Unexpected Discovery of Saturated Pyridine Mimetics

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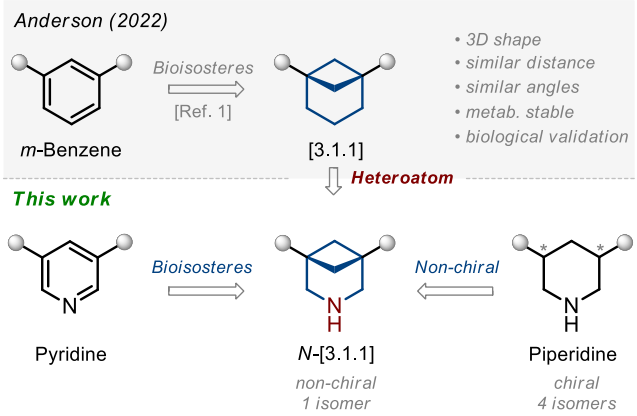
Dedicated to the people of Ukraine

Introduction. In 2022, bicyclo[3.1.1]heptanes were demonstrated to mimic the fragment of *meta*-substituted benzenes in biologically active compounds.[1,2] Both cores had similar angles between the exit vectors (119-120º), a similar distance between substituents (4.8-5.0 Å), and similar physicochemical properties (Scheme 1). Given our current interest in hetero-substituted bicycloalkanes,[3] we immediately became interested in adding a nitrogen atom to bicyclo[3.1.1]heptanes. Such systems could in theory mimic the fragment of pyridine and could also be additionally considered as non-chiral analogs of piperidines (Scheme 1). Both logics seemed to be interesting for medicinal chemistry applications. Having finished with a brilliant design of the target system, we faced a tiny problem, however: we had absolutely no clue how to make it.

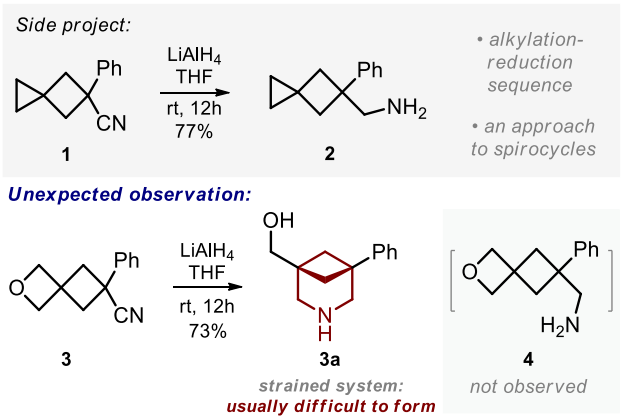
In this work, due to an unexpected observation from a side project, we present a general scalable approach to 3-aza-bicyclo[3.1.1] heptanes – saturated mimetics of pyridine. We have synthesized them, characterized them, and incorporated them into a structure on an antihistamine drug *Rupatidine* instead of the pyridine fragment.[4]



Scheme 1. Bicyclo[3.1.1]heptanes as bioisosteres of benzenes.[1] This work: 3-azabicyclo[3.1.1]heptanes as potential bioisosteres of pyridines.

