Reductive Alkylation of Hydrazine Derivatives with α-Picoline-Borane and Its Applications to the Syntheses of Useful Compounds Related to Active Pharmaceutical Ingredients

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Abstract: An efficient method for the direct reductive alkylation of hydrazine derivatives with α-picoline-borane has been developed to synthesize a variety of *N*-alkylhydrazine derivatives. This method provided *N*,*N*-dialkylhydrazine derivatives and *N*-monoalkylhydrazine derivatives upon fine-tuning of the substrates and the reagent equivalency in a one-pot manner. The method was applied to the synthesis of active pharmaceutical ingredients of therapeutic drugs such as isocarboxazid.

Key words: alkylation, hydrazones, reduction, hydrazines, α-picoline-borane

Hydrazine derivatives are widely used in the pharmaceutical, agricultural, photographic, and dyestuff industries as well as precursors for heterocyclic compounds such as pyrazoles, pyrazines, and indoles.[1] In particular, they are important compounds in the pharmaceutical field, because many compounds possessing a hydrazine moiety show various pharmacological activities and some of them are clinically used as active pharmaceutical ingredients (APIs) of therapeutic drugs (Figure 1). Atazanavir (**1**), which has a hydrazine-based peptidomimetic structure and shows potent inhibitive activity against HIV protease, is applied as a therapeutic agent against AIDS.[2] Benserazide (**2**), an acylhydrazide compound, inhibits DOPA decarboxylase to potentiate the anti-Parkinsonian effect of levodopa, and has been used as a therapeutic agent for Parkinsonism in combination with levodopa.[3] Isocarboxazid (**3**) is used as an antidepressant drug due to its monoamine oxidase inhibition.[4] *N*-Aminoazacycles, which possess an amino functionality on the nitrogen atom of cyclic amines, may also be new drug candidates.[5] For example, *N*-aminomorpholine derivative **4** has been studied as an oral-administrative antifungal agent.[5c]

For the syntheses of these APIs, highly selective and preparative methods for the N-alkylation of simple hydrazines are required.[6] Strategies for the sequent preparation and reduction of hydrazones, prepared from the corresponding hydrazines and carbonyl compounds, are usually applied for the N-alkylation of the hydrazine moieties. The isolated hydrazones are generally reduced by metal hydride reagents or by catalytic hydrogenation under the appropriate conditions.[7,8] Although these stepwise methods steadily provided the target *N*-alkylhydrazines, the methods require isolation of the hydrazones and, in some cases, highly toxic or explosive metal hydride reagents such as sodium cyanoborohydride and pyridine-borane for the reduction of the isolated hydrazones.[9] Therefore, there is still room in improvement for N-alkylation of hydrazines from a process chemistry point of view.

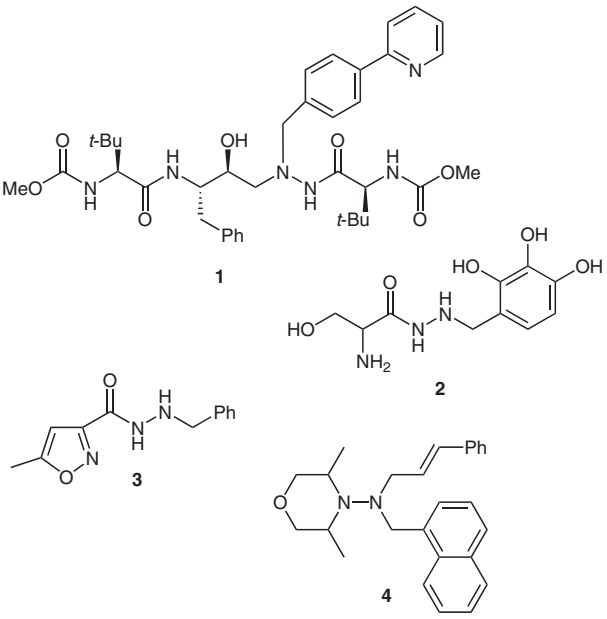

Figure 1 Hydrazine-based active pharmaceutical ingredients

To discover the method for selective N-alkylation of hydrazines applicable to the industrial processes, we considered reductive alkylation of hydrazines with carbonyl compounds using a stable and nontoxic metal hydride reagent.[9] The reductive alkylation can be conducted in a one-pot manner without isolation of hydrazones and should have some merits for the industrial preparation of *N*-alkylhydrazines on a large scale. We have recently reported on a safe and scalable procedure for the preparation

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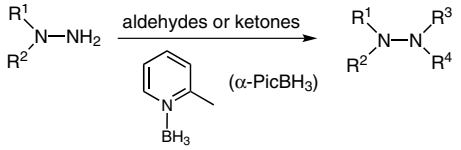
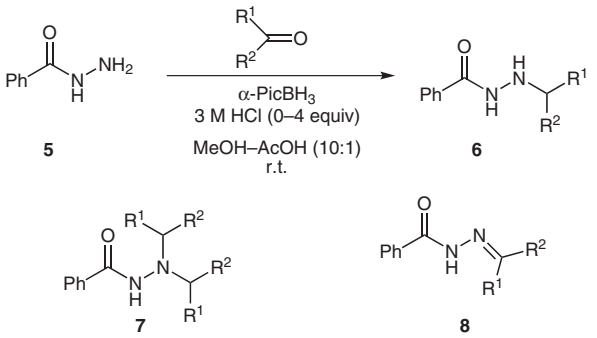
of α-picoline-borane (α-PicBH$_3$)[10] and its applications to the synthesis of alkoxyamine derivatives[11] and *N*-benzylamino acid derivatives through reductive alkylation sequences.[12] In this paper, we wish to describe the α-PicBH$_3$-mediated reductive alkylation of hydrazine derivatives (Scheme 1) as an extension of the previous reports.[13,14] Furthermore, in regard to the application of our method, we will also report on the efficient syntheses of **3** and an important synthetic intermediate of **1**.



Scheme 1 Reductive alkylation of hydrazines with α-PicBH$_3$

Reductive Alkylation of Acylhydrazines

We first tried to establish α-PicBH$_3$-mediated reductive alkylation of benzohydrazide (**5**) with aliphatic and aromatic carbonyl compounds (Scheme 2 and Table 1). The reductive alkylation was carried out under the conditions reported previously.[10,13] Thus, a mixture of **5** and one equivalent of cyclohexanecarbaldehyde was treated with α-PicBH$_3$ (1.5 equiv) in a mixture of methanol–acetic acid (10:1) at room temperature for 2 hours to give the corresponding *N*′-cyclohexylmethylbenzohydrazide (**6a**) in a 64% yield, along with 5% of *N*′,*N*′-dialkylbenzohydrazide **7a** (Table 1, entry 1). Similar results were observed for the reaction with *n*-hexanal under the same conditions (entry 2). On the other hand, the reactions of the aliphatic ketones gave the corresponding *N*′-monoalkylbenzohydrazides **6c** and **6d** in excellent yields under these conditions, respectively (entries 3 and 4). It is noteworthy that neither dialkylated compounds nor **5** were detected in these cases.



