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Synthesis and Evaluation of Diazine Containing Bioisosteres of (−)-Ferruginine as Ligands for Nicotinic Acetylcholine Receptors

Daniela Gündisch,[b] Klaus Harms,[c] Simone Schwarz,[a] Gunther Seitz,[a,*] Milton T. Stubbs[a] and Thomas Wegge[a]

[a]*Department of Pharmaceutical Chemistry, Philipps-University, Marbacher Weg 6, D-35032 Marburg, Germany*
[b]*Department of Pharmaceutical Chemistry, Rhein. Friedr.-Wilhelm-University, Kreuzbergweg 26, D-53115 Bonn, Germany*
[c]*Fachbereich Chemie, Philipps-University, Hans-Meerwein-Straße, D-35032 Marburg, Germany*

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Abstract—In this structure–affinity relationship (SAFIR) study, the bioisosteric potential of diazines in the field of ferruginine-type nAChR ligands was investigated. Novel enantiopure analogues of (−)-Ferruginine (**3**) such as **6**–**8** were synthesized utilizing enantiomerically pure *N*-protected (+)-2-tropanone **9** from the 'chiral pool' as versatile chiral building block and a palladium-catalyzed Stille cross-coupling of the tributylstannyl diazines **12**, **14** and **16** with the vinyl triflate **11** of (+)-2-tropanone **9**. The structures of the novel diazine analogues **6**–**8** of (−)-ferruginine (**3**) were assigned on the basis of spectral data, that of ligand **7** being additionally verified by X-ray crystallography. The bioisosteric replacement of the acetyl moiety as structural part of the lead compound **3** with the pyridazine, pyrimidine and pyrazine nucleus resulted in ligands with high to moderate affinity for the central α4β2 and remarkably low affinity for the α7* nAChR subtypes. Among the compounds synthesized and tested, **7** was the most active one with $K_i = 3.7$ nM (α4β2). Compared with the lead **3**, this value represents a 30-fold improvement in the affinity for the α4β2 subtype combined with a substantially improved selectivity ratio between the α4β2 and α7* subtypes. © 2001 Elsevier Science Ltd. All rights reserved.

Introduction

There is accumulating evidence, that ligands acting with high agonistic affinity at nicotinic acetylcholine receptors (nAChRs) may possibly be utilized as therapeutics in the treatment of various neurological and mental disorders related to a decrease in cholinergic function.[1] In addition, worldwide interest in nAChR agonists as potential analgesics has emerged.[1,2] In our efforts in developing new ligands with high affinity and better selectivity for the multifarious subtypes of nAChRs[3,4] as compared to naturally occurring prototypical agonists such as (±)-epibatidine (**1**) or (−)-nicotine (**2**), we were interested in the nAChR ligand properties of some variations of the alkaloidal toxine (−)-ferruginine (**3**); this is the unnatural enantiomer of (+)-ferruginine,[5] a potent neurotoxin from the arboreal species Darlingia ferruginea (J. F. Bailey) and darlingiana (F. Muell)[5,6] characterized by an 8-aza-bicyclo[3.2.1]octene skeleton.[7–9] (Scheme 1).

Bioisosteric replacement of the chloropyridyl moiety of (±)-epibatidine,[10] for example with methylisoxazole,[11] pyrimidine[12] or pyridazine[4] furnished novel agonists for investigation of the receptor subtypes involved in the central pharmacological activities of nicotine. In the case of the pyridazine bioisoster **4** of epibatidine much of the affinity of the natural alkaloid was retained, but with a substantially improved selectivity ratio between the α4β2 and α3β4 subtypes. Hence, we were interested in continuing this series by varying the nature of the two main ligand elements of the nicotinic pharmacophore, the positively charged sp^3-hybridized nitrogen in an azabicycle and the hydrogen bond acceptor group in the ligand, important for affinity for the nAChRs.[13]

Thus, we prepared and evaluated the novel diazine bioisosteres **6**, **7** and **8** of the lead compound **3** in order to examine the borders of the nicotinic pharmacophore.[13] All of these novel bioisosteric ligands **6**–**8** are characterized by the azabicyclo[3.2.1]octene pharmacophore of **3** and by replacement of the acetyl group in **3** with a diazine nucleus such as pyridazine, pyrimidine and pyrazine. Hence, the target ligands are provided with structural features for molecular recognition at