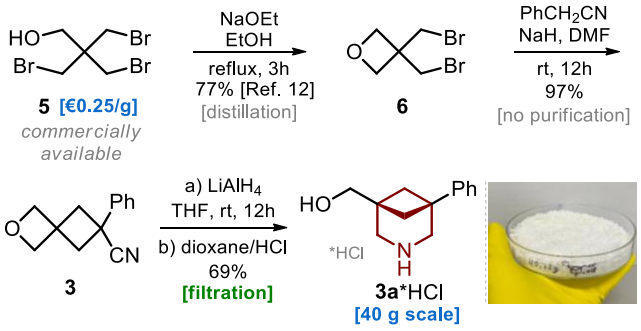
Unexpected observation. Not surprisingly, *mono*- and *poly*-substituted 3-azabicyclo[3.1.1]heptanes were known in the literature.[5] We needed, however, a modular approach that would provide compounds with only *two* substituents (two vectors) at the bridgehead positions of the core (Scheme 1) without additional (poly)substitution at other positions. Our previously used iodocyclization and photocyclization tactics[3] were unfortunately not appropriate here. A solution came unexpectedly from a side project. Spirocycles are currently popular in chemistry,[6] and we have several ongoing projects on making them.[7] One of those projects relies on the double alkylation of acetonitriles and the subsequent reduction of the nitrile group. For example, the reduction of nitrile **1** with $LiAlH_4$ in tetrahydrofuran at room temperature gave the spirocyclic amine **2**. At the same time, analogous reduction of oxetane **3** unexpectedly afforded the side product **3a** (Scheme 2). We were surprised to observe the formation of **3a** because a ring opening of even flexible oxetanes usually requires a Lewis acid catalysis.[8] In addition, the 3-azabicyclo[3.1.1]heptane system is conformationally rigid, and analogous rigid systems are often difficult to form via the common alkylation strategies.[9] Instead, photochemistry[3a,10] or a strain-release tactics[11] have to be used.

Formation of the expected primary amine **4** was not observed. From the general chemistry logic, we assumed that amine **4** formed initially and immediately isomerized into product **3a**.