Scheme 2 Reductive alkylation of benzohydrazide **5**

When the reductive alkylation of **5** with benzaldehyde was carried out under the same conditions, the desired *N*′-benzylbenzohydrazide (**6e**) was obtained in a 35% yield (entry 5). A large amount of unreduced hydrazone **8e** was recovered in a 43% yield from this reaction. Even though the reaction was carried out by prolongation of the reaction time from 2 to 7 hours, the yield of **6e** was not improved (entry 5 vs 6).

We have previously reported that reduction of oxime ethers with α-PicBH$_3$ to alkoxyamines was promoted by the addition of hydrochloric acid.[11] On the basis of these findings, we examined the reductive alkylation of **5** with benzaldehyde in the presence of 4 equivalents of 3 M aqueous HCl (entry 7). As expected, this reaction proceeded rapidly to give **6e** in a 78% yield, along with 7% of dialkylation product **7e**. For the reaction with acetophenone, addition of 3 M aqueous HCl was also required for promotion of the reaction to give N-alkylated product **6f** in a good yield similar to the reaction with benzaldehyde (entry 8 vs 9).

The reasons why hydrochloric acid accelerates the reductive alkylation with aromatic compounds are speculated as follows: 1) Complete protonation on the nitrogen of hy-

Table 1 Product Distribution of the α-PicBH$_3$-Mediated Reductive Alkylation of **5** with Various Carbonyl Compounds

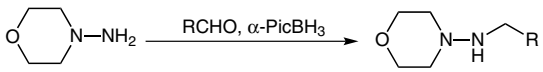
Entry	R^1	R^2	HCl (equiv)	Time (h)	**6** (Yield %)	**7** (Yield %)	**8** (Yield %)
1	*c*-C_6H_{11}	H	0	2	**6a** (64)[a]	**7a** (5)	**8a** (0)
2	*n*-C_5H_{11}	H	0	2	**6b** (49)[b]	**7b** (5)	**8b** (0)
3	*c*-C_6H_{11}	Me	0	2	**6c** (94)	**7c** (0)	**8c** (0)
4	*n*-Pr	*n*-Pr	0	2	**6d** (99)	**7d** (0)	**8d** (0)
5	Ph	H	0	2	**6e** (35)	**7e** (0)	**8e** (43)
6	Ph	H	0	7	**6e** (14)	**7e** (0)	**8e** (64)
7	Ph	H	4	2	**6e** (78)[c]	**7e** (7)	**8e** (0)
8	Ph	Me	0	2	**6f** (57)	**7f** (0)	**8f** (21)
9	Ph	Me	4	2	**6f** (70)	**7f** (0)	**8f** (0)

[a] Unreacted **5** was recovered in a 5% yield.
[b] Unreacted **5** was recovered in a 26% yield.
[c] Unreacted **5** was recovered in a 7% yield.

drazones with a strong acid is necessary for the smooth reduction of hydrazones derived from aromatic compounds, because the C=N bond of hydrazones derived from aromatic carbonyl compounds is less reactive than that of hydrazones derived from aliphatic carbonyl compounds against reduction with α-PicBH$_3$ due to their electronic nature. 2) Hydrochloric acid enhances the solubility of hydrazones in the solvent to accelerate the reactions. In the reaction of benzaldehyde and acetophenone, the heterogeneous reaction mixture turns to a clear solution upon addition of hydrochloric acid. Although a detailed investigation is still needed, we believe that the latter issue should be a main factor in promotion of the reactions, because the reaction of some aromatic aldehyde-derived hydrazone soluble in methanol–acetic acid proceeded smoothly without addition of hydrochloric acid as will be described later.

Reductive Alkylation of *N*-Aminoazacycles

Next, this method was extended to the N′-alkylation of *N*,*N*-dialkylhydrazines to prepare *N*-(dialkylamino)azacycles, which show various biological activities as described in the introduction.[5] These compounds are usually prepared by reduction of the isolated hydrazones with a reducing reagent such as NaBH(OCOMe)$_3$.[8] To develop a more facile method, the reductive alkylation of morpholin-4-amine (**9**) with various aldehydes was examined using α-PicBH$_3$ as a model study (Scheme 3 and Table 2).

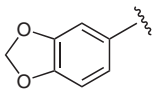


9 **10**

Scheme 3 Reductive alkylation of morpholin-4-amine **9** with α-PicBH$_3$

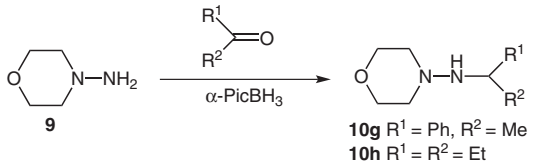
Initially, a mixture of **9** and benzaldehyde was treated with 1.5 equivalents of α-PicBH$_3$ in methanol–acetic acid (10:1) at room temperature for 2 hours. However, the reductive alkylation did not take place, while the formation of the corresponding hydrazone proceeded. On the other hand, the desired product **10a** was obtained in a 79% yield, when **9** was treated with benzaldehyde and α-PicBH$_3$ in methanol–acetic acid (10:1) for 2 hours at room temperature and subsequently the resulting mixture was treated with 1.5 equivalents of 6 M aqueous HCl for 1 hour (Table 2, entry 1). This reaction also proceeded in methanol containing 6 M aqueous HCl without acetic acid as a co-solvent (entry 2). Thus, a mixture of **9** and benzaldehyde in methanol was stirred in the presence of 0.3 equivalent of 6 M aqueous HCl at room temperature for 2 hours, followed by treatment of α-PicBH$_3$ (1.5 equiv) and 6 M aqueous HCl (1.5 equiv) for 1.5 hours to give **10a** in an 85% yield.[15] It is noteworthy that 6 M aqueous HCl could be replaced by readily handling oxalic acid to promote the reductive alkylation giving **10a** in an 82% yield (entry 3). These procedures can be applicable to the reductive alkylation with aromatic aldehydes bearing electron-withdrawing or electron-donating groups as well as aliphatic aldehydes (entries 4–15). Since all products are prone to be oxidized to the corresponding hydrazones upon standing in an atmosphere of air, they were isolated as the stable oxalates.

Table 2 Conditions and Yields of Reductive Alkylation of Morpholin-4-amine (**9**) with α-PicBH$_3$

Entry	R	Conditions[a,b,c]	Product[d]	Yield (%)
1	Ph	A	**10a**	79
2	Ph	B	**10a**	85
3	Ph	C	**10a**	82
4	4-ClC_6H_4	A	**10b**	87
5	4-ClC_6H_4	B	**10b**	72
6	4-ClC_6H_4	C	**10b**	86
7	4-MeC_6H_4	A	**10c**	89
8	4-MeC_6H_4	B	**10c**	85
9	4-MeC_6H_4	C	**10c**	78
10	(*E*)-PhCH=CH	B	**10d**	76
11	(*E*)-PhCH=CH	C	**10d**	91
12	*c*-C_6H_{11}	B	**10e**	74
13		A	**10f**	90
14		B	**10f**	56
15		C	**10f**	66

[a] Conditions A: MeOH–AcOH (10:1) for solvent and 6 M aq HCl (1.5 equiv) as an additive.
[b] Conditions B: MeOH for solvent and 6 M aq HCl (1.75 equiv) as an additive.
[c] Conditions C: MeOH for solvent and $(COOH)_2$ (3.0 equiv) as an additive.
[d] All products were isolated as the oxalate.

