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Bioisosteric Replacement Strategy for the Synthesis of 1-Azacyclic Compounds With High Affinity for the Central Nicotinic Cholinergic Receptors

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Abstract—Bioisosteric replacement of the isoxazole heterocycle in (3-methyl-5-isoxazolyl)methylene-azacyclic compounds with pyridine, oxadiazole, or an acyl group resulted in ligands with high to moderate affinity for the central nicotinic cholinergic receptors ($IC_{50} = 2.0$ to $IC_{50} > 1000$ nM) labeled by [^{3}H]methylcarbamylcholine. Additionally, further support of an important distance parameter for high-affinity nicotinic compounds has been provided.

Introduction

Replacement of bioisosterically equivalent moieties is an important and well recognized approach to analogue design. A bioisosteric replacement may help improve stability, optimize activity, and/or remove unwanted side effects. It has been shown that the isoxazole heterocycle can substitute the pyridine heterocycle present in nicotine and epibatidine, giving new nicotinic agonists, e.g., ABT 418 (Fig. 1).[1,2] In several cases the acetyl moiety is a structural part of ligands with high affinity for nicotinic receptors, e.g., in anatoxin-a,[3] and it has recently been shown that it is possible to replace the acetyl substituent in anatoxin-a with a pyridine unit, as in UB-165.[4]

We have previously described a novel series of 3-(isoxazolyl)methylene-1-azacycles (i.e., NNC 90-0270 and **1d**) as potent agonists for the central nicotinic acetylcholine receptors,[5,6] which are considered a therapeutically important drug target.[7,8] In addition, an improved nicotinic pharmacophore was developed by considering the site points **a** and **b**, where **a** is the site point corresponding to a protonated nitrogen atom and **b** is the site point corresponding to an electronegative atom capable of forming a hydrogen bond. For compounds possessing high affinity ($IC_{50} < 10$ nM) for the nicotinic receptors, these site points were separated by a distance of 7.0–8.0 Å.[6]

In this communication we report on the changes in the binding affinity observed after replacement of the isoxazole heterocycle present in the previously published series with the pyridine, oxadiazole, or acyl group. Additionally, further support for the important **a**–**b** distance parameter for high-affinity nicotinic compounds has been provided.

In the following sections, the different azacycles are designated in this manner: 1-azabicyclo[2.2.1]heptane (**a**), 1-azabicyclo[2.2.2]octane (**b**), 1-azabicyclo[3.2.1]-octane (**c**), and piperidine (**d**) (Fig. 2).

Results and Discussion

Chemistry

Focusing on the 3-substituted pyridine-ring, which is present in the natural compounds nicotine and epibatidine, the compounds **5b**–**d** were prepared by the Peterson reaction of the appropriate azacyclic ketone (**2**) with 3-[(*tert*-butyldimethylsilanyl)methyl]-pyridine (**3**) (Scheme 1). Yields were generally high, giving a mixture of the (*Z*)- and (*E*)-isomers, which were separated by column chromatography. The protected piperidine analogues (*Z*)-**5d** and (*E*)-**5d** were subsequently debenzylated by treatment with 1-chloroethyl chloroformate in toluene followed by reflux in methanol to give (*Z*)-**9d** and (*E*)-**9d** in moderate yield.

The pyridyl positional isomers, compounds **6b**, **7b** and **8b** (Scheme 1), were prepared from 1-azabicyclo[2.2.2]-

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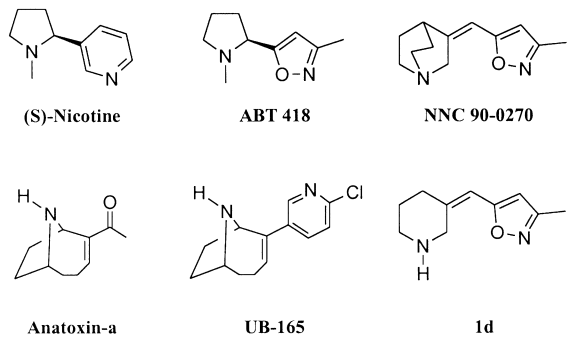


Figure 1. Ligands for the central nicotinic cholinergic receptors.

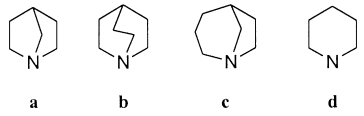
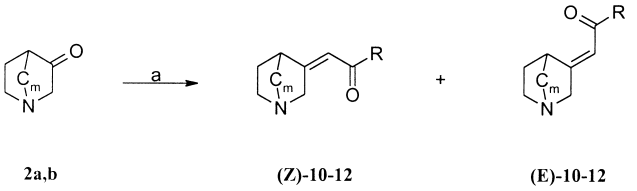


Figure 2. The azacyclic core of the compounds.

octan-3-one (**2b**) and the appropriate 2- or 4-[(trimethylsilanyl)methyl]-pyridines[9] or 2-[(trimethylsilanyl)methyl]-pyrazine (**4**), by a procedure similar to that described for compounds **5b–d**. The α,β-unsaturated ketones **10–12** were prepared by a Horner–Emmons–Wadsworth reaction of the appropriate 1-azabicyclic ketones (**2a**,**b**) and dimethyl 2-oxoalkylphosphonate (Scheme 2).[6]

Crystallization of the mixture of free bases **10–12** with an acid addition salt, e.g., hydrochloric acid or oxalic acid, resulted in isomerization to the thermodynamically more stable (*Z*)-isomers, and it has not been possible to obtain the (*E*)-isomers of **10–12** in pure form. Compounds (*Z*)-**10–12** were stable to neutral and acidic



Scheme 2. For m and R see Table 2. (a) Dimethyl 2-oxoalkylphosphonate/KOH in water.

solutions on prolonged standing, and no isomerization back to the (*E*)-isomers was detected.

In order to test if the oxadiazole showed bioisosterism with the isoxazole on the nicotinic receptor, (*Z*)-**14b** and (*Z*)-**15b** were prepared by reaction of the ester (*Z*)-**13b**[10] with sodium ethoxide and *N*-hydroxy-acetamidine or *N*-hydroxy-propionamidine (Scheme 3).

