1 H, 4-H), 9.85 (br. t, $^3J_{H,H}$ = 5.1 Hz, 1 H, 3-NH), 7.43 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ar-H), 7.13 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ar-H), 7.04 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ar-H), 6.77 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ar-H), 6.51 (br. s, 1 H, 1-H), 4.59 (d, $^3J_{H,H}$ = 5.1 Hz, 2 H, COCH$_2$N), 3.72 (s, 3 H, OMe), 1.45–1.90 (m, 9 H, 2×2′-H, 2×3′-H, 4′-H, 2×5′-H, 2×6′-H), 1.10–1.30 (m, 1 H, 4′-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 168.1, 161.3, 133.9, 126.7, 123.9, 119.1, 118.0, 115.8, 55.0, 52.9, 44.6, 30.8, 24.8, 19.6 ppm. HRMS: calcd. for $C_{16}H_{21}N_3O_2$ [M + H]$^+$ 288.1706; found 288.1710.

***N*-*tert*-Butyl-2,3,5,6-tetrahydro-1′*H*-spiro[pyran-4,2′-quinoxalin]-3′-amine Hydrochloride (Table 4, entry 4):** This compound was produced through the MCR of 1,2-phenylenediamine, tetrahydro-4*H*-pyran-4-one, and *tert*-butyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 10.76 (br. s, 1 H, 4-H), 8.21 (br. s, 1 H, 3-NH), 7.86 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar-H), 7.19 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 7.04–7.10 (m, 1 H, Ar-H), 6.93 (br. s, 1 H, 1-H), 6.78–6.84 (m, 1 H, Ar-H), 3.78–3.88 (m, 2 H, 2′-H, 6′-H), 3.68–3.75 (m, 2 H, 2′-H, 6′-H), 2.14–2.25 (m, 2 H, 3′-H, 5′-H), 1.56 (s, 9 H, *t*Bu), 1.47–1.54 (m, 2 H, 3′-H, 5′-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 156.2, 133.2, 126.6, 123.9, 119.3, 119.0, 116.3, 61.4, 56.0, 52.8, 30.0, 28.1 ppm. HRMS: calcd. for $C_{16}H_{23}N_3O$ [M + H]$^+$ 274.1914; found 274.1918.

***N*-*tert*-Butyl-2′,3′,5′,6′-tetrahydro-1*H*-spiro[quinoxaline-2,4′-thiopyran]-3-amine Hydrochloride (Table 4, entry 5):** This compound was produced through the MCR of 1,2-phenylenediamine, tetrahydro-4*H*-thiopyran-4-one, and *tert*-butyl isocyanide. ^{1}H NMR: (400 MHz, [D$_6$]DMSO): δ = 10.73 (br. s, 1 H, 4-H), 8.26 (br. s, 1 H, 3-NH), 7.85 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar-H), 7.23 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar-H), 7.04–7.09 (m, 1 H, Ar-H), 6.79–6.84 (m, 1 H, Ar-H), 6.71 (br. s, 1 H, 1-H), 3.07–3.18 (m, 2 H, 2′-H, 6′-H), 2.41–2.48 (m, 2 H, 2′-H, 6′-H), 2.17–2.28 (m, 2 H, 3′-H, 5′-H), 1.87–1.95 (m, 2 H, 3′-H, 5′-H), 1.56 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 157.4, 132.8, 126.8, 123.7, 119.5, 118.9, 116.2, 56.1, 53.9, 30.8, 28.2, 21.6 ppm. HRMS: calcd. for $C_{16}H_{23}N_3S$ [M + H]$^+$ 290.1685; found 290.1687.

***N*-*tert*-Butyl-6-(4-isopropylphenyl)-6,7-dihydro-[1,2,5]oxadiazolo-[3,4-*b*]pyrazin-5-amine Hydrochloride (Table 4, entry 6):** This compound was produced through the MCR of [1,2,5]oxadiazole-3,4-diamine, 4-isopropylbenzaldehyde, and *tert*-butyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.09 (br. s, 1 H, 4-H), 7.93 (br. s, 1 H, 5-NH), 7.88 (br. s, 1 H, 7-H), 7.22 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2×Ar-H), 7.14 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2×Ar-H), 5.13 (s, 1 H, 6-H), 2.80–2.87 (m, 1 H, CH of *i*Pr), 1.39 (s, 9 H, *t*Bu), 1.15 (d, $^3J_{H,H}$ = 7.0 Hz, 6 H, 2×Me of *i*Pr) ppm. ^{13}C NMR (125 MHz, [D$_6$]-DMSO): δ = 161.1, 152.2, 148.2, 147.2, 137.8, 126.7, 126.1, 54.5, 52.3, 33.0, 27.1, 23.8 ppm. HRMS: calcd. for $C_{17}H_{23}N_5O$ [M + H]$^+$ 314.1975; found 314.1977.