In an effort to survey the generality of the reductive alkylation of *N*-aminoazacycles, the respective reactions of **9** with acetophenone and pentan-3-one were examined (Scheme 4). However no desired products were observed upon conducting the reactions under the conditions C using oxalic acid and methanol as an additive and the solvent, respectively. On the other hand, we found that the desired reaction proceeded to give **10g** and **10h** in 68% and 63% yield, respectively, when the reaction was conducted in methanol–acetic acid in the presence of 6 M aqueous HCl (conditions A).

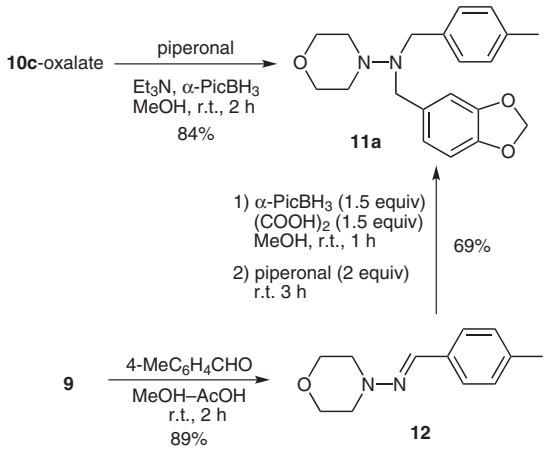


Scheme 4 α-PicBH$_3$-mediated reductive alkylation of morpholin-4-amine (**9**) with ketones

Synthesis of Symmetrical and Unsymmetrical *N*-(*N*′,*N*′-Dialkylamino)azacycles

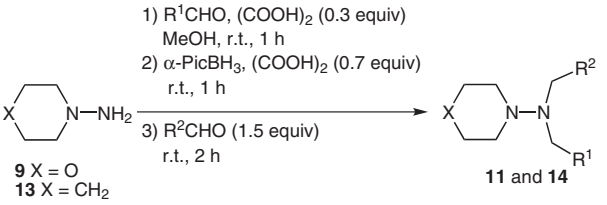
As described in the introduction, some unsymmetrical *N*-(*N*′,*N*′-dialkylamino)azacycles show interesting biological activities and are used as APIs. Double reductive alkylation of the primary amine of *N*-aminoazacycles should be a useful method to introduce appropriate functional groups to the nitrogen atom. Therefore, we tried the double reductive alkylation of **9** and *N*-aminopiperidine (**13**) using α-PicBH$_3$.

First, the reductive alkylation of the **10c**-oxalate, prepared in the previous section, was examined to verify the efficacy of the reductive alkylation at the secondary amine derived from **9** through our method (Scheme 3). Thus, a mixture of **10c**-oxalate and piperonal was treated with 1.5 equivalents of α-PicBH$_3$ for 2 hours in methanol in the presence of 1 equivalent of triethylamine to give **11a** in an 84% yield. Compound **11a** could be also prepared in a 69% yield, when the isolated hydrazone **12** was reduced with α-PicBH$_3$ in the presence of oxalic acid in methanol and subsequently the resulting mixture was treated with piperonal in the same flask (Scheme 5).



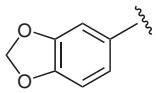
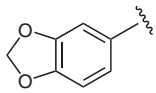
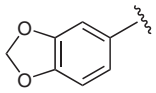
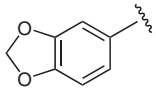
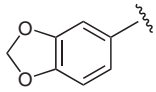
Scheme 5 Synthesis of **11a** from **10c**-oxalate and amine **9**

The above results suggest that oxalic acid is a reliable acid to promote our double reductive N-alkylation of hydrazines. As such, this method was expanded to the one-pot synthesis of *N*-(*N*′,*N*′-dialkylamino)azacycles **11** and **14** through sequential double reductive alkylation of *N*-aminoazacycles **9** and **13** (Scheme 6 and Table 3).[15]



Scheme 6 Reductive double alkylation of **9** and **13** in a one-pot synthesis

Table 3 Yields for the Double Reductive Alkylation of **9** and **13**

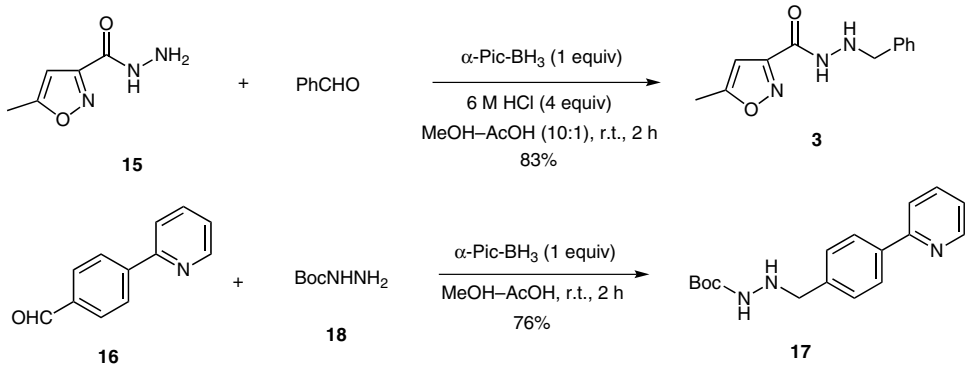
Entry[a]	R^1	R^2	X	Product	Yield (%)
1	4-MeC$_6$H$_4$	4-MeC$_6$H$_4$	O	**11b**	72
2	4-MeC$_6$H$_4$	4-MeC$_6$H$_4$	O	**11b**	39[b]
3	Ph	Ph	O	**11c**	69
4	4-ClC$_6$H$_4$	4-ClC$_6$H$_4$	O	**11d**	69
5			O	**11e**	66
6		Et	O	**11f**	66
7			CH_2	**14**	43
8	naphthalen-1-yl	(*E*)-PhCH=CH	O	**11g**	44
9	(*E*)-PhCH=CH	Et	O	**11h**	44

[a] All reactions were carried out in MeOH in the presence of oxalic acid (1.0 equiv) and α-PicBH$_3$ (1.5 equiv), unless otherwise stated.
[b] The yield refers to the reaction using 6 M aqueous HCl as an acid promoter.

The results showed that this method gave not only symmetrical *N*-(*N*′,*N*′-dialkylamino)azacycles **11b–e** and **14** but also unsymmetric *N*-(*N*′,*N*′-dialkylamino)azacycles **11f–h** in good to moderate yields by fine-tuning the combination and equivalency of aromatic and aliphatic aldehydes in the individual reductive alkylation step.[16]

Application to the Synthesis of APIs

As for the application of the method to the synthesis of API-related compounds, we tried to synthesize isocarboxazid (**3**) and the important segment **17** of atazanavir (**1**) (Scheme 7). Isocarboxazid (**3**) is usually synthesized by aminolysis of 5-methyl-3-isoxazole carboxylic acid esters with benzylhydrazine or reduction of the benzhydrazone derived from 5-methyl-3-isoxazole carboxazide with LiAlH$_4$.[4] We have synthesized **3** in a 83% yield through reductive alkylation method using α-PicBH$_3$ in methanol–acetic acid in the presence of 6 M aqueous HCl.