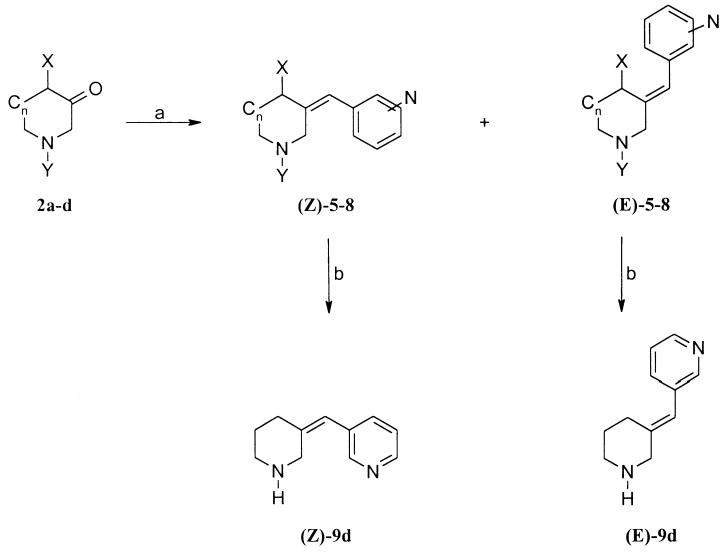
The relative configuration of the compounds was assigned on the basis of NOE ^{1}H NMR analysis.

For the (*Z*)-isomers a strong interaction between the bridgehead hydrogen and the methine hydrogen was present, whereas a strong interaction between the methine hydrogen and the C2-hydrogens for the (*E*)-isomers was observed.

All compounds **a** and **c** were obtained and tested as racemic mixtures, and **8b** was tested as a (*Z*/*E*)-mixture.

Biology

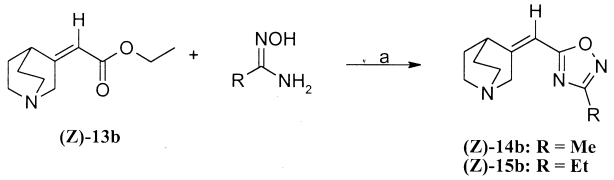
The ability of the compounds to displace the nicotinic agonist [^{3}H]methylcarbamylcholine (MCC) from native cholinergic binding sites in rat brain cortex was determined as previously described (Tables 1 and 2).[6,11,12] All



Scheme 1. For X, Y, *n* see Figure 2 and Table 1. (a) **5**: 3-[(*tert*-Butyldimethylsilanyl)methyl]-pyridine (**3**)/LDA in THF, −78 °C. **6**: 2-[(Trimethylsilanyl)methyl]-pyridine/LDA in THF, −78 °C. **7**: 2-[(Trimethylsilanyl)methyl]-pyrazine (**4**)/LDA in THF, −78 °C. **8**: 4-[(Trimethylsilanyl)methyl]-pyridine/LDA in THF, −78 °C. (b) **5d**: (i) 1-Chloroethyl chloroformate in toluene, reflux. (ii) Reflux in methanol.

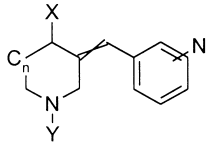
the compounds, except (*Z*/*E*)-**8b** and (*Z*)-**6b**, bound to the nicotinic binding site with moderate to high affinity.

For pairs of regio-isomers the highest nicotinic receptor affinity for the [2.2.2]azabicyclic ring system was obtained with the (*Z*)-isomer (*Z*)-**5b** (IC_{50} = 2.0 nM), whereas both isomers with the [3.2.1]azabicyclic ring system had affinities in the same range, (*E*)-**5c** (IC_{50} = 35 nM) and (*Z*)-**5c** (IC_{50} = 24 nM). For the positional isomers (*Z*)-**6b** and (*E*/*Z*)-**8b** a dramatic decrease in nicotinic affinity for the compounds was observed with IC_{50} values higher than 1000 nM. Adding an additional nitrogen to the aromatic ring such as the pyrazinyl analogues (*Z*)-**7b** and (*E*)-**7b** also resulted in a significant drop in affinity for the nicotinic receptors by a factor of 80. The same order of decrease in affinity was observed by addition of a nitrogen to the aromatic ring of the NNC 90-0270, giving the oxadiazole-analogue ((*Z*)-**14b**). Extending the R substituent from methyl, (*Z*)-**14b** to ethyl, (*Z*)-**15b** leads to a decrease in affinity just as described for the analogues of NNC 90-0270.



Scheme 3. (a) NaOEt in EtOH, N_2, 80 °C.

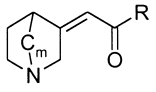
Table 1. In vitro binding data for pyridyl (**5**, **6**, **8**, **9**) and 2-pyrazinyl (**7**) methylene-1-azacycles

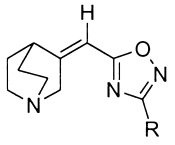


Compound	*n*	X		Y	N-position	Isomeric purity[a] (%)	[^{3}H]MCC cortex[b] IC_{50} (nM)
(*Z*)-**5b**	1		-CH_2CH_2-		*Meta*	98	2.0±1.2
(*E*)-**5b**	1		-CH_2CH_2-		*Meta*	90	66±21
(*Z*)-**5c**	2		-CH_2-		*Meta*	>99	35±16
(*E*)-**5c**	2		-CH_2-		*Meta*	>99	24±21
(*Z*)-**6b**	1		-CH_2CH_2-		*Ortho*	91	>1000*
(*Z*)-**7b**	1		-CH_2CH_2-		*Ortho* and *meta*	92	169±106
(*E*)-**7b**	1		-CH_2CH_2-		*Ortho* and *meta*	75	339±1.4
(*E*/*Z*)-**8b**	1		-CH_2CH_2-		*Para*	57:43	>1000*
(*Z*)-**9d**	1	H		H	*Meta*	>99	227±119
(*E*)-**9d**	1	H		H	*Meta*	>99	160±32
NNC 90-0270	—		—		—	—	3.9
(±)-Epibatidine	—		—		*Meta*	—	0.30
(*S*)-Nicotine	—		—		*Meta*	—	6.6

[a]Measured by GC.
[b]Values represent mean ± S.E.M. $n \geq 3$, except *n = 2.