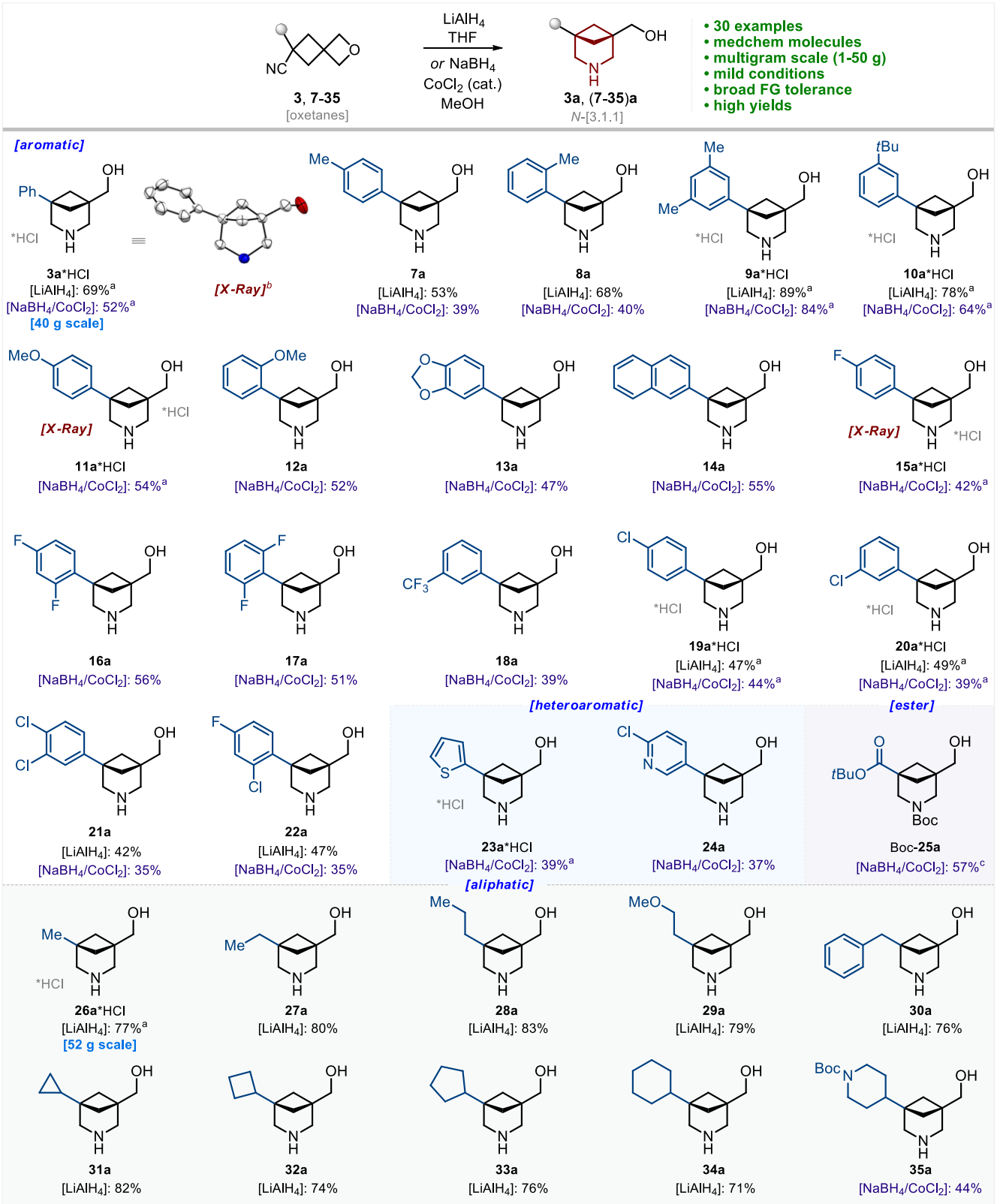


Scheme 2. Unexpected formation of product **3a**.

Scalable synthesis. Having an unexpected procedure in hand, we performed the whole sequence once again on a scale. The synthesis commenced from the commercially available alcohol **5** (ca. 0.25€/g, Scheme 3). Treatment of the latter with NaOEt in



Scheme 3. Scalable synthesis of compound **3a***HCl.



Scheme 4. Reaction conditions: [$LiAlH_4$]: nitrile (1 eq.), $LiAlH_4$ (1 eq.), THF, 12 h, rt. [$NaBH_4/CoCl_2$]: nitrile (1 eq.), $NaBH_4$ (10 eq.), $CoCl_2 \cdot 6H_2O$ (0.1 eq.), MeOH, 20 h, reflux. [a]Products were isolated as hydrochloride salts. [b]X-Ray crystal structure of compound **3a**•HCl. Hydrogen and chlorine atoms are omitted for clarity. [c]*N*-Boc protection was additionally performed.

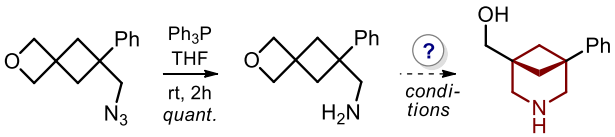
ethanol under reflux led to the formation of oxetane **6** following the literature procedure.[12] We obtained the product in a 77% yield after distillation. Cyclization of the latter with sodium hydride in DMF smoothly proceeded at room temperature to provide the spirocyclic compound **3** with a 97% yield. No purification was needed at this step. Finally, the reduction of the nitrile group with $LiAlH_4$ gave the desired amine **3a** in a slightly lower yield of 69% yield. After the standard workup, we added MeO*t*Bu to the reaction mixture, and the white solid was isolated by simple filtration. Also, we subsequently converted it into a more stable on-air crystalline hydrochloride salt. Importantly, we optimized the whole reaction sequence to avoid column chromatography at any step. This tactic allowed us to easily obtain 40 g of product **3a***HCl in one run. The structure of the product was confirmed by X-Ray analysis.[13]

Scope. Moving forward, we studied the generality of the developed method. During the process, we also found that the reduction of nitrile **3** could be alternatively performed with $NaBH_4/CoCl_2$ (cat.) in methanol under reflux in 52% yield. In studying the scope, we allowed some flexibility and used both protocols. The reduction and the recyclization steps tolerated well various substituents on the aromatic core (Scheme 4). Among them were the alkyl groups (**7a**-**10a**), fluorine (**15a**-**17a**), chlorine atoms (**19a**-**22a**), methoxy groups (**11a**, **12a**), and trifluoromethyl groups (**18a**). The reaction was also compatible with the substituted thiophene (**23a**), pyridine (**24a**), and even the ester group (**25a**). Importantly, products with aliphatic (**26a**-**34a**) and even *N*-Boc groups (**35a**) were obtained as well. Most compounds were isolated as free bases, however, in some cases, we converted them into crystalline hydrochloride salts. All syntheses were performed on a gram scale, and products **3a** and **26a** were also synthesized in 40 to 50-gram amounts. The structure of compounds **11a***HCl and **15a***HCl was confirmed by X-Ray analysis (Scheme 4).[13]