Scheme 7 Synthesis of API-related compounds

Compound **17** has usually been synthesized through the catalytic hydrogenation of the hydrazone derived from aldehyde **16** and *tert*-butoxycarbonylhydrazide (**18**).[2] To synthesize **17** more efficiently, reductive alkylation of **18** with the benzaldehyde derivative **16** was carried out in methanol–acetic acid for 2 hours using α-PicBH$_3$ as a reducing reagent. This reaction proceeded homogeneously and was completed without addition of hydrochloric acid to give **17** in a 76% yield.

In conclusion, an efficient synthesis of *N*-alkylhydrazine derivatives by reductive alkylation with α-PicBH$_3$ and its application to the syntheses of two API-related compounds have been achieved. We believe that this study will be of value for the development of new processes for the synthesis of hydrazine derivatives as well as for the discovery of new hydrazine-based compounds showing interesting biological activity.

All melting points are uncorrected. IR spectra were measured directly between a NaCl plate or as KBr disks. ^{1}H NMR spectra (400 or 500 MHz) and ^{13}C NMR spectra (100 or 125 MHz) were measured for a solution in $CDCl_3$, CD_3OD, or D_2O. The chemical shift data for each signal on ^{1}H NMR are given in units of δ relative to $CHCl_3$ (δ = 7.26), CH_3OH (δ = 3.30), or H_2O (δ = 4.79). For ^{13}C NMR spectra, the chemical shifts are recorded relative to $CDCl_3$ (δ = 77.0), CD_3OD (δ = 49.0), or $(COOH)_2$ (δ = 162.3). Mass spectra were measured by electrospray ionization or direct insertion at 70 eV.

***N′*-(Cyclohexylmethyl)benzohydrazide (6a) and *N′*,*N′*-Bis(cyclohexylmethyl)benzohydrazide (7a); Typical Procedure**

To a solution of cyclohexanecarbaldehyde (211 mg, 1.88 mmol) and **5** (256 mg, 1.88 mmol) in MeOH (5 mL) were added AcOH (0.5 mL) and α-PicBH$_3$ (201 mg, 1.88 mmol) at 0 °C. The mixture was stirred for 2 h at r.t. and concentrated in vacuo. The residue was treated with 10% aq HCl (10 mL) at 0 °C and stirred at r.t. for 30 min. The mixture was basified with 25% aq Na_2CO_3 (10 mL) and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (3 × 10 mL), dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 20:1 → 10:1 → 3:1 and EtOAc–MeOH, 20:1) to give **6a** and **7a**, along with 16% of unreacted **5**.

6a

Yield: 277 mg (64%); colorless crystals; mp 93–94 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (2 H, m), 1.25 (3 H, m), 1.56 (1 H, m), 1.72 (3 H, m), 1.82 (2 H, m), 2.79 (2 H, d, *J* = 6.7 Hz), 7.43 (2 H, m), 7.50 (1 H, m), 7.74 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 26.6, 31.3, 36.7, 59.0, 126.8, 128.7, 131.8, 133.0, 167.1.

MS (ESI, MeOH): *m*/*z* = 233 ([M + H]$^+$).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{21}N_2O$: 233.1654; found: 233.1653.

7a

Yield: 30 mg (5%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (4 H, m), 1.23 (6 H, m), 1.46 (2 H, m), 1.66 (6 H, m), 1.88 (4 H, m), 2.71 (3 H, d, *J* = 7.1 Hz), 6.81 (1 H, br d), 7.26–7.49 (3 H, m), 7.70 (1 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 26.8, 36.3, 64.8, 126.9, 128.6, 128.7, 131.4, 134.4, 166.2.

MS (ESI, MeOH): *m*/*z* = 329 ([M + H]$^+$).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{33}N_2O$: 329.2593; found: 329.2581.

***N′*-(1-Hexyl)benzohydrazide (6b) and *N′*,*N′*-Bis(1-hexyl)benzohydrazide (7b)**

Prepared from hexanal (188 mg, 1.88 mmol) and **5** (256 mg, 1.88 mmol) in an analogous manner for the preparation of **6a** and **7a**.

6b

Yield: 203 mg (49%); colorless crystals; mp 163–165 °C.

IR (KBr): 3272, 1627 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (3 H, t, *J* = 6.7 Hz), 1.28 (6 H, m), 1.53 (2 H, m), 2.93 (2 H, t, *J* = 7.2 Hz), 7.43 (2 H, m), 7.51 (1 H, m), 7.75 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.5, 26.8, 28.0, 31.7, 52.4, 126.8, 128.6, 131.7, 132.9, 167.2.

MS (ESI, MeOH): *m*/*z* = 221 ([M + H]$^+$).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{21}N_2O$: 221.1654; found: 221.1637.

7b

Yield: 29 mg (5%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (6 H, t, *J* = 6.8 Hz), 1.11–1.31 (12 H, m), 1.53 (4 H, br quint, *J* = 7.2 Hz), 2.87 (4 H, t, *J* = 7.3 Hz), 7.40–7.45 (2 H, m), 7.48–7.49 (1 H, m), 7.73–7.77 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (2 C), 22.6 (2 C), 26.9 (2 C), 27.0 (2 C), 31.7 (2 C), 58.2 (2 C), 126.9 (2 C), 128.6 (2 C), 131.5, 134.1, 166.6.

MS (ESI, MeOH): *m*/*z* = 305 ([M + H]$^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{19}H_{33}N_2O$: 305.2593; found: 305.2614.

N′-(1-Cyclohexylethyl)benzohydrazide (6c)
Prepared from 1-cyclohexylethanone (237 mg, 1.88 mmol) and **5** (256 mg, 1.88 mmol) in an analogous manner for the preparation of **6a**; yield: 434 mg (94%); colorless oil.

IR (neat): 3320, 1632 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (3 H, d, *J* = 6.5 Hz), 1.08–1.28 (4 H, m), 1.41–1.46 (1 H, m), 1.67–1.70 (1 H, m), 1.76–1.80 (5 H, m), 2.91 (1 H, quint, *J* = 6.5 Hz), 7.42–7.46 (2 H, m), 7.49–7.52 (1 H, m), 7.73–7.76 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2, 26.4, 26.5, 26.6, 27.9, 29.8, 41.5, 60.5, 126.8 (2 C), 128.6 (2 C), 131.7, 133.0, 167.3.

MS (ESI, MeOH): *m/z* = 247 ([M + H]$^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{15}H_{23}N_2O$: 247.1810; found: 247.1828.

N′-(Heptan-4-yl)benzohydrazide (6d)
Prepared from heptan-4-one (215 mg, 1.88 mmol) and **5** (256 mg, 1.88 mmol) in an analogous manner for the preparation of **6a**; yield: 439 mg (99%); colorless oil.

IR (neat): 3289, 1632 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90–0.94 (6 H, m), 1.37–1.46 (8 H, m), 2.92 (1 H, m), 7.39–7.43 (2 H, m), 7.48–7.49 (1 H, m), 7.75–7.78 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 18.9, 34.9, 59.9, 126.9 (2 C), 128.5 (2 C), 131.6, 133.0, 167.3.

MS (ESI, MeOH): *m/z* = 235 ([M + H]$^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{14}H_{23}N_2O$: 235.1810; found: 235.1793.