Table 2. In vitro binding data for the 3-acyl (**10**, **11**, **12**) and 3-oxadiazolyl (**14**, **15**) methylene-1-azabicycles



Compound	m	R	Isomeric purity[a] (%)	[^{3}H]-MCC cortex[b] IC_{50} (nM)
(*Z*)-**10a**	1	CH_3	96	45±11
(*Z*)-**11a**	1	CH_2CH_3	95	81±23
(*Z*)-**10b**	2	CH_3	97	13±8.5
(*Z*)-**11b**	2	CH_2CH_3	96	12±0.7*
(*Z*)-**12b**	2	$CH_2CH_2CH_3$	86	103±41
(*Z*)-**13b**	2	OCH_2CH_3	95	490±150
				
(*Z*)-**14b**	—	CH_3	93	92±8.0
(*Z*)-**15b**	—	CH_2CH_3	>99	590±270

[a]Measured by GC.
[b]Values represent mean ± S.E.M. $n \geq 3$, except *n = 2.

Substitution of the 3-pyridyl moiety to an acyl substituent results in a minor reduction in affinity for the nicotinic receptor, by a factor 7 when comparing (*Z*)-**5b** and (*Z*)-**10b**. Increasing the carbon chain length in the ketone-[2.2.2] series from methyl, (*Z*)-**10b** to propyl, (*Z*)-**12b** decreases the affinity for nicotinic receptors by a factor 10. Interestingly, the ester analogue, (*Z*)-**13b**, was not substantially less active than (*Z*)-**12b**.

Changing the azabicyclo[2.2.2]-system in (*Z*)-**5b** to piperidine in (*Z*)-**14d** also results in a significant drop in affinity for the nicotinic receptors.

Basically, the same SAR is observed as those described for analogues of NNC 90-0270, with the (*Z*)-isomers of compounds containing the [2.2.2]azabicyclic ring system having the highest affinity. For the [3.2.1]azabicycle equal affinity between the (*Z*)- and (*E*)-isomers was obtained, again the same pattern as previously observed for the NNC 90-0270 analogues. The data show that the 3-pyridyl and acyl substituents are excellent bioisosters to the isoxazole heterocycle but that even a small change in the aromatic ring, pyridyl to pyrazinyl or isoxazolyl to oxadiazolyl, results in compounds with significantly less affinity.

Computational studies

For a further investigation of the SAR, 12 compounds were chosen for computational studies: seven compounds from the pyridyl-series (**5**, **6**, **9**), two pyrazinyl compounds ((*Z*)- and (*E*)-**7b**), two acyl (**10a,b**), and one oxadiazolyl compound (**14b**).

As the conformational freedom in the compounds containing an azabicycle is very limited, a conformational search was performed by rotation around the single bond connecting the azabicycle and the aromatic heterocycle or the acyl group.

The more flexible piperidine compounds were investigated using the molecular dynamics option in Sybyl.[13] The results from the conformational study are summarized in Table 3. For the further studies only low-energy conformers with a $\Delta E < 3.0$ kcal/mol were considered relevant.

The compounds were superimposed on **16** (Fig. 3), which previously has been shown to possess only one low-energy conformation.[6] The compounds were superimposed using the sp^3 hybridized nitrogen atom (N^+), its complementary anionic site point (**a**), and the hydrogen bond donor site point (**b**) complementary to a nitrogen atom in the heteroaromatic ring or the oxygen atom in the acyl group. The site points were placed 2.9 Å away from the nitrogen atoms (Fig. 3).

In the previously published series the compounds containing a piperidine ring or a (*Z*)-compound containing an azabicyclo[3.2.1]octane ring possessed lower affinities than expected, as the compounds displayed good overlap with the reference compound (**16**).[6] These findings were ascribed to unfavorable steric and electrostatic properties of the compounds.[6] When the molecules in the present pyridine series are superimposed on **16**, the same good overlap between the piperidine compounds ((*Z*)- and (*E*)-**9d**), the (*Z*)-azabicyclo[3.2.1]octane compound ((*Z*)-**5c**), and the oxadiazole compound (**14b**) with **16** is seen. Thus, in view of their moderate affinities, these compounds probably also possess unfavorable steric or electrostatic properties. The pyrazine compound ((*Z*)-**7b**) would be expected to bind to the nicotinic receptors in the same conformation as the *meta*-pyridine (*Z*)-**5b**. However, the conformational analysis shows that this conformation is energetically unfavored by 4.0 kcal/mol. Hence, due to conformational changes the pyrazine ring cannot be used as a bioisoster for the isoxazole ring in this system.

Table 3. Results from the molecular modelling[a]

Compound	Torsion[b]	ΔE (kcal/mol)	RMS[c]	**a**–**b** distance[d]
(*Z*)-**5b**	±54	0	0.110	7.4
(*E*)-**5b**	±53	0	1.800	11.0
(*R*)-(*Z*)-**5c**	−52	0	0.156	—
(*R*)-(*E*)-**5c**	63	0	1.450	10.5
(*Z*)-**6b**	0	0	2.441	2.7
(*Z*)-**7b**	0	0	1.696	11.2
	±130	4.0	0.096	
(*E*)-**7b**	±130	1.8	0.829	8.5
(*Z*)-**9d**	±54	0	0.110	—
(*E*)-**9b**	±128	0	0.746	—
(*R*)-(*Z*)-**10a**	0	0	0.547	8.1
(*Z*)-**10b**	0	0	0.277	7.5
(*Z*)-**14b**	180	0.4	0.187	—

[a]Only the supposed binding conformations are listed.
[b]For chiral compounds only the results for the (*R*)-enantiomers are shown.
[c]Superimposing with **16**.
[d]The **a**–**b** distance was measured only for the molecules in which electrostatic and substituent effects could be ruled out.