Mechanism. Even though we had a solid protocol for 3-azabicyclo[3.1.1]heptanes in hand, out of scientific curiosity, we wanted to understand the mechanism of the reaction. Did the reduction of nitrile **3** into product **3a** proceed via amine **4**? The problem was that we never could isolate this invisible intermediate. Reducing the reaction time only led to a mixture of the product and the starting material. Luckily, we could synthesize azide **36** (please, see SI for its preparation). Its mild Staudinger reduction with PPh_3 in THF at room temperature led to the formation of amine **4** as a free base (Table 1). The compound formed with ca. 90% purity, but we could fully characterize it by NMR and HRMS.

Surprisingly, amine **4** was stable in THF at room temperature and even under prolonged heating (entries 1-4). However, in the presence of LiCl (cat.), the isomerization into product **3a** smoothly proceeded already at room temperature (entry 5). This experiment explained why we never observed "invisible" intermediate **4** in the reduction of nitrile **3** with $LiAlH_4$ (Scheme 2): amine **4** formed in the first place and immediately isomerized into product **3a** in the presence of Li^+ ions.

We also checked the stability of amine **4** in other solvents. In acetonitrile, dimethylsulfoxide, and chloroform it was stable even under prolonged heating (entries 6-11). However, in methanol, the isomerization already took place even under room temperature (entries 12, 13). Under heating, it was much faster (entry 14). This experiment explained why we never observed amine **4** in the reduction of nitrile **3** with $NaBH_4$, $CoCl_2$ (cat.) in methanol under reflux: the initially formed amine **4** isomerized into product **3a** in methanol.



36 **4** [free base] **3a**

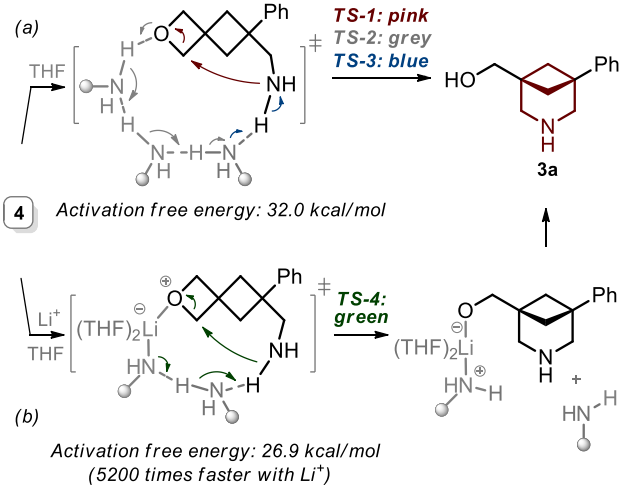
entry	conditions	conv.[a]
1	THF, rt, 6h	0% (SM)
2	THF, rt, 12h	0% (SM)
3	THF, rt, 24h	0% (SM)
4	THF, reflux, 6h	0% (SM)
5	THF, LiCl (10% mol.), rt, 6h	100%
6	CH_3CN, rt, 6h	0% (SM)
7	CH_3CN, reflux, 3h	0% (SM)
8	DMSO, rt, 6h	0% (SM)
9	DMSO, 90 °C, 3h	0% (SM)
10	$CHCl_3$, rt, 12h	0% (SM)
11	$CHCl_3$, reflux, 3h	0% (SM)
12	MeOH, rt, 12h	50%
13	MeOH, rt, 24h	100%
14	MeOH, reflux, 2h	100%

[a] Reaction conversion analyzed by ^{1}H-NMR.

Table 1. Isomerization of amine **4** into product **3a** under various conditions.