N′-Benzylbenzohydrazide (6e)[17] and N′,N′-Dibenzylbenzohydrazide (7e)
To a solution of benzaldehyde (200 mg, 1.88 mmol) and **5** (256 mg, 1.88 mmol) in MeOH (5 mL) was added AcOH (0.5 mL) at 0 °C. The mixture was stirred for 1 h at r.t. The resulting mixture was treated with α-PicBH_3 (201 mg, 1.88 mmol) and stirred for 5 min at the same temperature. To the mixture was added 3 M aq HCl (2.51 mL, 7.52 mmol) at 0 °C and the mixture was stirred for 30 min at r.t. The reaction was quenched with 25% aq Na_2CO_3 (10 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 10:1–1:20) to give **6e** and **7e** along with 7% of **5**.

6e
Yield: 333 mg (78%); colorless crystalline powder; mp 114–116 °C.

IR (KBr): 3281, 1637 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.09 (2 H, s), 7.25–7.45 (7 H, m), 7.49 (1 H, m), 7.68–7.69 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 128.6 (2 C), 127.7, 128.6 (2 C), 128.7 (2 C), 129.1 (2 C), 131.9, 132.9, 137.5, 167.4.

MS (ESI, MeOH): *m/z* = 227 ([M + H]$^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O$: 227.1184; found: 227.1173.

7e
Yield: 42 mg (7%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.31 (4 H, m), 6.93 (1 H, br s), 7.26–7.32 (10 H, m), 7.40 (5 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 59.3, 126.7 (2 C),127.5 (2 C), 128.4 (2 C), 128.5 (2 C), 129.3 (2 C), 134.0, 137.4, 167.3.

MS (ESI, MeOH): *m/z* = 317 ([M + H]$^+$).

HRMS-ESI: *m/z* [M + H] calcd for $C_{21}H_{21}N_2O$: 317.1654; found: 317.1642.

N′-(1-Phenylethyl)benzohydrazide (6f)
Prepared from acetophenone (226 mg, 1.88 mmol) and **5** (256 mg, 1.88 mmol) in an analogous manner for the preparation of **6e**; yield: 316 mg (70%); colorless oil.

IR (neat): 3308, 1632 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (3 H, d, *J* = 6.6 Hz), 4.26 (1 H, q, *J* = 6.6 Hz), 7.26–7.36 (1 H, m), 7.37–7.40 (6 H, m), 7.41–7.43 (1 H, m), 7.60–7.63 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 60.0, 126.8 (2 C), 127.2 (2 C), 127.6 (2 C), 128.57 128.60 (2 C), 137.7, 132.9, 143.1, 167.3.

MS (ESI, MeOH): *m/z* = 241 ([M + H]$^+$).

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{15}H_{17}N_2O$: 241.1341; found: 241.1343.

***N*-Benzylmorpholin-4-amine Oxalate (10a);[18] Typical Procedures**
Conditions A: A mixture of benzaldehyde (106 mg, 1 mmol) and **9** (102 mg, 1 mmol) in MeOH–AcOH (10:1, 3 mL) was stirred for 2 h at r.t. To the mixture was added α-PicBH_3 (160 mg, 1.5 mmol) and 6 M aqueous HCl (0.25 mL, 1.5 mmol). After stirring for 1.5 h at r.t., the mixture was treated with 6 M aq HCl (0.25 mL, 1.5 mmol) for 15 min at r.t. After removal of the solvents by evaporation in vacuo, the residue was diluted with $CHCl_3$ (10 mL) and the organic layer was washed with 10% aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 5 mL), the combined organic layers were dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. The residual oil was diluted with xylene (5 mL). The volatile components of the mixture were evaporated in vacuo to remove α-picoline. The residue was dissolved in Et_2O (2 mL) and the solution was treated with a solution of oxalic acid (135 mg, 1.5 mmol) in Et_2O (6 mL). The resulting precipitate was collected by filtration to give the oxalate of **10a**; yield: 222 mg (79%); colorless plates; mp 156–157 °C.

^{1}H NMR (500 MHz, D_2O): δ = 2.76 (4 H, br s), 3.41 (4 H, br s), 3.92 (2 H, s), 7.01 (5 H, s).

^{13}C NMR (125 MHz, D_2O): δ = 56.5, 59.7, 72.3, 136.3, 136.7, 137.2, 162.3.

MS (free base, EI): *m/z* = 192 (M$^+$), 101 (base peak).

Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.22; H, 6.49; N, 9.94.

Conditions B: To a mixture of benzaldehyde (106 mg, 1 mmol) and **9** (102 mg, 1 mmol) in MeOH (3 mL) was added 6 M aq HCl (0.05 mL, 0.3 mmol) and the mixture was stirred for 2 h at r.t. To the resulting mixture was successively added α-PicBH_3 (160 mg, 1.5 mmol) and 6 M aq HCl (0.25 mL, 1.5 mmol). After stirring for 1.5 h at r.t., the mixture was treated with 6 M aq HCl (0.25 mL, 1.5 mmol) and stirred for 15 min at r.t. After removal of MeOH by evaporation in vacuo, the residue was diluted with $CHCl_3$ (10 mL) and the organic layer was washed with 10% aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 5 mL), the combined organic layers were dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. The residual oil was diluted with xylene (5 mL) and the volatile components of the mixture were evaporated in vacuo to remove α-picoline. The residue was dissolved in Et_2O (2 mL) and the solution was treated with a solution of oxalic acid (135 mg, 1.5 mmol) in Et_2O (6 mL). The resulting precipitate was collected by filtration to give the oxalate of **10a** (240 mg, 85%) as colorless plates.

Conditions C: To a mixture of benzaldehyde (106 mg, 1 mmol) and **9** (102 mg, 1 mmol) in MeOH (3 mL) was added oxalic acid (135 mg, 1.5 mmol). The mixture was stirred for 2 h at r.t. To this mixture was added α-PicBH$_3$ (160 mg, 1.5 mmol) and oxalic acid (135 mg, 1.5 mmol). After stirring for 1.5 h at r.t., MeOH was removed by evaporation in vacuo. The residue was diluted with $CHCl_3$ (10 mL) and the organic layer was washed with 10% aq $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (2 × 5 mL), the combined organic layers were dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. The residual oil was diluted with xylene (5 mL) and the volatile component of the mixture was evaporated in vacuo to remove α-picoline. The residue was dissolved in Et_2O (2 mL) and the solution was treated with a solution of oxalic acid (135 mg, 1.5 mmol) in Et_2O (6 mL). The resulting precipitate was collected by filtration to give the oxalate of **10a** (232 mg, 82%) as colorless plates.

***N*-(4-Chlorobenzyl)morpholin-4-amine Oxalate (10b)**
Prepared from 4-chlorobenzaldehyde (141 mg, 1 mmol) and **9** (102 mg, 1 mmol) in an analogous manner for the synthesis of **10a** by conditions A–C.

Yield: conditions A, 276 mg (87%); conditions B, 228 mg (72%); conditions C, 272 mg (86%); colorless prisms; mp 180–181 °C.

^{1}H NMR (500 MHz, D_2O): δ = 2.93 (4 H, br s), 3.67 (4 H, br s), 4.04 (2 H, s), 7.13 (2 H, d, *J* = 8.5 Hz), 7.16 (2 H, d, *J* = 8.5 Hz).

^{13}C NMR (125 MHz, D_2O): δ = 45.4, 49.3, 61.7, 125.7, 125.9, 128.2, 131.5, 162.3.