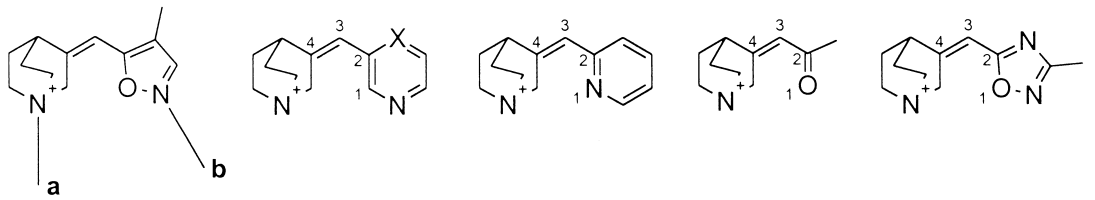
To test whether these compounds display the correlation between the **a**–**b** distance and affinity as previously reported for the isoxazole compounds,[6] the **a**–**b** distance was measured for the molecules in which electrostatic and substituent effects could be ruled out (Table 3). The molecules were represented by their supposed binding conformations. The **a**–**b** distance of the most active compounds ((*Z*)-**5b** and (*Z*)-**10b**) corresponds to the previously reported[6] optimal distance of 7.0–8.0 Å.

Conclusion

The compounds described here comprise a series of compounds with a unique structure compared to other nicotinic agonists described previously. We have shown that it is possible to use a pyridine or an acyl moiety as bioisosteric replacements for the isoxazole heterocycle in this series of nicotine analogues. Additional studies are needed to substantiate the therapeutic potential for these compounds with respect to treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

Experimental

^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC-300 MHz FT-NMR instrument, and COESY,



16 **5,7** **(Z)-6b** **(Z)-10b** **(Z)-14b**

Figure 3. The position of the elements (N^+, **a**, **b**) used for superpositioning the compounds is shown in **16**. (**a**) and (**b**) are placed 2.9 Å away from the nitrogen or oxygen atoms. The numbering refers to the atoms used for measuring the torsional angles.

NOESY and ROESY spectra were recorded at 400 MHz on a Bruker AC-400 MHz FT-NMR instrument. Mass spectra were recorded on a Finnigan 5100 mass spectrometer, and melting points (uncorrected) were determined on a Buchi capillary melting point apparatus. Column chromatography was performed on silica gel 60 (70–230 mesh, ASTM, Merck). Elemental analyses were performed by Novo Nordisk Micro Analytical Laboratory, Denmark, and except for (*Z*)-**7b**, they were within 0.4% of the calculated values. All the reactions described are non-optimized, therefore the yields are not always as high as could be otherwise obtained. The (*Z*/*E*)-purity of the compounds subjected to biological testing was measured by gas chromatography (Chrompack CP9001).

(*Z*)-3-(1-Azabicyclo-[2.2.2]oct-3-ylidene)-3-acetic acid ethyl ester ((*Z*)-**13b**),[10] 2- or 4-(trimethylsilanyl)methylpyridines,[9] and 2-[(*tert*-butyldimethylsilanyl)methyl]-pyridine[14] were synthesized according to modified literature procedures. 3-Acetonylidene-1-azabicyclo[2.2.2]-octane ((*Z*)-**10b**), 3-propionylidene-1-azabicyclo[2.2.1]-heptane ((*Z*)-**11a**), and 3-propionylidene-1-azabicyclo-[2.2.2]octane ((*Z*)-**11b**) were synthesized following a published procedure.[6]

3-[(*tert*-Butyldimethylsilanyl)methyl]-pyridine 3. *n*-Butyllithium (1.6 M, 15.6 mL, 25 mmol) was added to a solution of diisopropylamine (3.6 mL, 25 mmol) in THF (50 mL). The mixture was stirred for 45 min at 0 °C and 3-picoline (2.6 mL, 25 mmol) dissolved in THF (10 mL) was added. The reaction mixture was stirred for 30 min at 0 °C, then cooled to −78 °C and transferred via a cannula to a −78 °C solution of *tert*-butyldimethylsilyl chloride (7.5 g, 50 mmol) in THF (50 mL). The reaction mixture was stirred for another 30 min at −78 °C, then allowed to warm to 20 °C over a 90 min period. Quenching with ice (250 mL) and basification (K_2CO_3) was followed by extraction with diethyl ether (3×150 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The impurities present in the crude product were distilled off, and the residue (4.4 g, 85%) was used without further purification. MS (EI) *m*/*z* 207 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (m, 2H, ArH-2, ArH-6); 7.42 (m, 1H, ArH-5); 7.23 (m, 1H, ArH-4); 2.18 (s, 2H, CH_2); 1.00 (s, 9H, CH_3); 0.00 (s, 6H, CH_3).

2-[(Trimethylsilanyl)methyl]-pyrazine 4. *n*-Butyllithium (2.5 M, 24 mL, 60 mmol) was added to a 0 °C solution of 2,2,6,6-tetramethylpiperidine (6.7 mL, 60 mmol) in dry THF (75 mL) under N_2. The mixture was stirred for 45 min at 0 °C, upon which 2-methylpyrazine (5.5 mL, 60 mmol) dissolved in dry THF (20 mL) was added over a period of 5 min. The reaction mixture was then stirred for another 45 min at 0 °C, whereupon trimethylsilyl chloride (15 mL, 120 mmol) dissolved in THF (50 mL) was added at −78 °C. Stirring was continued at −78 °C for 30 min, followed by an additional 1.5 h, during which the temperature was allowed to rise up to 20 °C. The reaction mixture was poured on ice (600 mL) and stirred until all the ice had melted. Extraction with diethyl ether (2×300 mL), drying (Na_2SO_4) of the combined organic phases, and concentration in vacuo gave 4.8 g (48%) of the title compound as a red oil. The product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (m, 1H, H-*meta*); 8.24 (m, 1H, H-*ortho*); 8.21 (m, 1H, H-*para*); 2.30 (s, 2H, CH_2); 0.09 (s, 9H, CH_3).