DFT-calculations[14] were performed to rationalize the observed results. A mechanism for ring opening of amine **4** involving only three additional amines (as methylamine) in the proton transfer process is shown in Scheme 5 (model "a"). It is a stepwise reaction in which the first stage involves an intramolecular S_N2 mechanism (TS-1) followed by a cascade of much lower energy proton transfers in a chain (TS-2, TS-3) to form the exoenergic product **3a**. The calculated free energy barrier for the rate-limiting S_N2 step was 32.9 kcal/mol at the ωB97XD/Def2-SVPP and 32.0 at the ωB97XD/Def2-TZVPP levels (THF continuum solvent model applied), indicating only a small basis set dependence.

A mechanism for ring opening of amine **4** involving $Li(THF)_2^+$ ions and two amines as proton transfer agents was also calculated (Scheme 5; model "b") and again the S_N2 step precedes the proton transfers along a chain. The free energy the barrier is reduced to 26.9 kcal/mol, 5.1 kcal/mol lower than that

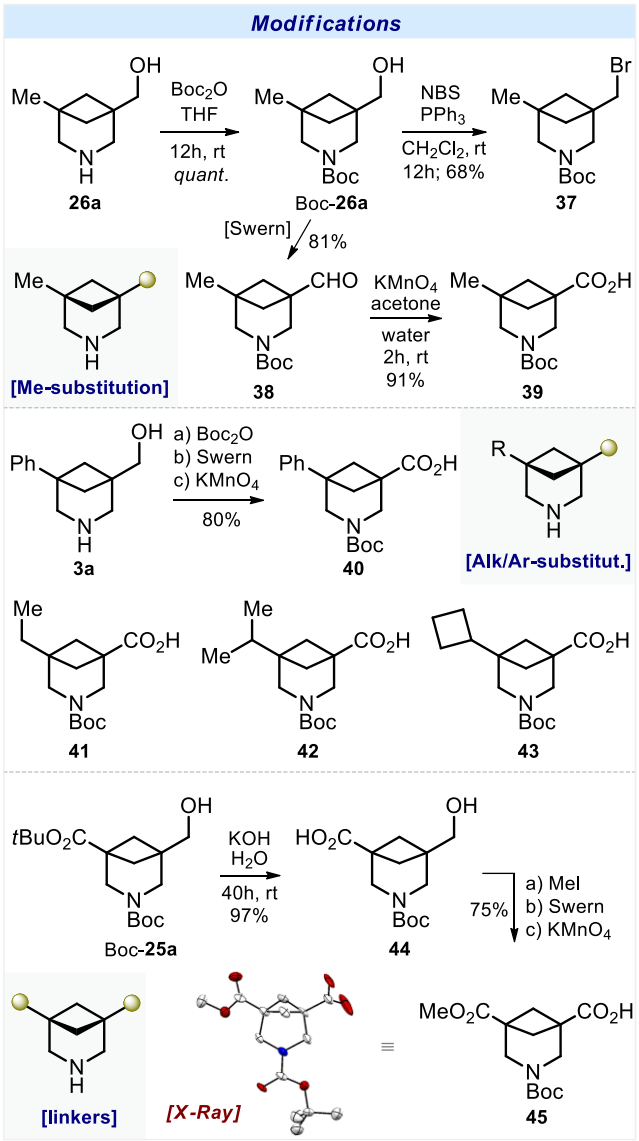


Scheme 5. Reaction mechanisms for isomerization of amine **4** into product **3a**: (a) in THF. (b) In THF in the presence of Li^+ ions. TS: transition state.

without lithium salts (model “a”), and corresponds to a 5200-fold acceleration of the reaction at 298K.

A mechanism for ring opening of amine **4** in pure MeOH was finally calculated (model “c”),[14] modeled with three molecules of methanol. The S_N2-step and proton transfers all happened on a single energy surface with no formal intermediates along the route, an asynchronous concerted reaction (Def2-TZVPP basis). The calculated free energy barrier was 26.1 kcal/mol, similar in effect to the $Li(THF)_2^+$ model and leading to a similar rate of acceleration.