MS (free base, EI): *m*/*z* = 226 (M^+), 101 (base peak).

Anal. Calcd for $C_{13}H_{17}ClN_2O_5$: C, 49.30; H, 5.41; N, 8.84. Found: C, 49.21; H, 5.31; N, 8.87.

***N*-(4-Methylbenzyl)morpholin-4-amine Oxalate (10c)**
Prepared from *p*-tolualdehyde (120 mg, 1 mmol) and **9** (102 mg, 1 mmol) in an analogous manner for the synthesis of **10a** by conditions A–C.

Yield: conditions A, 264 mg (89%); conditions B, 252 mg (85%); conditions C, 231 mg (78%); colorless prisms; mp 190–192 °C (MeOH–EtOAc).

^{1}H NMR (500 MHz, D_2O): δ = 2.06 (3 H, s), 2.92 (4 H, br s), 3.58 (4 H, br s), 4.07 (2 H, s), 7.02 (2 H, d, *J* = 8.0 Hz), 7.09 (2 H, d, *J* = 8.0 Hz).

^{13}C NMR (125 MHz, D_2O): δ = 42.4, 71.4, 74.7, 87.4, 149.1, 151.9, 152.3, 162.3.

MS (free base, EI): *m*/*z* = 206 (M^+), 101 (base peak).

***N*-[(*E*)-Cinnamyl]morpholin-4-amine Oxalate (10d)**
Prepared from cinnamaldehyde (132 mg, 1 mmol) and **9** (102 mg, 1 mmol) in an analogous manner for the synthesis of **10a** by conditions B and C.

Yield: conditions B, 234 mg (76%); conditions C, 281 mg (91%); colorless plates; mp 182–183 °C (MeOH–EtOAc).

^{1}H NMR (500 MHz, D_2O): δ = 3.01 (4 H, br s), 3.70 (4 H, br s), 3.84 (2 H, d, *J* = 7.4 Hz), 6.12 (1 H, dt, *J* = 16.0, 7.4 Hz), 6.71 (1 H, d, *J* = 16.0 Hz), 7.18–7.27 (3 H, m), 7.35 (2 H, d, *J* = 6.8 Hz).

^{13}C NMR (125 MHz, D_2O): δ = 44.2, 49.1, 62.0, 113.9, 162.3.

MS (free base, EI): *m*/*z* = 218 (M^+), 101 (base peak).

Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.24; H, 6.68; N, 9.10.

***N*-(Cyclohexylmethyl)morpholin-4-amine Oxalate (10e)**
Prepared from cyclohexanecarbaldehyde (112 mg, 1 mmol) and **9** (102 mg, 1 mmol) in an analogous manner for the synthesis of **10a** by conditions B.

Yield: 213 mg (74%); colorless needles; mp 160–162 °C (MeOH–EtOAc).

^{1}H NMR (500 MHz, D_2O): δ = 0.80–0.9 (2 H, m), 0.94–1.14 (4 H, m), 1.46–1.51 (1 H, m), 1.51–1.64 (4 H, m), 2.92 (2 H, d, *J* = 6.9 Hz), 2.95 (4 H, br s), 3.69 (4 H, br s).

^{13}C NMR (125 MHz, D_2O): δ = 34.5, 35.0, 39.6, 43.2, 60.8, 61.7, 75.1, 162.3.

MS (free base, EI): *m*/*z* = 198 (M^+), 115 (base peak).

Anal. Calcd for $C_{13}H_{24}N_2O_5$: C, 54.15; H, 8.39; N, 9.72. Found: C, 53.87; H, 8.33; N, 9.70.

***N*-(1-Phenylethyl)morpholin-4-amine Oxalate (10g)**
Prepared from acetophenone (120 mg, 1 mmol) and **9** (102 mg, 1 mmol) in an analogous manner for the synthesis of **10a** by conditions A.

Yield: 201 mg (68%); colorless crystalline powder; mp 177–178 °C.

^{1}H NMR (400 MHz, D_2O): δ = 1.68 (3 H, d, *J* = 6.8 Hz), 3.12 (2 H, m), 3.20 (2 H, m), 3.82 (4 H, br t, *J* = 4.4 Hz), 4.76 (1 H, q, *J* = 6.8 Hz), 7.51–7.57 (5 H, m).

^{13}C NMR (100 MHz, D_2O): δ = 14.0, 49.9 (2 C), 53.7, 62.0 (2 C), 124.7 (2 C), 126.2 (2 C), 126.5, 132.8, 162.3.

MS (free base, ESI): *m*/*z* = 207 ([M + H]$^+$).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{19}N_2O$: 207.1497; found: 207.1503.

***N*-(Pentan-3-yl)morpholin-4-amine Oxalate (10h)**
Prepared from 3-pentanone (86 mg, 1 mmol) and **9** (102 mg, 1 mmol) in an analogous manner for the synthesis of **10a** by conditions A.

Yield: 164 mg (63%); colorless crystalline powder; mp 135–137 °C.

^{1}H NMR (400 MHz, D_2O): δ = 0.99 (6 H, t, *J* = 7.5 Hz), 1.77 (4 H, br quint, *J* = 7.1 Hz), 3.11 (4 H, m), 3.45 (1 H, br quint, *J* = 5.9 Hz), 3.88 (4 H, m).

^{13}C NMR (100 MHz, D_2O): δ = 6.3 (2 C), 19.0 (2 C), 50.4 (2 C), 57.3, 63.6 (2 C), 162.3.

MS (free base, ESI): *m*/*z* = 173 ([M + H]$^+$).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_9H_{21}N_2O$: 173.1654; found: 173.1655.

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)morpholin-4-amine Oxalate (10f)**
Prepared from piperonal (150 mg, 1mmol) and **9** (102 mg, 1 mmol) in an analogous manner for the synthesis of **10a** by conditions A–C.

Yield: conditions A, 294 mg (90%); conditions B, 183 mg (56%); conditions C, 215 mg (66%); colorless needles; mp 162–163 °C (MeOH–EtOAc).

^{1}H NMR (500 MHz, D_2O): δ = 3.10 (4 H, br s), 3.77 (4 H, br s), 4.20 (2 H, s), 5.89 (2 H, s), 6.80 (1 H, d, *J* = 7.4 Hz), 6.87 (1 H, d, *J* = 7.4 Hz), 6.88 (1 H, s).

^{13}C NMR (125 MHz, D_2O): δ = 46.5, 49.7, 62.4, 98.7, 106.0, 107.4, 120.7, 121.6, 144.8, 145.3, 162.3.

MS (free base, EI): *m*/*z* = 236 (M^+), 101 (base peak).

Anal. Calcd for $C_{14}H_{18}N_2O_7$: C, 51.53; H, 5.56; N, 8.59. Found: C, 51.28; H, 5.43; N, 8.57.