3-(3-Pyridyl)methylene-1-azabicyclo[2.2.2]octane 5b. *n*-Butyllithium (1.6 M, 5 mL, 8 mmol) was added to a solution of diisopropylamine (1.15 mL, 8.0 mmol) in THF (25 mL). The mixture was stirred for 45 min at 0 °C, and 3-[(*tert*-butyldimethylsilanyl)methyl]-pyridine (**3**) (1.7 g, 8 mmol) dissolved in THF (5 mL) was added. The reaction mixture was stirred for another 45 min at 0 °C, then cooled to −78 °C, and 1-azabicyclo-[2.2.2]octan-3-one (0.85 g, 7.6 mmol) dissolved in THF (10 mL) was added. The reaction mixture was stirred at −78 °C for 1.5 h, then quenched with water (100 mL) and made alkaline (K_2CO_3). The aqueous phase was extracted with diethyl ether (3×75 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was purified by column chromatography on silica (eluent ethanol:ethyl acetate:ammonium hydroxide, 25% in water: 1:2:0.02). The first fractions contained the (*Z*)-isomer contaminated with small amounts of the (*E*)-isomer. The crude material was crystallized with oxalic acid from methanol to give (*Z*)-3-(3-pyridyl)methylene-1-azabicyclo[2.2.2]octane ((*Z*)-**5b**) in 635 mg (22%) yield as the oxalate salt. The later fractions contained (*E*)-3-(3-pyridyl)methylene-1-azabicyclo[2.2.2]octane ((*E*)-**5b**), which was crystallized as the oxalate salt from acetone in 430 mg (15%) yield.

(*Z*)-5b. Mp 197–200 °C. MS (EI) *m*/*z* 200 (M^+). GC: 98% *Z*. ^{1}H NMR (DMSO-d_6) δ 1.85 (m, 2H, CH_2), 2.05 (m, 2H, CH_2), 2.78 (m, 1H, CH), 3.28 (m, 4H, NCH_2),

4.39 (s, 2H, NCH_2C), 6.50 (s, 1H, CH=), 7.40 (dd, 1H, H-*meta*), 7.63 (dd, 1H, H-*ortho*), 8.40 (d, 1H, H-*para*), 8.47 (s, 1H, H-*ortho*). Anal. ($C_{13}H_{16}N_2$, $2\frac{1}{2}$ $C_2H_2O_4$) C, H, N.

(*E*)-5b. Mp 145–146 °C. MS (EI) *m*/*z* 200 (M^+). GC: 90% *E*. ^1H NMR (DMSO-d_6) δ 1.90 (m, 2H, CH_2), 2.00 (m, 2H, CH_2), 3.12 (m, 1H, CH), 3.32 (m, 4H, NCH_2), 4.05 (s, 2H, NCH_2C=), 6.45 (s, 1H, CH=), 7.40 (dd, 1H, H-*meta*), 7.70 (dd, 1H, H-*ortho*), 8.40 (m, 2H, H-*ortho*/*para*). Anal. ($C_{13}H_{16}N_2$, 2.25 $C_2H_2O_4$) C, H, N.

Compounds **5c** and **5d** were prepared as described for compound **5b** with the variations stated.

(*R*/*S*)-6-(3-Pyridyl)methylene-1-azabicyclo[3.2.1]octane 5c. Starting from 1-azabicyclo[3.2.1]octane-3-one and 3-[(*tert*-butyldimethylsilanyl)methyl]-pyridine (**3**). (*Z*)-**5c** was crystallized as the oxalate salt from acetone. Mp 178–180 °C. MS (EI) *m*/*z* 200 (M^+). GC: 100% Z. ^1H NMR (DMSO-d_6) δ 1.72 (m, 2H, CH_2), 1.88 (m, 2H, CH_2), 3.18 (s, 1H, CH), 3.2–3.4 (m, 4H, NCH_2), 4.35 (d, 1H, J_{gem} = 14 Hz, NCH_2C=), 4.55 (d, 1H, J_{gem} = 14 Hz, NCH_2C=), 6.60 (s, 1H, CH=), 7.43 (dd, 1H, H-*meta*), 7.73 (d, 1H, H-*ortho*), 8.47 (d, 1H, H-*para*), 8.58 (s, 1H, H-*ortho*). Anal. ($C_{13}H_{16}N_2$, 2 $C_2H_2O_4$) C, H, N.

(*E*)-5c. This was crystallized as the hydrochloride salt from ethyl acetate. Mp 254–255 °C. MS (EI) *m*/*z* 200 (M^+). GC: 100% *E*. ^1H NMR (DMSO-d_6) δ 1.7–2.0 (m, 4H, CH_2), 3.3–3.5 (m, 4H, NCH_2), 3.55 (s, 1H, CH), 4.20 (m, 2H, NCH_2C=), 6.68 (s, 1H, CH=), 7.85 (dd, 1H, H-*meta*), 8.28 (d, 1H, H-*ortho*), 8.70 (d, 1H, H-*para*), 8.80 (s, 1H, H-*ortho*). Anal. ($C_{13}H_{16}N_2$, $2\frac{1}{2}$ HCl) C, H, N.

1-Benzyl-3(3-pyridylmethylene)-piperidine 5d. Starting from 1-benzyl-3-piperidone and 3-[(*tert*-butyldimethylsilanyl)methyl]-pyridine (**3**). Column chromatography was performed in ethyl acetate and gave 25% (*Z*)-3-(1-benzyl-3-pyridylmethylene)-piperidine ((*Z*)-**5d**) and 23% (*E*)-3-(1-benzyl-3-pyridylmethylene)-piperidine ((*E*)-**5d**).

The compounds were used without further purification.

(*Z*)-5d. ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (m, 2H, H-*ortho*/*para*); 7.25 (m, 6H, Ar-H + H-*ortho*); 7.03 (dd, 1H, *J* = 9 Hz, H-*meta*); 6.22 (s, 1H, CH=); 3.50 (s, 2H, NCH_2); 3.10 (s, 2H, Ar-CH_2); 2.59 (t, 2H, *J* = 6 Hz, NCH_2); 2.30 (t, 2H, *J* = 6 Hz, CH_2C=); 1.76 (quintet, 2H, *J* = 6 Hz, CH_2).