The calculations above explained why the presence of Li^+-salts (Table 1, entry 5) or the presence of methanol as a solvent (Table 1, entries 13, 14) facilitated the isomerization of amine **4** into product **3a** and rationalizes why we never isolated the intermediate amine **4** in the reduction of nitrile **3** (Schemes 2, 4).



Scheme 6. Modifications of the 3-azabicyclo[3.1.1]heptane core: one and two exit vectors (linkers).

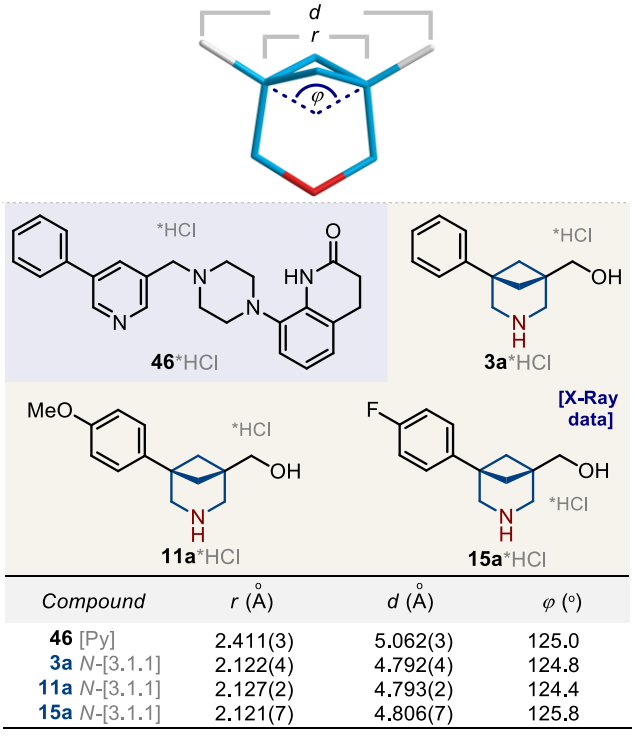
Modifications. Modifications of some representative 3-azabicyclo[3.1.1]heptanes into the building blocks ready for direct use in medicinal chemistry projects were undertaken in the next step.

Standard *N*-Boc protection of amine **26a** (via Boc-**26a**), followed by the Staundinger reaction gave bromide **37**. Swern oxidation of alcohol Boc-**26a** gave aldehyde **38** that was subsequently oxidized into *N*-Boc protected amino acid **39** (Scheme 6). Using this tactic, alcohol **3a** was easily converted into *N*-Boc amino acid **40**. Amino acids **41**-**43** were synthesized analogously.

Saponification of ester Boc-**25a** gave amino acid **44** with three functional groups. Methylation of the carboxylic group in **44**, followed by extensive oxidation of the alcohol group provided valuable linker **45**. The structure of the product was confirmed by X-ray analysis (Scheme 6).[13]

Crystallographic analysis. Next, we compared the geometric properties of 3-azabicyclo[3.1.1]heptanes with those of pyridines. For that, we measured two C-C distances *r* and *d* to see the overall similarity of cores; and angle *φ* between two exit vectors to see the similarity of angular models (Figure 1).

We calculated the values of *r*, *d*, and *φ* of 3-azabicyclo[3.1.1]heptanes from the X-ray data of compounds **3a***HCl, **11a***HCl, and **15a***HCl. The related parameters for the representative bioactive pyridine **46** were calculated from the X-ray data published in the literature. [15] The distance *r* in 3-azabicyclo[3.1.1]heptanes was ca. 0.3 Å shorter than that in the pyridine ring: 2.12 Å *vs* 2.41 Å (*pyridine*). The distance *d* between substituents in 3-azabicyclo[3.1.1]heptanes was also



Compound	*r* (Å)	*d* (Å)	*φ* (°)
46 [Py]	2.411(3)	5.062(3)	125.0
3a *N*-[3.1.1]	2.122(4)	4.792(4)	124.8
11a *N*-[3.1.1]	2.127(2)	4.793(2)	124.4
15a *N*-[3.1.1]	2.121(7)	4.806(7)	125.8