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-(4-methylbenzyl)morpholin-4-amine (11a) from 10c-oxalate**
To a mixture of **10c**-oxalate (148 mg, 0.5 mmol), piperonal (150 mg, 1 mmol), and α-PicBH$_3$ (80 mg, 0.75 mmol) in MeOH (2 mL) was added Et_3N (51 mg, 0.5 mmol) with stirring and the reaction mixture was stirred for 3 h at r.t. The mixture was concentrated in

vacuo and the residue diluted with $CHCl_3$ (10 mL). The organic layer was washed with 10% aq Na_2CO_3 (10 mL) and the aqueous layer was extracted with $CHCl_3$ (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was diluted with xylenes (5 mL) and the volatile components were evaporated in vacuo to remove α-picoline. The residual oil was purified by silica gel column chromatography ($CHCl_3$–*n*-hexane, 2:1) to give **11a**; yield: 143 mg (84%); colorless needles; mp 65–67 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.32 (3 H, s), 2.78 (4 H, t, *J* = 4.6 Hz), 3.60 (2 H, s), 3.62 (4 H, t, *J* = 4.6 Hz), 3.67 (2 H, s), 5.92 (2 H, s), 6.70 (1 H, d, *J* = 7.4 Hz), 6.73 (1 H, br d, *J* = 7.4 Hz), 6.87 (1 H, br s), 7.09 (2 H, d, *J* = 8.0 Hz), 7.21 (2 H, d, *J* = 8.0 Hz).

^{13}C NMR (125 MHz, D_2O): δ = 21.1, 49.0, 53.0, 53.2, 67.3, 100.7, 107.6, 109.1, 121.6, 128.6, 128.7, 134.0, 136.2, 136.7, 147.3.

MS (free base, EI): *m*/*z* = 340 (M^+), 205 (base peak).

Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.22. Found: C, 70.53; H, 7.25; N, 8.25.

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-(4-methylbenzyl)morpholin-4-amine (11a) from Morpholin-4-amine (9) via 1-(4-Methylphenyl)-*N*-(morpholin-4-yl)methanimine (12)**

A solution of **9** (102 mg, 1 mmol) and 4-methylbenzaldehyde (120 mg, 1 mmol) in MeOH–AcOH (10:1, 3 mL) was stirred at r.t. for 2 h. The resulting precipitate was collected by filtration to give **12**. Compound **12** was used without further purification for the next reaction.

12

Yield: 182 mg (89%); colorless crystals; mp 91–92 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (3 H, s), 3.15 (4 H, t, *J* = 4.1 Hz), 3.88 (4 H, t, *J* = 4.1 Hz), 7.15 (2 H, d, *J* = 10.0 Hz), 7.49 (2 H, d, *J* = 10.0 Hz), 7.59 (1 H, s).

To a solution of **12** (102 mg, 0.5 mmol) in MeOH (2 mL) were added α-PicBH_3 (80 mg, 0.75 mmol) and oxalic acid (68 mg, 0.75 mmol), and the mixture was stirred for 1 h at r.t. To the reaction mixture was added piperonal (150 mg, 1 mmol) and the mixture was stirred for 3 h at r.t. and concentrated in vacuo. The residue was diluted with $CHCl_3$ (10 mL). The organic layer was washed with 10% aq Na_2CO_3 (10 mL), and the aqueous layer was extracted with $CHCl_3$ (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was diluted with xylenes (5 mL) and the volatile components were evaporated in vacuo to remove α-picoline. The residual oil was purified by silica gel column chromatography (EtOAc–*n*-hexane, 1:3) to give **11a**. The spectral data were identical to those of **11a** prepared from **10c**-oxalate.

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-propylmorpholin-4-amine (11f) from Molpholin-4-amine (9); Typical Procedure**

To a mixture of piperonal (150 mg, 1 mmol) and morpholin-4-amine (**9**; 102 mg, 1 mmol) in MeOH (2 mL) was added oxalic acid (27 mg, 0.3 mmol) and the mixture was stirred for 1 h at r.t. To this mixture was successively added α-PicBH_3 (160 mg, 1.5 mmol) and oxalic acid (63 mg, 0.7 mmol) with stirring. After stirring for 1 h at r.t., the mixture was treated with propionaldehyde (87 mg, 1.5 mmol) for an additional 2 h at r.t. The reaction mixture was concentrated in vacuo and the residue was diluted with $CHCl_3$ (10 mL). The organic layer was washed with 10% aq Na_2CO_3 (10 mL) and the aqueous layer was extracted with $CHCl_3$ (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was diluted with xylene (5 mL) and the volatile components of the mixture were evaporated in vacuo to remove α-picoline. The residual oil was purified by silica gel column chromatography (EtOAc–*n*-hexane, 1:3) to give **11f**; yield: 184 mg (66%); colorless prisms; mp 80–81 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (3 H, t, *J* = 7.4 Hz), 1.49 (2 H, sext, *J* = 6.9 Hz), 2.40 (2 H, t, *J* = 6.9 Hz), 2.74 (4 H, t, *J* = 4.6 Hz), 3.59 (2 H, s), 3.70 (4 H, t, *J* = 4.6 Hz), 5.94 (2 H, s), 6.72 (1 H, d, *J* = 7.4 Hz), 6.74 (1 H, dd, *J* = 7.4, 1.0 Hz), 6.88 (1 H, d, *J* = 1.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.8, 21.1, 48.7, 51.7, 53.0, 67.5, 100.8, 107.7, 109.0, 121.4, 134.3, 146.2, 147.4.

MS (EI): *m*/*z* = 278 (M^+), 143 (base peak).

Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.58; H, 8.05; N, 10.00.

***N*,*N*-Dibenzylmorpholin-4-amine (11c)**

Prepared from benzaldehyde (265 mg, 2.5 mmol) and morpholin-4-amine (**9**; 102 mg, 1 mmol) in an analogous manner for preparation of **11f**; yield: 195 mg (69%); colorless prisms; mp 75 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.81 (4 H, t, *J* = 4.6 Hz), 3.61 (4 H, t, *J* = 4.6 Hz), 3.72 (4 H, s), 7.21 (2 H, t, *J* = 7.4 Hz), 7.25–7.31 (6 H, m), 7.33 (2 H, d, *J* = 7.4 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 49.0, 53.5, 67.3, 126.6, 128.0, 128.7, 140.0.

MS (free base, EI): *m*/*z* = 282 (M^+), 191 (base peak).

Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.46; H, 7.68; N,9.81.

***N*,*N*-Bis(4-chlorobenzyl)morpholin-4-amine (11d)**

Prepared from 4-chlorobenzaldehyde (351 mg, 2.5 mmol) and morpholin-4-amine (**9**; 102 mg, 1 mmol) in an analogous manner for the preparation of **11f**; yield: 242 mg (69%); colorless prisms; mp 80 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.77 (4 H, t, *J* = 4.6 Hz), 3.61 (4 H, t, *J* = 4.6 Hz), 3.65 (4 H, s), 7.21–7.27 (8 H, m).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 48.9, 52.8, 67.2, 128.2, 129.9, 132.4, 138.1.

MS(EI): *m*/*z* = 350 (M^+), 225 (base peak).

Anal. Calcd for $C_{18}H_{20}Cl_2N_2O$: C, 61.55; H, 5.74; N,7.97. Found: C, 61.37 H, 5.72; N, 8.03.

***N*,*N*-Bis(benzo[*d*][1,3]dioxol-5-ylmethyl)morpholin-4-amine (11e)**

Prepared from piperonal (450 mg, 2.5 mmol) and morpholin-4-amine (**9**; 102 mg, 1mmol) in an analogous manner for the preparation of **11f**; yield: 244 mg (66%); colorless prisms; mp 129–130 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.77 (4 H, t, *J* = 4.6 Hz), 3.60 (4 H, s), 3.62 (4 H, t, *J* = 4.6 Hz), 5.93 (4 H, s), 6.72 (4 H, m), 6.86 (4 H, br s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 49.0, 53.1, 67.3, 100.7, 107.7, 109.1, 121.6, 133.8, 146.2, 147.4.