***N*-Benzyl-6-(4-isopropylphenyl)-6,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]-pyrazin-5-amine Hydrochloride (Table 4, entry 7):** This compound was produced through the MCR of [1,2,5]oxadiazole-3,4-diamine, 4-isopropylbenzaldehyde, and benzyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.78 (br. t, $^3J_{H,H}$ = 5.9 Hz, 1 H, 5-NH), 7.96 (br. s, 1 H, 4-H), 7.88 (br. s, 1 H, 7-H), 7.16–7.29 (m, 9 H, 9 Ar-H), 5.22 (s, 1 H, 6-H), 4.53 (d, $^3J_{H,H}$ = 5.9 Hz, 2 H, PhCH$_2$N), 2.79–2.86 (m, 1 H, CH of *i*Pr), 1.17 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H, 2×Me of *i*Pr) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 162.3, 152.1, 148.6, 147.2, 138.2, 137.9, 128.3, 127.4, 127.0, 126.7, 126.3, 54.9, 43.6, 33.1, 23.8 ppm. HRMS: calcd. for $C_{20}H_{21}N_5O$ [M + H]$^+$ 348.1819; found 348.1827.

4-[6-(Cyclohexylamino)-4,5-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyrazin-5-yl]phenol Hydrochloride (Table 4, entry 8): This compound was produced through the MCR of [1,2,5]oxadiazole-3,4-diamine, 4-hydroxybenzaldehyde, and cyclohexyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.43 (br. d, $^3J_{H,H}$ = 7.0 Hz, 1 H, 6-NH), 7.87 (br. s, 1 H, 7-H), 7.03 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, 2×Ar-H), 6.71 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, 2×Ar-H), 6.38 (very brs, 2 H, 4-H, OH), 5.09 (s, 1 H, 5-H), 3.81–3.93 (m, 1 H, NCH of cyclohexyl), 1.83–1.95 (m, 1 H), 1.48–1.79 (m, 4 H), 1.00–1.30 (m, 5 H) (5×CH$_2$ of cyclohexyl) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.8, 158.0, 152.3, 148.0, 131.3, 128.0, 116.1, 55.0, 50.0, 32.3, 32.0, 25.7, 25.1, 24.9 ppm. HRMS: calcd. for $C_{16}H_{19}N_5O_2$ [M + H]$^+$ 314.1611; found 314.1611.

4-{6-[(2-Chlorobenzyl)amino]-4,5-dihydro[1,2,5]oxadiazolo[3,4-*b*]-pyrazin-5-yl}phenol Hydrochloride (Table 4, entry 9): This compound was produced through the MCR of [1,2,5]oxadiazole-3,4-diamine, 4-hydroxybenzaldehyde, and 2-chlorobenzyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.62 (br. d, $^3J_{H,H}$ = 5.5 Hz, 1 H, 6-NH), 7.85 (br. s, 1 H, 7-H), 7.42 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.1 Hz, 1 H, Ar-H), 7.25–7.30 (m, 1 H, Ar-H), 7.18–7.24 (m, 1 H, Ar-H), 7.14 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.5 Hz, 1 H, Ar-H), 7.05 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2×Ar-H), 6.74 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2×Ar-H), 5.19 (s, 1 H, 6-H), 4.61 (dd, $^2J_{H,H}$ = 15.8, $^3J_{H,H}$ = 5.5 Hz, 1 H), 4.52 (dd, $^2J_{H,H}$ = 15.8, $^3J_{H,H}$ = 5.5 Hz, 1 H) (ArCH$_2$N) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 163.5, 158.1, 152.6, 147.9, 135.8, 132.9, 131.5, 130.0, 129.9, 129.6, 128.3, 127.7, 116.1, 55.3, 42.3 ppm. HRMS: calcd. for $C_{17}H_{14}ClN_5O_2$ [M + H]$^+$ 356.0909; found 356.0904.

***N*-*tert*-Butyl-7,11-diazaspiro[5.6]dodec-11-en-12-amine Hydrochloride (Table 5, entry 1):** This compound was produced through the MCR of propane-1,3-diamine, cyclohexanone, and *tert*-butyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.06 (br. t, $^3J_{H,H}$ = 4.5 Hz, 1 H, 11-H), 7.41 (br. s, 1 H, 12-NH), 3.75–3.79 (m, 2 H, 2×10-H), 2.82 (br. t, $^3J_{H,H}$ = 6.0 Hz, 1 H, 7-H), 2.72–2.80 (m, 2 H, 2×8-H), 1.81–1.91 (m, 2 H, 2×9-H), 1.67–1.76 (m, 4 H, 2×1-H, 2×5-H), 1.29–1.64 (m, 6 H, 2×2-H, 2×3-H, 2×4-H), 1.40 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 172.9, 61.7, 54.1, 42.5, 32.3, 29.9, 28.4, 28.3, 24.1, 21.0 ppm. HRMS: calcd. for $C_{14}H_{27}N_3$ [M + H]$^+$ 238.2278; found 238.2285.