Figure 1. Selected parameters of 3-azabicyclo[3.1.1]heptanes **3a***HCl, **11a***HCl, **15a***HCl, and the substituted pyridine **46***HCl according to X-ray crystal data: angle γ (°), and distances r, d (Å).

ca. 0.2 Å shorter than that in the pyridine ring: 4.79-4.81 Å *vs* 5.06 Å (*pyridine*). However, angle *φ* was identical in both scaffolds: 124-126° *vs* 125° (*pyridine*). It must be noted, that all three parameters, - *r*, *d*, and *φ*, - were very close in

3-azabicyclo[3.1.1]heptanes (**3a**, **11a**, **15a**) and pyridines (**46**). The key characteristics of both cores and their superposition are shown in Figure 2.

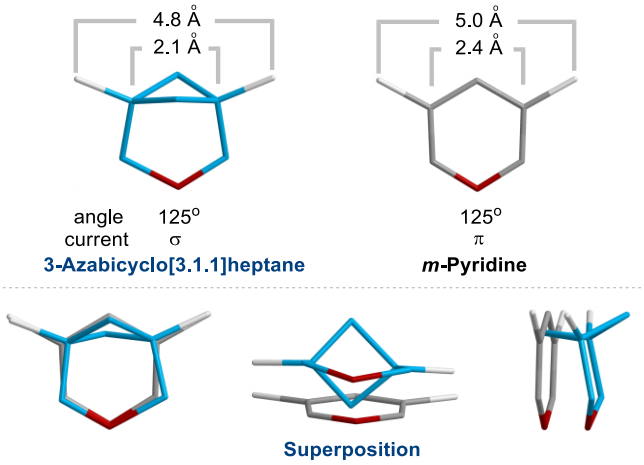


Figure 2. Visualized comparison of 3-azabicyclo[3.1.1]heptane and 3,5-disubstituted pyridine.

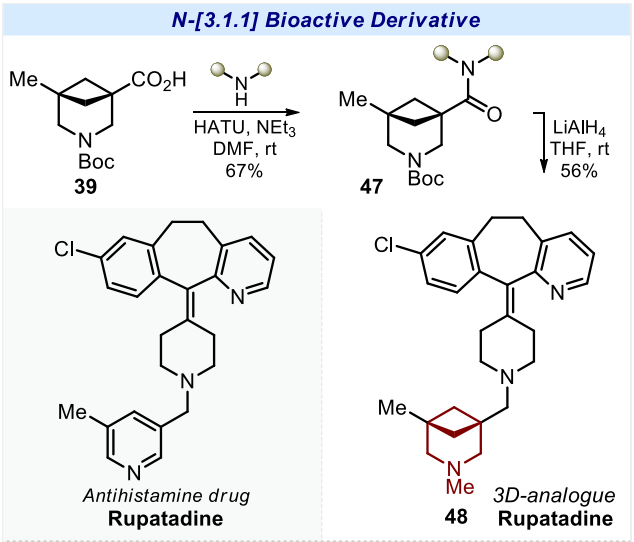
In short summary, the 3-azabicyclo[3.1.1]heptane core resembled well the pyridine ring, as the geometric parameters *r*, *d*, *φ* remained very similar.

Incorporation into the bioactive compound. To demonstrate the practical utility of the 3-azabicyclo[3.1.1]heptane scaffold, we incorporated it into the structure of the antihistamine drug *Rupatidine*,[16] instead of the pyridine ring (Scheme 7). The reaction of *N*-Boc amino acid **39** with the substituted piperidine in the presence of HATU as an activating agent gave amide **47**. Reduction of the latter with $LiAlH_4$ gave compound **48** – a saturated analog of *Rupatadine*. The commercialized drug *Rupatadine* is used in practice as a fumarate salt.[17] However, to experimentally evaluate the impact of the replacement of the pyridine ring with 3-azabicyclo[3.1.1]heptane core on the physicochemical properties, we prepared and studied both compounds, - **48** and *Rupatadine*, - as free bases.