MS (EI): *m*/*z* = 370 (M^+), 135 (base peak).

Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.61; H, 6.03; N, 7.56.

***N*,*N*-Bis(benzo[*d*][1,3]dioxol-5-ylmethyl)piperidin-1-amine (14)**

Prepared from piperonal (450 mg, 2.5 mmol) and *N*-aminopiperidine (**13**; 100 mg, 1 mmol) in an analogous manner for the preparation of **11f**; yield: 158 mg (43%); colorless prisms; mp 86–87 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (2 H, m), 1.50 (4 H, m), 2.92 (4 H, m), 3.58 (4 H, s), 5.92, 5.917, and 5.915 (each 2 H, s), 6.69 (2 H, d, *J* = 8.0 Hz), 6.72 (2 H, d, *J* = 8.0 Hz), 6.87 (2 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.7, 26.4, 49.7, 53.0, 100.7, 107.6, 109.2, 121.5, 134.5, 146.1, 147.4, 162.3.

MS (EI): *m*/*z* = 368 (M^+), 233 (base peak).

Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.31; H, 6.56; N, 7.61.

***N*-[(*E*)-Cinnamyl]-*N*-(naphthalen-1-ylmethyl)morpholin-4-amine (11g)**

Prepared from 1-naphthaldehyde (156 mg, 1 mmol), cinnamaldehyde (198 mg, 1.5 mmol) and morpholin-4-amine (**9**; 102 mg, 1 mmol) in an analogous manner for the preparation of **11f**; yield: 158 mg (44%); colorless needles; mp 92 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.88 (4 H, t, *J* = 4.6 Hz), 3.47 (2 H, dd, *J* = 6.3, 1.1 Hz), 3.65 (4 H, t, *J* = 4.6 Hz), 4.23 (2 H, s), 6.27 (1 H, dt, *J* = 16.0, 6.3 Hz), 6.47 (1 H, d, *J* = 16.0 Hz,), 7.25–7.32 (5 H, m), 7.39 (1 H, dd, *J* = 6.9, 8.0 Hz), 7.44–7.51 (3 H, m), 7.74 (1 H, d, *J* = 8.0 Hz), 7.84 (1 H, dd, *J* = 7.4, 1.7 Hz), 8.32 (1 H, d, *J* = 7.4 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 49.1, 52.5, 52.8, 67.4, 124.5, 125.1, 125.4, 125.5, 126.2, 127.2, 127.4, 127.6, 128.4, 128.5, 128.6, 131.3, 132.4, 133.8, 135.0.

MS (EI): *m*/*z* = 358 (M^+), 241 (base peak).

Anal. Calcd for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.23; H, 7.47; N, 7.77.

***N*-[(*E*)-Cinnamyl]-*N*-propylmorpholin-4-amine (11h)**

Prepared from cinnamaldehyde (132 mg, 1 mmol), propionaldehyde (87 mg, 1.5 mmol) and molpholin-4-amine (**9**; 102 mg, 1 mmol) in an analogous manner for the preparation of **11f**; yield: 115 mg (44%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (3 H, t, *J* = 7.4 Hz), 1.55 (2 H, sext, *J* = 7.4 Hz), 2.49 (2 H, t, *J* = 7.4 Hz), 2.74 (4 H, t, *J* = 4.6 Hz), 3.35 (2 H, dd, *J* = 6.6, 1.7 Hz), 3.70 (4 H, t, *J* = 4.6 Hz), 6.26 (1 H, dt, *J* = 16.0, 6.3 Hz), 6.49 (1 H, d, *J* = 16.0 Hz), 7.20–7.24 (2 H, m), 7.29–7.34 (2 H, m), 7.37 (1 H, dd, *J* = 7.4, 1.1 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.9, 21.3, 48.7, 52.0, 52.2, 67.5, 126.2, 127.2, 128.5, 128.8, 131.2, 137.3.

MS (EI): *m*/*z* = 260 (M^+), 143 (base peak).

***N′*-Benzyl-5-methylisoxazole-3-carbohydrazide (3, Isocarboxazid)**[4]

To a stirred solution of 5-methylisoxazole-3-carbohydrazide (**15**; 265 mg, 1.88 mmol) in MeOH (3 mL) was added a solution of benzaldehyde (200 mg, 1.88 mmol) in MeOH (2 mL) under an atmosphere of N_2 and the mixture was stirred for 10 min at r.t. After cooling to 0 °C, AcOH (0.5 mL) and α-PicBH$_3$ (201 mg, 1.88 mmol) were added and the mixture was stirred for 5 min at the same temperature. To the mixture was added 3 M aq HCl (2.51 mL, 7.52 mmol) at 0 °C, and was allowed to warm to r.t. After stirring for 30 min, the mixture was poured into 25% aq Na_2CO_3 (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 9:1) to give **3**; yield: 339 mg (83%); colorless crystals: mp 105–106 °C.

IR (KBr): 3227, 1674 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 2.46 (3 H, s), 4.03 (2 H, s), 6.41 (1 H, s), 7.26–7.28 (1 H, m), 7.30–7.34 (2 H, m), 7.39 (2 H, d, *J* = 7.7 Hz).

^{13}C NMR (100 MHz, CD_3OD): δ = 11.9, 56.4, 101.9, 128.6, 129.4 (2 C), 130.1 (2 C), 138.6, 159.1, 160.4, 172.8.

ESI-MS: *m*/*z* = 232 ($[M + H]^+$).

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{14}N_3O_2$: 232.1086; found:232.1077.

***tert*-Butyl 2-[4-(Pyridin-2-yl)benzyl]hydrazinecarboxylate (17);[2] Intermediate for the Synthesis of Atazanavir (1)**

To a mixture of *N*-*tert*-butoxycarbonylhydrazine (**18**; 249 mg, 1.88 mmol) and 4-(pyridin-2-yl)benzaldehyde (**16**; 344 mg, 1.88 mmol) in MeOH (5 mL) was added AcOH (0.5 mL) and α-PicBH$_3$ (201 mg, 1.88 mmol) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 2 h at the same temperature. The mixture was concentrated in vacuo and to the residue was added 10% aq HCl (10 mL) at 0 °C. The mixture was warmed to r.t. and stirred for 30 min at the same temperature. After cooling to 0 °C, 25% aq Na_2CO_3 (20 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 5:1–1:1) to give **17**; yield: 437 mg (78%); colorless oil.

IR (neat): 3410, 1683 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (9 H, s), 4.11 (2 H, s), 7.23 (1 H, m), 7.45 (2 H, d, *J* = 7.7 Hz), 7.73 (2 H, m), 7.96 (2 H, d, *J* = 7.9 Hz), 8.69 (1 H, br s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 28.3 (3 C), 55.4, 120.4, 122.0, 127.0 (2 C), 129.3 (2 C), 136.7, 138.6, 149.7, 156.6, 157.2.

ESI-MS: *m*/*z* = 300 ($[M + H]^+$).

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{22}N_3O_2$: 300.1712; found: 300.1721.

Supporting Information

for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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