***N*-Cyclopentyl-7,11-diazaspiro[5.6]dodec-11-en-12-amine Hydrochloride (Table 5, entry 2):** This compound was produced through the MCR of propane-1,3-diamine, cyclohexanone, and cyclopentyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.96 (br. s, 1 H, 11-H), 8.29 (br. d, $^3J_{H,H}$ = 6.8 Hz, 1 H, 12-NH), 3.97–4.07 (m, 1 H, NCH of cyclohexyl), 3.55–3.65 (m, 2 H, 2×10-H), 2.72–2.85 (m, 3 H, 7-H, 2×8-H), 1.25–1.98 (m, 20 H, 2×9-H, 10×1–5-H, 4×CH$_2$ of cyclohexyl) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 173.2, 60.9, 54.0, 41.7, 39.5, 32.5, 31.6, 30.0, 24.3, 24.2, 20.9 ppm. HRMS: calcd. for $C_{15}H_{27}N_3$ [M + H]$^+$ 250.2278; found 250.2277.

***N*-Benzyl-7,11-diazaspiro[5.6]dodec-11-en-12-amine Hydrochloride (Table 5, entry 3):** This compound was produced through the MCR of propane-1,3-diamine, cyclohexanone, and benzyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.41 (br. t, $^3J_{H,H}$ = 5.7 Hz, 1 H, 12-NH), 9.06 (br. t, 1 H, 11-H), 7.24–7.38 (m, 5 H, Ar-H), 4.56 (d, $^3J_{H,H}$ = 5.7 Hz, 2 H, PhCH$_2$N), 3.50–3.57 (m, 2 H, 2×10-H), 2.87 (br. t, $^3J_{H,H}$ = 6.1 Hz, 1 H, 7-H), 2.76–2.83 (m, 2 H, 2×8-H), 1.40–1.92 (m, 11 H, 2×9-H, 2×1-H, 2×2-H, 3-H, 2×4-H, 2×5-H), 1.21–1.33 (m, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 173.9, 136.2, 128.9, 127.9, 127.5, 61.1, 44.8, 41.9, 32.8,

30.0, 24.6, 20.9 ppm. HRMS: calcd. for $C_{17}H_{25}N_3$ [M + H]$^+$ 272.2121; found 272.2125.

***N*-(4-Chlorobenzyl)-7,11-diazaspiro[5.6]dodec-11-en-12-amine Hydrochloride (Table 5, entry 4):** This compound was produced through the MCR of propane-1,3-diamine, cyclohexanone, and 4-chlorobenzyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.45 (br. s, 1 H, 12-NH), 9.15 (br. s, 1 H, 11-H), 7.41 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 2 × Ar-H), 7.36 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 2 × Ar-H), 4.57 (s, 2 H, PhCH_2N), 3.49–3.56 (m, 2 H, 2 × 10-H), 2.74–2.87 (m, 3 H, 7-H, 2 × 8-H), 1.75–1.92 (m, 4 H), 1.38–1.74 (m, 7 H), 1.20–1.33 (m, 1 H) (6 × CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 173.7, 135.4, 132.5, 129.6, 128.8, 61.1, 44.2, 41.9, 32.8, 30.0, 24.6, 20.9 ppm. HRMS: calcd. for $C_{17}H_{24}ClN_3$ [M + H]$^+$ 306.1731; found 306.1733.

***N*-Cyclohexyl-3-thia-7,11-diazaspiro[5.6]dodec-11-en-12-amine Hydrochloride (Table 5, entry 5):** This compound was produced through the MCR of propane-1,3-diamine, tetrahydro-4*H*-thiopyran-4-one, and cyclohexyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 9.22 (br. m, 1 H, 11-H), 8.22 (br. d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 12-NH), 3.70–3.75 (m, 1 H, NCH of cyclohexyl), 3.55–3.63 (m, 2 H, 2 × 10-H), 2.97–3.08 (m, 3 H, 7-H, 2 × 8-H), 2.74–2.82 (m, 2 H, 2-H, 4-H), 2.25–2.34 (m, 2 H, 2-H, 4-H), 2.07–2.17 (m, 2 H, 1-H, 5-H), 1.96–2.04 (m, 2 H, 1-H, 5-H), 1.52–1.79 (m, 7 H), 1.23–1.41 (m, 4 H), 0.98–1.11 (m, 1 H) (6 × CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 171.3, 60.5, 51.7, 41.1, 38.9, 33.2, 31.3, 29.7, 25.2, 24.8, 22.3 ppm. HRMS: calcd. for $C_{15}H_{27}N_3S$ [M + H]$^+$ 282.1998; found 282.1995.