(*E*)-5d. ^1H NMR (300 MHz, $CDCl_3$) δ 8.49–8.38 (m, 2H, H-*ortho*/*para*); 7.48 (d, 1H, *J* = 9 Hz, H-*ortho*); 7.38–7.14 (m, 6H, Ar-H + H-*meta*); 6.22 (s, 1H, CH=); 3.58 (s, 2H, NCH_2); 3.08 (s, 2H, Ar-CH_2); 2.56 (t, 2H, *J* = 6 Hz, NCH_2); 2.39 (t, 2H, *J* = 6 Hz, CH_2C=); 1.64 (quintet, 2H, *J* = 6 Hz, CH_2).

3-(2-Pyridylmethylene)-1-azabicyclo[2.2.2]octane 6b. A 2.5 M solution of *n*-butyllithium in hexanes (3.4 ml, 8.5 mmol) was added over 5 min to a stirred solution of 2,2,6,6-tetramethylpiperidine (1.19 g, 8.5 mmol) in 10 ml of dry THF under nitrogen at −78 °C. The mixture was stirred for 10 min, whereupon 2-[(trimethylsilanyl)-methyl]-pyridine[9] (1.4 g, 8.5 mmol) was added drop wise over a period of 10 min to the solution of lithium tetramethylpiperidine. After stirring for 10 min a solution of 1-azabicyclo[2.2.2]octan-3-one (1.8 g, 14 mmol) in 5 mL of THF was added over 15 min. Stirring was continued at −78 °C for 1 h. Then the mixture was allowed to warm to room temperature and 25 mL of water was added. The mixture was extracted with diethyl ether (3×25 mL). The extracts were combined and dried (Na_2SO_4). Removal of the solvent in vacuo gave 1.55 g of a slowly crystallizing oil. The crystals were collected by filtration yielding 0.64 g (38%) of (*Z*)-3-(2-pyridylmethylene)-1-azabicyclo[2.2.2]-octane ((*Z*)-**6b**), which was crystallized as the oxalate salt from acetone. The mother liquor was concentrated in vacuo and purified by column chromatography (eluent dichloromethane: methanol:ammonium hydroxide, 25 % in water: 80:20: 0.5%). The last fractions gave 13 mg (0.8%) of a (*Z*/*E*)-mixture.

(*Z*)-6b. Mp 162–164 °C. MS (EI) *m*/z 200 (M^+). GC: 91% *Z*. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.7–2.0 (m, 4H, CH_2), 2.45–2.60 (m, 1H, CH), 2.8–3.1 (m, 4H, NCH_2), 4.00–4.15 (m, 2H, NCH_2C=), 6.20–6.35 (m, 1H, CH=), 7.00–7.20 (m, 2H, H-*ortho*/*para*), 7.5–7.7 (m, 1H, H-*meta*), 8.55–8.65 (m, 1H, H-*meta*). Anal. ($C_{13}H_{16}N_2$, $2\frac{1}{2}$ $C_2H_2O_4$) C, H, N.

Compounds **7b** and **8b** were prepared as described for compound **6b** with the variations stated.

3-(2-Pyrazinyl)methylene-1-azabicyclo[2.2.2]octane 7b. Starting from 2-[(trimethylsilanyl)methyl]-pyrazine (**4**) and 1-azabicyclo[2.2.2]octan-3-one. The reaction mixture was poured on ice (400 mL) and stirred until all the ice had melted. Extraction with diethyl ether (2×250 mL), drying (Na_2SO_4) of the combined organic phases, and concentration in vacuo gave 0.90 g (37%) of the crude product. The product was purified by column chromatography on silica (eluent dichloromethane: methanol:ammonium hydroxide, 25% in water: 80:20: 0.5%). The first fractions contained 80 mg (3.3%) pure (*Z*)-3-(2-pyrazinyl)methylene-1-azabicyclo[2.2.2]octane ((*Z*)-**7b**). The following fractions contained 250 mg (10%) of a mixture of the two isomers, and the last fractions contained 90 mg (3.7%) (*E*)-3-(2-pyrazinyl)-methylene-1-azabicyclo[2.2.2]octane ((*E*)-**7b**) contaminated with some (*Z*)-isomer.

Crystallization with oxalic acid from acetone gave the title compounds as their oxalate salts. The compounds were recrystallized from methanol/acetone.

(*Z*)-7b. Mp 147–152 °C. MS (EI) *m*/*z* 201 (M^+). GC: 92% *Z*. ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, 1H, *J* = 2 Hz, H-*para*); 8.40 (s, 1H, H-*ortho*); 8.28 (d, 1H, *J* = 2 Hz, H-*meta*); 6.29 (s, 1H, CH=); 4.05 (s, 2H, NCH_2C=); 3.10–2.77 (m, 4H, NCH_2); 2.59 (m, 1H, CH); 1.93–1.68 (m, 4H, CH_2). Anal. ($C_{12}H_{15}N_3$, 2 $C_2H_2O_4$, 0.50 CH_3OH) Calcd: C, 49.87; H, 5.33; N, 10.57. Found: C, 50.13; H, 4.92; N, 10.32.

(*E*)-**7b**. Mp 149–150 °C. MS (EI) *m*/*z* 201 (M^+). GC: 75% *E*. ^{1}H NMR (300 MHz, DMSO) δ 8.63 (s, 1H, H-*ortho*); 8.58 (s, 1H, H-*para*); 8.47 (s, 1H, H-*meta*); 6.51 (s, 1H, CH=); 4.24 (m, 1H, CH); 4.11 (s, 2H, NCH_2C=); 3.49–3.18 (m, 4H, NCH_2); 2.13 (m, 4H, CH_2). Anal. ($C_{12}H_{15}N_3$, 1.5 $C_2H_2O_4$, 0.25 H_2O) C, H, N.

(*Z*/*E*)-3-(4-Pyridylmethylene)-1-azabicyclo[2.2.2]octane 8b. Starting from 4-[(trimethylsilanyl)methyl]-pyridine[9] and 1-azabicyclo[2.2.2]octan-3-one. The product mixture was crystallized with oxalic acid from acetone.

(*Z*/*E*)-8b. Mp 185–88 °C. MS (EI) *m*/*z* 200 (M^+). GC: 57% *Z*, 43% *E*. Anal. ($C_{13}H_{16}N_2$, 3 $C_2H_2O_4$) C, H, N.