Physicochemical properties. Replacement of the pyridine ring in *Rupatadine* by 3-azabicyclo[3.1.1]heptane (**48**) increased the water solubility by more than one order of a magnitude: 29 μM (*Rupatadine*) *vs* 365 μM (**48**) (Scheme 7).

To estimate the influence of the replacement of the pyridine ring with the saturated bioisostere on lipophilicity, we used two parameters: calculated (clogP) [18] and experimental (logD) lipophilicities. Replacement of the pyridine ring with 3-azabicyclo[3.1.1]heptane almost did not affect clogP: 5.1 (*Rupatadine*) *vs* 5.2 (**48**). However, the effect of such replacement on the decrease of the experimental lipophilicity was significant, logD: >4.5 (*Rupatadine*) *vs* 3.8 (**48**).

The effect of the saturated bioisostere on metabolic stability was also studied. The incorporation of the 3-azabicyclo[3.1.1]heptane (**48**) into *Ruparadine* dramatically



Compound	*Sol.*	*clogP*	*logD (7.4)*	Cl_{int}	$t_{1/2}$
Rupatadine	29±1	5.1	>4.5	517	3.2
48 *N*-[3.1.1]	365±1	5.2	3.8	47	35.7

Scheme 7. Synthesis of compound **48** - saturated analog of *Rupatadine*. Solubility (*Sol.*): experimental kinetic solubility in phosphate-buffered saline, pH 7.4 (μM). *clogP*: calculated lipophilicity. *logD* (7.4): experimental distribution coefficient in *n*-octanol/phosphate-buffered saline, pH 7.4. Reliable *logD* measured were obtained within a range of 1.0-4.5. Cl_{int}: experimental metabolic stability in human liver microsomes (μl/min/mg). $t_{1/2}$ (min): experimental half-time of a metabolic decomposition.

increased the metabolic stability in human liver microsomes: Cl_{int} (mg/(min•μL))=517 (*Rupatadine*) *vs* 47 (**48**). In other words, incorporation of the 3-azabicyclo[3.1.1]heptane core into *Rupatadine* increased its life half time by more than ten times: $t_{1/2}$ (min)=3.2 (*Rupatadine*) *vs* 35.7 (**48**).

In summary, the replacement of the pyridine ring in *Rupatadine* with 3-azabicyclo[3.1.1]heptane (**48**) led to a dramatic improvement of all measured physicochemical parameters: solubility, metabolic stability, and lipophilicity.

Summary. In 2022, bicyclo[3.1.1]heptanes were demonstrated to mimic the fragment of *meta*-substituted benzenes in biologically active compounds (Scheme 1).[1] Here, we unexpectedly developed a general approach to their aza-analogs: 3-azabicyclo[3.1.1]heptanes (Scheme 2). The key reaction was a reduction of oxetanyl nitriles with lithium aluminum hydride. The mechanism, scope, and scalability of this method were studied. The reaction proceeded via an "invisible" intermediate **4** (Scheme 2) that was caught by back-synthesis. Crystallographic analysis revealed a high similarity of the 3-azabicyclo[3.1.1]heptane core with the pyridine ring. This scaffold was also incorporated into the *Rupatadine* drug instead of the pyridine ring which led to dramatic improvement of all physicochemical parameters: solubility, metabolic stability, and lipophilicity.

This study increases the repertoire of saturated bioisosteres for (hetero)aromatic rings used in drug discovery campaigns.

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Keywords: 3-azabicyclo[3.1.1]heptane • pyridine • oxetane • bicyclo[3.1.1]heptane • bioisosteres

Data availability: The authors declare that data supporting the findings of this study are available within the paper and its supplementary information files.

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Abstract

Unexpected Discovery of Saturated Pyridine Mimetics

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A general approach to 3-azabicyclo[3.1.1]heptanes was unexpectedly discovered. The mechanism, scope, and scalability of this method were studied. The core was incorporated into the structure of the antihistamine drug Rupatidine instead of the pyridine ring, which led to a dramatic improvement in physicochemical properties.