***tert*-Butyl 12-(Cyclohexylamino)-3,7,11-triazaspiro[5.6]dodec-11-ene-3-carboxylate Hydrochloride (Table 5, entry 6):** This compound was produced through the MCR of propane-1,3-diamine, *N*-Boc-piperidin-4-one, and cyclohexyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.24 (br. m, 1 H, 11-H), 8.01 (br. d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 12-NH), 3.64–3.85 (m, 3 H, 2-H, 4-H, NCH of cyclohexyl), 3.57–3.63 (m, 2 H, 2 × 10-H), 2.88–3.10 (m, 3 H, 7-H, 2 × 8-H), 2.75–2.85 (m, 2 H, 2-H, 4-H), 1.50–1.94 (m, 11 H), 1.18–1.36 (m, 4 H), 0.98–1.11 (m, 1 H) (8 × CH_2), 1.37 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 171.1, 154.2, 79.2, 59.4, 51.8, 41.6, 32.1, 31.3, 29.9, 28.6, 25.2, 24.8 ppm. HRMS: calcd. for $C_{20}H_{36}N_4O_2$ [M + H]$^+$ 365.2911; found 365.2913.

***N*-Cyclohexyl-2-(4-methoxyphenyl)-2,5,6,7-tetrahydro-1*H*-1,4-diazepin-3-amine Hydrochloride (Table 5, entry 7):** This compound was produced through the MCR of propane-1,3-diamine, 4-methoxybenzaldehyde, and cyclohexyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.78 (br. m, 1 H, 4-H), 9.52 (br. d, approx. $^3J_{H,H}$ = 5 Hz, 1 H, 3-NH), 7.16 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 2 × Ar-H), 6.99 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 2 × Ar-H), 5.21 (d, $^3J_{H,H}$ = 3.9 Hz, 1 H, 2-H), 3.76–3.85 (m, 1 H, NCH of cyclohexyl), 3.74 (s, 3 H, OMe), 3.62–3.68 (m, 1 H, 5-H), 3.39–3.48 (m, 1 H, 5-H), 2.90–3.00 (m, 1 H, 7-H), 2.75–2.83 (m, 1 H, 7-H), 2.60–2.70 (br. m, 1 H, 1-H), 1.84–1.96 (m, 2 H, 2 × 6-H), 1.64–1.75 (m, 2 H), 1.04–1.61 (m, 8 H) (5 × CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 167.1, 159.2, 128.3, 126.8, 114.9, 61.3, 55.6, 51.4, 43.2, 42.8, 31.6, 31.5, 29.8, 25.2, 24.6, 24.5 ppm. HRMS: calcd. for $C_{18}H_{27}N_3O$ [M + H]$^+$ 302.2227; found 302.2228.

***N*-Cyclohexyl-2-(1-methyl-1*H*-pyrrol-2-yl)-2,5,6,7-tetrahydro-1*H*-1,4-diazepin-3-amine Hydrochloride (Table 5, entry 8):** This compound was produced through the MCR of propane-1,3-diamine, 1-methyl-pyrrole-2-carbaldehyde, and cyclohexyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.58 (br. s, 1 H, 4-H), 9.31 (br. d, $^3J_{H,H}$ = 6.3 Hz, 1 H, 3-NH), 6.78–6.80 (m, 1 H, Pyr-H), 5.93–5.96 (m, 1 H, Pyr-H), 5.83–5.85 (m, 1 H, Pyr-H), 5.30 (d, $^3J_{H,H}$ = 2.5 Hz, 1 H, 2-H), 3.64–3.78 (m, 1 H, NCH of cyclohexyl), 3.60 (s, 3 H, N-Me), 3.42–3.58 (m, 2 H, 1-H, 5-H), 3.23–3.31 (m, 1 H, 5-H), 2.77–2.87 (m, 1 H, 7-H), 2.32–2.43 (m, 1 H, 7-H), 1.79–1.89 (m, 2 H, 2 × 6-H), 1.47–1.73 (m, 5 H), 1.24–1.38 (m, 3 H), 1.04–1.17 (m, 2 H) (5 × CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 167.5, 124.7, 124.6, 109.3, 106.9, 57.4, 51.1, 44.2, 43.3, 34.5, 31.5, 31.2, 30.6, 25.2, 24.5, 24.4 ppm. HRMS: calcd. for $C_{16}H_{26}N_4$ [M + H]$^+$ 275.2230; found 275.2231.