(*Z*)-8b. ^{1}H NMR ($CDCl_3$-free base, 300 MHz) δ 1.7–2.0 (m, 4H, CH_2), 2.55–2.65 (m, 1H, CH), 2.8–3.1 (m, 4H, NCH_2), 3.80–3.90 (m, 2H, NCH_2C=), 6.15–6.25 (m, 1H, CH=), 7.05–7.15 (m, 2H, H-*ortho*), 8.45–8.55 (m, 2H, H-*meta*).

(*E*)-8b. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.7–2.0 (m, 4H, CH_2), 2.55–2.65 (m, 1H, CH), 2.8–3.1 (m, 4H, NCH_2), 3.80–3.90 (m, 2H, NCH_2C=), 6.15–6.25 (m, 1H, CH=), 7.05–7.15 (m, 2H, H-*ortho*), 8.45–8.55 (m, 2H, H-*meta*).

(*Z*)-3-(3-Pyridylmethylene)-piperidine (*Z*)-9d. (*Z*)-1-Benzyl-3(3-pyridylmethylene)-piperidine ((*Z*)-**5d**) (650 mg, 2.46 mmol) was dissolved in toluene (50 mL) and concentrated in vacuo. The now anhydrous (*Z*)-**5d** was then redissolved in toluene (50 mL) under N_2 and cooled to 0 °C on an ice bath. Addition of 1-chloroethyl chloroformate (400 μL, 3.70 mmol) was followed by removal of the ice bath, upon which the reaction mixture was refluxed for 4 h. The reaction mixture was then cooled to 20 °C, concentrated in vacuo, and the residue dissolved in methanol (25 mL). Upon stirring at reflux temperature for 2 h, the mixture was evaporated and the resulting oil dissolved in 1 N HCl (75 mL). The water phase was extracted with diethyl ether (3×50 mL), made alkaline (K_2CO_3), and extracted with ethyl acetate (3×75 mL). The combined ethyl acetate extracts were washed with brine (75 mL), dried ($MgSO_4$), and evaporated. The crude product (310 mg) was dissolved in ethyl acetate (15 mL) and crystallized with 2 M HCl in ethyl acetate to give 55 mg (11%) of (*Z*)-3-(3-pyridylmethylene)-piperidine ((*Z*)-**9d**) hydrochloride.

(*Z*)-9d. Mp 218–221 °C. MS (EI) *m*/*z* 174 (M^+). GC: 97% (*Z*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (m, 2H, H-*ortho*/*para*); 7.45 (d, 1H, *J* = 9 Hz, H-*ortho*); 7.23 (dd, 1H, *J* = 9 Hz, H-*meta*); 6.22 (s, 1H, CH=); 3.55 (s, 2H, NCH_2C=); 2.95 (t, 2H, *J* = 5 Hz, NCH_2); 2.51–2.32 (m, 3H, NH + CH_2C=); 1.76 (quintet, 2H, *J* = 5 Hz, CH_2). Anal. ($C_{11}H_{14}N_2$, 2 HCl, 1.25 H_2O) C, H, N.

(*E*)-3-(3-Pyridylmethylene)-piperidine (*E*)-9d. The title compound was prepared as described for (*Z*)-**9d**, starting from (*E*)-1-benzyl-3(3-pyridylmethylene)-piperidine ((*E*)-**5d**). The crude product was crystallized as the oxalate salt in 15% overall yield.

(*E*)-9d. Mp 133–134 °C. MS (EI) *m*/*z* 174 (M^+). GC: 100% (*Z*). ^{1}H NMR (400 MHz, DMSO) δ 9.1 (bs, 3H, H^+); 8.48 (m, 2H, H-*ortho*/*para*); 7.69 (d, 1H, *J* = 9 Hz, H-*ortho*); 7.42 (dd, 1H, *J* = 9 Hz, H-*meta*); 6.60 (s, 1H, CH=); 3.89 (s, 2H, NCH_2C=); 3.18 (m, 2H, NCH_2); 2.53 (m, 2H, CH_2C=); 1.76 (m, 2H, CH_2). Anal. ($C_{11}H_{14}N_2$, 2.25 $C_2H_2O_4$) C, H, N.

(*Z*)-3-Acetonylidene-1-azabicyclo[2.2.2]octane (*Z*)-10b.[6] Dimethyl 2-oxopropylphosphonate (4.9 g, 30 mmol) was added dropwise to a −5 °C solution of 1-azabicyclo[2.2.2]octan-3-one (2.0 g, 16 mmol) and KOH (1.93 g, 30 mmol) in water (7.7 mL). The reaction mixture was stirred between 0 °C and −5 °C for 90 h. The reaction mixture was quenched with 1 N HCl (50 mL), rinsed three times with diethyl ether, made alkaline (K_2CO_3), and extracted with dichloromethane (5×50 mL). The solvent was removed after drying ($MgSO_4$). The crude compound was crystallized as the oxalate salt from ethanol (100 mL) and then recrystallized from ethanol (50 mL) to give the title compound in 800 mg (21%) yield.

(*Z*)-10b. Mp 189–190 °C. MS (EI) *m*/*z* 165 (M^+). GC: 97% *Z*. ^{1}H NMR (DMSO-d_6) δ 1.80 (m, 2H, CH_2), 2.00 (m, 2H, CH_2), 2.18 (s, 3H, CH_3), 2.71 (m, 1H, CH), 3.28 (m, 4H, NCH_2), 4.29 (s, 2H, NCH_2C=), 6.35 (s, 1H, CH=). Anal. ($C_{10}H_{15}NO$, HCl, $1\frac{1}{2}$ H_2O) C, H, N.

Compounds **10a** and **12b** were prepared as described for compound **10b** with the variations stated.

(*R*/*S*)-(*Z*)-3-Acetylmethylene-1-azabicyclo[2.2.1]heptane (*Z*)-10a. Starting from 1-azabicyclo[2.2.1]heptan-3-one and dimethyl 2-oxoethylphosphonate. (*Z*)-**10a**. Mp 176–177 °C. MS (EI) *m*/*z* 151 (M^+). GC: 96% *Z*. ^{1}H NMR (DMSO-d_6) δ 1.55 (m, 1H, CH_2), 2.15 (s, 3H, CH_3), 2.20 (m, 1H, CH_2), 3.15 (s, 2H, NCH_2), 3.20 (m, 1H, NCH_2), 3.35 (m, 1H, NCH_2), 3.50 (d, 1H, CH), 4.17 (s, 2H, NCH_2C=), 6.50 (s, 1H, CH=). Anal. (C_{13} $H_{16}N_2$, $C_2H_2O_4$, $\frac{1}{4}$ H_2O) C, H, N.