***N*-(1,1,3,3-Tetramethylbutyl)-3-thia-7,11-diazaspiro[5.6]dodec-11-en-12-amine Hydrochloride (Table 5, entry 9):** This compound was produced through the MCR of propane-1,3-diamine, tetrahydro-4*H*-thiopyran-4-one, and 1,1,3,3-tetramethylbutyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.85 (br. m, 1 H, 11-H), 7.55 (br. s, 1 H, 12-NH), 3.74–3.81 (m, 2 H, 2 × 10-H), 2.99–3.14 (m, 3 H, 7-H, 2 × 8-H), 2.73–2.81 (m, 2 H, 2-H, 4-H), 2.19–2.34 (m, 4 H, 2-H, 4-H, 1-H, 5-H), 1.94–2.01 (m, 2 H, 1-H, 5-H), 1.81 (s, 2 H, 2 × 2-H of TMB), 1.70–1.78 (m, 2 H, 2 × 9-H), 1.43 (s, 6 H, 2 × 1-Me of TMB), 0.94 (s, 9 H, 3 × 3-Me of TMB) ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20 (br. t, $^3J_{H,H}$ = 4.9 Hz, 1 H, 11-H), 5.86 (br. s, 1 H, 12-NH), 4.19–4.26 (m, 2 H, 2 × 10-H), 3.20–3.30 (m, 2 H, 2 × 8-H), 2.95–3.03 (m, 2 H, 2-H, 4-H), 2.33–2.42 (m, 4 H, 1-H, 2-H, 4-H, 5-H), 2.26 (br. t, $^3J_{H,H}$ = 6.1 Hz, 1 H, 7-H), 1.95 (s, 2 H, 2 × 2-H of TMB), 1.80–1.91 (m, 4 H, 1-H, 5-H, 2 × 9-H), 1.67 (s, 6 H, 2 × 1-Me of TMB), 1.05 (s, 9 H, 3 × 3-Me of TMB) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 172.0, 61.5, 58.5, 49.6, 42.2, 38.9, 32.8, 31.4, 29.5, 22.3 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 61.6, 59.4, 52.8, 43.2, 40.3, 35.1, 31.9, 31.8, 29.9, 28.6, 23.0 ppm. HRMS: calcd. for $C_{17}H_{33}N_3S$ [M + H]$^+$ 312.2468; found 312.2468.

2-(1-Methyl-1*H*-pyrrol-2-yl)-*N*-(1,1,3,3-tetramethylbutyl)-2,5,6,7-tetrahydro-1*H*-1,4-diazepin-3-amine Hydrochloride (Table 5, entry 10): This compound was produced through the MCR of propane-1,3-diamine, 1-methylpyrrole-2-carbaldehyde, and 1,1,3,3-tetramethylbutyl isocyanide. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.76 (br. s, 1 H, 4-H), 8.41 (br. s, 1 H, 3-NH), 6.78–6.81 (m, 1 H, Pyr-H), 5.95–5.99 (m, 1 H, Pyr-H), 5.84–5.87 (m, 1 H, Pyr-H), 5.48 (s, 1 H, 2-H), 3.70–3.80 (m, 1 H, 5-H), 3.59 (s, 3 H, N-Me), 3.52–3.64 (m, 1 H, 5-H), 3.22–3.28 (m, 1 H, 7-H), 2.78–2.87 (m, 1 H, 7-H), 2.39–2.46 (br. m, 1 H, 1-H), 1.97 (d, $^2J_{H,H}$ = 15.2 Hz, 1 H, 2-H of TMB), 1.46–1.70 (m, 2 H, 2 × 6-H), 1.56 (d, $^2J_{H,H}$ = 15.2 Hz, 1 H, 2-H of TMB), 1.42 (s, 3 H, 1-Me of TMB), 1.41 (s, 3 H, 1-Me of TMB), 0.95 (s, 9 H, 3 × 3-Me of TMB) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 167.3, 124.8, 124.7, 109.4, 107.0, 58.1, 57.7, 50.2, 44.8, 43.9, 34.5, 31.8, 31.5, 30.3, 28.9, 28.1 ppm. HRMS: calcd. for $C_{18}H_{32}N_4$ [M + H]$^+$ 305.2700; found 305.2705.

***tert*-Butyl 5-[(1,1,3,3-Tetramethylbutyl)amino]-1,4,9-triazaspiro[5.5]undec-4-ene-9-carboxylate Hydrochloride (28):** This compound was produced through the MCR of ethylenediamine, *N*-Boc-piperidin-4-one, and 1,1,3,3-tetramethylbutyl isocyanide, General procedure B, yield 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.08 (br. s, 1 H, 4-H, exch. D_2O), 5.85 (br. s, 1 H, 5-NH, exch. D_2O), 3.85–4.05 (m, 2 H, 8-H, 10-H), 3.78 (t, $^3J_{H,H}$ = 4.8 Hz, 2 H, 2 × 3-H), 3.16–3.32 (m, 2 H, 8-H, 10-H), 3.03 (t, $^3J_{H,H}$ = 4.8 Hz, 2 H, 2 × 2-H), 2.40 (br. s, exch. D_2O, 1 H, 1-H), 1.92–2.05 (m, 4 H, 7-H, 11-H, 2 × 2-H of TMB), 1.61–1.76 (m, 2 H, 7-H, 11-H), 1.67 (s, 6 H, 2 × 1-Me of TMB), 1.46 (s, 9 H, *t*Bu), 1.05 (s, 9 H, 3 × 3-Me of TMB) ppm. ^{13}C NMR APT (100 MHz, $CDCl_3$): δ = 164.9 (C), 154.7 (C), 80.3 (C), 58.8 (C), 55.0 (CH_2), 52.2 (CH_2), 42.8 (C), 36.5 (CH_2), 33.8 (C), 32.0 (CH_2), 31.8 (CH_3), 29.0 (CH_3), 28.6 (CH_3) ppm. HRMS: calcd. for $C_{21}H_{40}N_4O_2$ [M + H]$^+$ 381.3224; found 381.3219.

General Procedure for the MCR/de-Boc Sequence of 1,2-Phenylenediamine, *N*-Boc-piperidin-4-one, and Isocyanides: A mixture of 1,2-

phenylenediamine (21.6 g, 0.2 mol), *N*-Boc-piperidin-4-one (39.8 g, 0.2 mol), and CH_2Cl_2 (800 mL) was stirred for 2 h at ambient temperature, solvent was removed under reduced pressure, the oily residue was treated with hexane, and the resulting mixture was stirred to form a semi-solid precipitate. The solvent was removed by decantation and the precipitate was dried on a rotary evaporator to remove residual solvent and dissolved in CH_3CN (1500 mL). TMSCl (21.7 g, 0.2 mol) was added dropwise to the obtained solution, the mixture was stirred for 1 h, isocyanide (0.2 mol) was added in one portion, and the resulting mixture was stirred at 50 °C for 5 h and allowed to cool. The formed precipitate was filtered off, washed with CH_3CN and Et_2O, dried, and added portionwise to a stirred solution of HCl in EtOH/EtOAc (6 M, 200 mL, preliminarily prepared from AcCl and EtOH). The reaction mixture was stirred at ambient temperature for 1 h to allow the reaction to go to completion (LC-MS monitoring). The residue after solvent removal was dissolved in water, aq. NaOH (2 N) was added to achieve pH 9, and the mixture was extracted with $CHCl_3$. The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated. After residue sonification with an excess of hexane, a precipitate was filtered off and washed with hexane. The following are data for spiro-piperazines obtained by this procedure.

***N*-Cycloheptyl-1′*H*-spiro[piperidine-4,2′-quinoxalin]-3′-amine (27a):** Yield 51.2 g (82%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.74 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 6.66 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 6.57 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 6.45 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 5.94 (br. d, $^3J_{H,H}$ = 7.3 Hz, 1 H, 3′-NH), 5.71 (br. s, 1 H, 1′-H), 3.95–4.04 (m, 1 H, NCH of cycloheptyl), 2.74–2.85 (m, 2 H, 2-H, 5-H), 2.55–2.64 (m, 2 H, 2-H, 5-H), 1.85 (br. s, 1 H, 1-H), 1.26–1.83 (m, 16 H, 8 × CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 158.2, 135.9, 135.7, 122.9, 122.1, 118.3, 114.1, 51.3, 51.0, 40.8, 34.5, 32.3, 28.6, 24.7 ppm. HRMS: calcd. for $C_{19}H_{28}N_4$ [M + H]$^+$ 313.2387; found 313.2387.

***N*-(2-Methylbenzyl)-1′*H*-spiro[piperidine-4,2′-quinoxalin]-3′-amine (27b):** Yield 46.1 g (72%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.18 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, Ar-H), 7.03–7.11 (m, 3 H, 3 × Ar-H), 6.85 (br. t, $^3J_{H,H}$ = 5.5 Hz, 1 H, 3′-NH), 6.77 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 6.64 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 6.59 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 6.45 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar-H), 5.80 (br. s, 1 H, 1′-H), 4.40 (d, $^3J_{H,H}$ = 5.5 Hz, 2 H, NCH_2Ar), 2.78–2.88 (m, 2 H, 2-H, 5-H), 2.59–2.67 (m, 2 H, 2-H, 5-H), 2.28 (s, 3 H, Me), 1.94 (br. s, 1 H, 1-H), 1.69–1.78 (m, 2 H, 3-H, 5-H), 1.38–1.45 (m, 2 H, 3-H, 5-H) ppm. ^{13}C NMR: (100 MHz, [D$_6$]DMSO): δ = 159.1, 138.8, 136.0, 135.9, 135.5, 130.3, 127.8, 126.9, 126.2, 123.0, 122.4, 118.3, 114.2, 51.6, 42.0, 40.7, 32.7, 19.4 ppm. HRMS: calcd. for $C_{20}H_{24}N_4$ [M + H]$^+$ 321.2074; found 321.2074.