(*R*/*S*)-3-Propionylmethylene-1-azabicyclo[2.2.1]heptane (*Z*)-11a.[6] GC: 95% *Z*.

3-Propionylmethylene-1-azabicyclo[2.2.2]octane (*Z*)-11b.[6] GC: 100% *Z*.

(*Z*)-3-Butyrylmethylene-1-azabicyclo[2.2.2]octane (*Z*)-12b. Starting from 1-azabicyclo[2.2.2]octan-3-one and dimethyl 2-oxopentylphosphonate.[15] Mp 135–137 °C. MS (EI) *m*/*z* 193 (M^+). GC: 86% *Z*. ^{1}H NMR (300 MHz, MeOH) δ 6.41 (m, 1H, CH=); 4.50 (s, 2H, NCH_2C=); 3.52–3.29 (m, 4H, NCH_2); 2.82 (m, 1H, CH); 2.53 (t, 2H, *J* = 7 Hz, CH_2CO); 2.26–2.12 (m, 2H, CH_2); 2.18–1.93 (m, 2H, CH_2); 1.61 (sextet, 2H, *J* = 7 Hz, CH_2); 0.94 (t, 3H, *J* = 7 Hz, CH_3). Anal. ($C_{12}H_{19}NO$, $C_2H_2O_4$, 0.25 H_2O) C, H, N.

(*Z*)-3-(3-Methyl-[1,2,4]-oxadiazol-5-yl)methylene-1-azabicyclo[2.2.2]octane (*Z*)-14b. Sodium (150 mg, 6.0 mmol) was dissolved in dry ethanol (15 mL) under N_2, and (*Z*)-3-(ethoxycarbonyl-methylene)-1-azabicyclo[2.2.2]octane

((*Z*)-**13b**) (600 mg, 3.0 mmol) and *N*-hydroxy-acetamidine (450 mg, 6.0 mmol) were added dissolved in dry ethanol (8 mL). Upon this the reaction mixture was stirred for 90 min at 80 °C, then at 20 °C overnight. The reaction mixture was filtered, the residue washed thoroughly with methanol, and the combined filtrates concentrated in vacuo. The resulting oil was dissolved in ethyl acetate (50 mL) and the organic phase was washed with brine (2×50 mL). Drying ($MgSO_4$) and evaporation gave 790 mg (128%) of a yellow oil. Column chromatography (eluent: ethyl acetate:methanol: ammonium hydroxide, 25% in water: 80:20:0.5%) gave 570 mg (93%) of (*Z*)-**14b**.

Crystallization with oxalic acid from acetone gave 700 mg of (*Z*)-**14b** oxalate as white crystals.

Mp 146–147 °C. MS (EI) *m*/*z* 205 (M^+). GC: 100% *Z*. ^{1}H NMR (400 MHz, DMSO): δ 6.68 (s, 1H, CH=), 4.41 (s, 2H, NCH_2C=), 3.40–3.22 (m, 4H, NCH_2), 2.96 (s, 1H, CH), 2.37 (s, 3H, CH_3), 2.08 (m, 2H, CH_2), 1.86 (m, 2H, CH_2). Anal. ($C_{11}H_{15}N_3O$, $C_2H_2O_4$, $\frac{1}{4}$ H_2O) C, H, N.

(*Z*)-3-(3-Ethyl-[1,2,4]oxadiazol-5-yl)methylene-1-azabicyclo[2.2.2]octane (*Z*)-15b. The title compound was prepared in 46% yield as described for (*Z*)-**14b** starting from (*Z*)-3-(ethoxycarbonyl-methylene)-1-azabicyclo-[2.2.2]octan ((*Z*)-**13b**) and *N*-hydroxy-propionamidine.

The reaction mixture was stirred for 5 h at 80 °C, before stirring at 20 °C overnight. Mp 125–127 °C. MS (EI) *m*/*z* 219 (M^+). GC: 100% *Z*. ^{1}H NMR (400 MHz, DMSO): δ 6.69 (s, 1H, CH=), 4.44 (s, 2 H, NCH_2C=), 3.32 (m, 4H, NCH_2), 2.98 (s, 1H, CH), 2.74 (quartet, 2H, J = 10 Hz, Ar-CH_2), 2.08 (m, 2H, CH_2), 1.88 (m, 2H, CH_2), 1.25 (t, 3H, J = 10 Hz, CH_3). Anal. ($C_{12}H_{17}N_3O$, 1.5 $C_2H_2O_4$) C, H, N.

Molecular modelling

The calculations were performed using Sybyl 6.5.[13] The structures were built by combining and altering standard fragments from Sybyl. Using Gasteiger–Hückel charges the structures were minimized until a local minimum was reached.

Grid search. The conformational search employing rotation around the single bond connecting the bicycle and the heteroaromatic ring or the ketone was done using the GRID SEARCH command, which contains an energy minimization method that keeps the torsion angle under examination constant. The torsional scans were performed from 0 to 360° in 5° intervals, and the inherent minimization used the TRIPOS force field and Gasteiger–Hückel charges. The maximum number of iterations was set to 1000 and the termination gradient to 0.001. As the compounds were protonated, the dielectric constant was set to 4 while keeping the cut-off value at 8 Å. The resulting low-energy structures were then minimized, but this time without any constraints.

Molecular dynamics. The remaining compounds were investigated using the molecular dynamics option in Sybyl. In the simulation, the compounds were heated to 1000 K for 100 ps. The step size was 10 fs, and every 500 fs a structure was selected giving a total of 201 structures. The maximum number of iterations was set to 10,000. Due to the amount of heat applied, some of the compounds racemized and/or *Z*/*E* interchanged. The 200 structures resulting from a dynamics run were then minimized.[16] The structures were superpositioned using the FIT ATOMS command.

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