***N*-(2-Chlorobenzyl)-1′*H*-spiro[piperidine-4,2′-quinoxalin]-3′-amine (27c):** Yield 51.0 g (75%). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.37 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, Ar-H), 7.17–7.27 (m, 3 H, 3 × Ar-H), 7.02 (br. t, $^3J_{H,H}$ = 5.5 Hz, 1 H, 3′-NH), 6.78 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, Ar-H), 6.58–6.65 (m, 2 H, 2 × Ar-H), 6.44 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, Ar-H), 5.86 (br. s, 1 H, 1′-H), 4.50 (d, $^3J_{H,H}$ = 5.5 Hz, 2 H, NCH_2Ar), 2.81–2.90 (m, 2 H, 2-H, 5-H), 2.63–2.69 (m, 2 H, 2-H, 5-H), 2.24 (br. s, 1 H, 1-H), 1.72–1.81 (m, 2 H, 3-H, 5-H), 1.43–1.50 (m, 2 H, 3-H, 5-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 159.1, 138.0, 135.9, 135.3, 132.5, 129.6, 128.9, 128.7, 127.6, 123.1, 122.7, 118.3, 114.2, 51.6, 41.8, 40.6, 32.6 ppm. HRMS: calcd. for $C_{19}H_{21}ClN_4$ [M + H]$^+$ 341.1527; found 341.1521.

Procedures for Selective Cleavage of the Boc Group in Spiro Compound 28. Synthesis of *N*-(1,1,3,3-Tetramethylbutyl)-1,4,9-triazaspiro[5.5]undec-4-en-5-amine Trihydrochloride (30)

TFA-Induced Cleavage: A mixture of compound **28** (208 mg, 0.5 mmol), CH_2Cl_2 (2 mL), and TFA (1 mL) was stirred overnight and the solvents were evaporated to dryness under reduced pressure. The residue was dissolved in THF and treated with an excess of HCl in dioxane (8 M) and then with Et_2O. The white precipitate was separated by centrifugation, washed with acetonitrile and then EtOAc, followed each time by centrifugation, and dried. Yield 160 mg (86%) of compound **30**.

HCl-Induced Cleavage: A mixture of compound **28** (208 mg, 0.5 mmol) and of HCl in EtOAc/EtOH (6 M, 2 mL, prepared from AcCl and EtOH) was stirred for 2 h and then treated with an excess of Et_2O. The white precipitate was centrifuged, washed with Et_2O, acetonitrile, and EtOAc, and dried. Yield 170 mg (92%) of compound **30**.

Data for Compound 30: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.47 (br. m, 1 H, N–H, exch. D_2O), 9.22 (br. s, 1 H, N–H, exch. D_2O), 9.06 (br. m, 1 H, N–H, exch. D_2O), 8.50 (br. s, 1 H, N–H, exch. D_2O), 3.65–3.75 (m, 2 H, 2 × 3-H), 3.27–3.57 (m, 6 H, 2 × 2-H, 2 × 8-H, 2 × 10-H), 3.10–3.24 (m, 2 H, 7-H, 11-H), 2.42–2.52 (m, 2 H, 7-H, 11-H), 1.83 (s, 2 H, 2 × 2-H of TMB), 1.51 (s, 6 H, 2 × 1-Me of TMB), 0.97 (s, 9 H, 3 × 3-Me of TMB) ppm. ^{13}C NMR APT (100 MHz, [D$_6$]DMSO): δ = 161.9 (C), 59.4 (C), 55.6 (CH_2), 49.4 (C), 40.0 (CH_2), 39.2 (CH_2), 35.6 (CH_2), 32.1 (CH_2), 31.6 (CH_3), 29.6 (CH_3), 28.4 (C) ppm. HRMS: calcd. for $C_{16}H_{32}N_4$ [M + H]$^+$ 281.2700; found 281.2699.

Cleavage of the TMB Group in Compounds 28 and 30. Synthesis of 1,4,9-Triazaspiro[5.5]undec-4-en-5-amine Trihydrobromide (29): A mixture of compound **28** or **30** (0.3 mmol) and HBr in AcOH (33%, 2 mL) was stirred at 80 °C for 2 h and was then treated with excess Et_2O. The resulting white precipitate was centrifuged, washed with Et_2O, acetonitrile, and EtOAc, and dried. Yields of compound **29**: 75% (from compound **28**) and 83% (from compound **30**).

Data for Compound 29: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.77 (br. s, 1 H, N–H, exch. D_2O), 9.16 (br. m, 1 H, N–H, exch. D_2O), 8.91 (br. s, 1 H, N–H, exch. D_2O), 8.78 (br. s, 1 H, N–H, exch. D_2O), 8.07 (br. m, 2 H, 2 × N–H, exch. D_2O), 7.35 (br. s, 2.2 H, N–H and H_2O, exch. D_2O), 3.41 (br. t, 2 H, 2 × 3-H), 3.23–3.36 (m, 4 H, 2 × 8-H, 2 × 10-H), 3.18 (br. t, 2 H, 2 × 2-H), 2.23–2.42 (m, 4 H, 2 × 7-H, 2 × 11-H) ppm. ^{13}C NMR APT (100 MHz, [D$_6$]-DMSO): δ = 166.3 (C), 54.7 (C), 38.1 (CH_2), 36.8 (CH_2), 36.0 (CH_2), 28.3 (CH_2) ppm. HRMS: calcd. for $C_8H_{16}N_4$ [M + H]$^+$ 169.1448; found 169.1448.

General Procedure for the Partial Oxidation of the Tetrahydropyrazine Ring (Synthesis of 5,6-Dihydropyrazine-2-amines 33 and 34): The MCRs of pyridine-2- and -4-carbaldehydes with *tert*-butyl isocyanide and ethylenediamine under the conditions of General Procedure A provided crude products (Table 3, entries 15 and 17, respectively) that were contaminated with ethylenediamine hydrochloride. Attempts to purify these compounds by their conversion into free bases as described in General Procedure A led to the target tetrahydropyrazines **31** and **32**, respectively, contaminated by dihydropyrazines **33** and **34**. These mixtures were dissolved in $CHCl_3$ and stirred overnight in open vials. Evaporation of the solvent under reduced pressure provided pure compounds **33** (55 mg, overall yield including IMCR step 48%) and **34** (43 mg, overall yield 37%).

Data for *N*-*tert*-Butyl-3-pyridin-2-yl-5,6-dihydropyrazin-2-amine (33): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, Py-H), 8.05 (br. s, 1 H, 2-NH, exch. D_2O), 8.01 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Py-H), 7.75–7.83 (m, 1 H, Py-H), 7.31–7.38 (m, 1 H,

Py-H), 3.64 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, 2 × 6-H), 3.36 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, 2 × 5-H), 1.43 (s, 9 H, *t*Bu) ppm. ^{13}C NMR APT (100 MHz, $CDCl_3$): δ = 156.3 (C), 155.9 (C), 148.7 (C), 147.1 (CH), 137.5 (CH), 124.4 (CH), 123.6 (CH), 50.9 (C), 47.9 (CH_2), 43.1 (CH_2), 28.9 (CH_3) ppm. HRMS: calcd. for $C_{13}H_{18}N_4$ [M + H]$^+$ 231.1604; found 231.1597.

Data for *N-tert*-Butyl-4-pyridin-4-yl-5,6-dihydropyrazin-2-amine (34): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, $^3J_{H,H}$ = 4.4 Hz, 2 H, 2 × Py-H), 7.50 (d, $^3J_{H,H}$ = 4.4 Hz, 2 H, 2 × Py-H), 3.90 (br. s, 1 H, 2-NH, exch. D_2O), 3.60 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, 2 × 6-H), 3.38 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, 2 × 5-H), 1.37 (s, 9 H, *t*Bu) ppm. ^{13}C NMR APT (100 MHz, $CDCl_3$): δ = 158.5 (C), 150.4 (CH), 146.9 (C), 144.0 (C), 122.7 (CH), 51.8 (C), 47.8 (CH_2), 43.2 (CH_2), 28.8 (CH_3) ppm. HRMS: calcd. for $C_{13}H_{18}N_4$ [M + H]$^+$ 231.1604; found 231.1605.

Procedure for Aromatization of the Dihydropyrazine Ring in Compound 34: A mixture of dihydropyrazine **34** (92 mg, 0.4 mmol), DDQ (182 mg, 0.8 mmol), and $CHCl_3$ (3 mL) was stirred in a sealed tube at 70 °C overnight. The reaction mixture was cooled and filtered. Purification of the concentrated filtrate by flash chromatography on silica ($CHCl_3$/THF) furnished the pyrazinamine **35** (32 mg, 35%, non-optimized yield).

Procedure for Aromatization of the Dihydropyrazine Ring in Compound 32 Hydrochloride: A mixture of the crude product obtained from the MCR (Table 3, entry 17) of pyridine-4-carbaldehyde, *tert*-butyl isocyanide, and ethylenediamine (107 mg, 0.4 mmol), together with Pd on charcoal (10%, 20 mg) and 2-methoxyethanol (5 mL), was stirred and heated under reflux overnight. The reaction mixture was filtered, the filtrate was concentrated, the residue was dissolved in $CHCl_3$, and the obtained solution was washed with aq. NaOH (10%, twice), water (twice), and then brine. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography on silica ($CHCl_3$/THF). Non-optimized yield of compound **35**: 25 mg (27%).

Data for *N-tert*-Butyl-4-pyridin-4-yl-pyrazin-2-amine (35): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, $^3J_{H,H}$ = 5.5 Hz, 2 H, 2 × Py-H), 8.02 (d, $^3J_{H,H}$ = 2.7 Hz, 1 H, 6-H), 7.87 (d, $^3J_{H,H}$ = 2.7 Hz, 1 H, 5-H), 7.58 (d, $^3J_{H,H}$ = 5.5 Hz, 2 H, 2 × Py-H), 4.77 (br. s, 1 H, 2-NH), 1.43 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0, 150.7, 145.4, 141.5, 138.3, 131.9, 122.7, 52.1, 28.9 ppm. HRMS: calcd. for $C_{13}H_{16}N_4$ [M + H]$^+$ 229.1448; found 229.1451.

Supporting Information (see also the footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR spectra for all synthesized compounds.

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