*Corresponding author. Tel.: +49-6421-282-5809; fax: +49-6421-282-6652; e-mail: seitzg@mailer.uni-marburg.de

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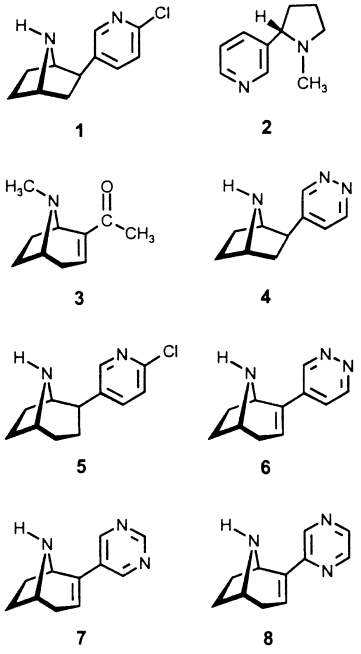
nAChRs similar to the only recently evaluated epibatidine-related ligand **5** with significant inhibition of [^{3}H]epibatidine binding at nAChRs ($IC_{50} = 7.1\,\mu M$) although distinctly weaker in comparison with (±)-epibatidine (**1**).[14]

Herein, we wish to report the first syntheses of these three analogues of (−)-ferruginine (**3**), the bioisosteres **6**–**8** utilizing enantiopure *N*-protected (+)-2-tropanone **9**[15,16] from the 'chiral pool' as a versatile starting material and a palladium-catalyzed Stille cross-coupling of the tributylstannyl diazines **12**, **14** and **16** with the vinyl triflate **11** of the tropanoid ketone **9**. Additionally, the new ligands were tested for in vitro affinity to central nAChRs such as α4β2 and α7* subtypes.

Chemistry

The synthetic routes to the novel target ligands **6**–**8**, in which the acetyl group of the lead **3** is replaced by a diazine moiety, started with the enantiomerically pure *N*-protected 2-tropanone **9** as chiral building block, easily available by degradation of (−)-cocaine hydrochloride[16] in a high-yielding three-step synthesis. This includes a *N*-demethylation with ethyl chloroformate/K_2CO_3.[14,15] A convenient and practical procedure for the introduction of the diazine nucleus into the tropane moiety seemed to be an approach with the Stille-type cross-coupling as the key step.[17–19] This requires the vinyl triflate **11** and the corresponding organostannanes of the diazines as starting materials.

The pyridazine containing bioisostere **6** was prepared by a Stille-cross-coupling of the vinyl triflate **11** and 4-tributylstannyl-pyridazine **12**.[20] Compound **11** was readily available from ketone **9** with KHMDS/Comins' reagent **10**[21] (Scheme 2). A successful coupling of the organostannane **12** with the azabicycloalkene triflate **11** appeared difficult. Therefore, extensive studies were conducted in the hope of optimizing the yield of the cross-coupling reaction. Hence, we initially examined the coupling process to form the coupled product **13** under a variety of conditions with regard to the catalyst, solvent, temperature and presence of LiCl, CuI and $As(Ph)_3$. Neither of the classical catalysts examined such as $Pd[P(Ph)_3]_4$, $Pd(PPh_3)_2Cl_2$ or $Pd_2(dba)_3$ worked satisfactorily with or without co-catalytic CuI and LiCl as promoter of the cross-coupling reaction. Finally, it was found that of the catalysts tested $Pd(PhCN)_2Cl_2$ was the only one which afforded the coupled product in more than 80% yield. Of the solvents tested (THF, DMF, DME, NMP) DMF and NMP were effective and the highly polar NMP was the best choice. In summary, the desired coupling product **13** was reproducibly obtained from **11** and **12** as starting materials using 10 mol% of $Pd(PhCN)_2Cl_2$ as the catalyst and 10 mol% of CuI as a co-catalyst. After heating the complex mixture for 3 days at 110 °C in dry NMP as the solvent in the presence of three equivalents of LiCl and Ph_3As the ferruginine analogue **13** was obtained in 82% yield. Removal of the protecting carbamate group in the last step of the sequence by $(CH_3)_3SiI$ in boiling $CHCl_3$[22] afforded ligand **6** as the base in satisfying 75% yield.



Scheme 1.

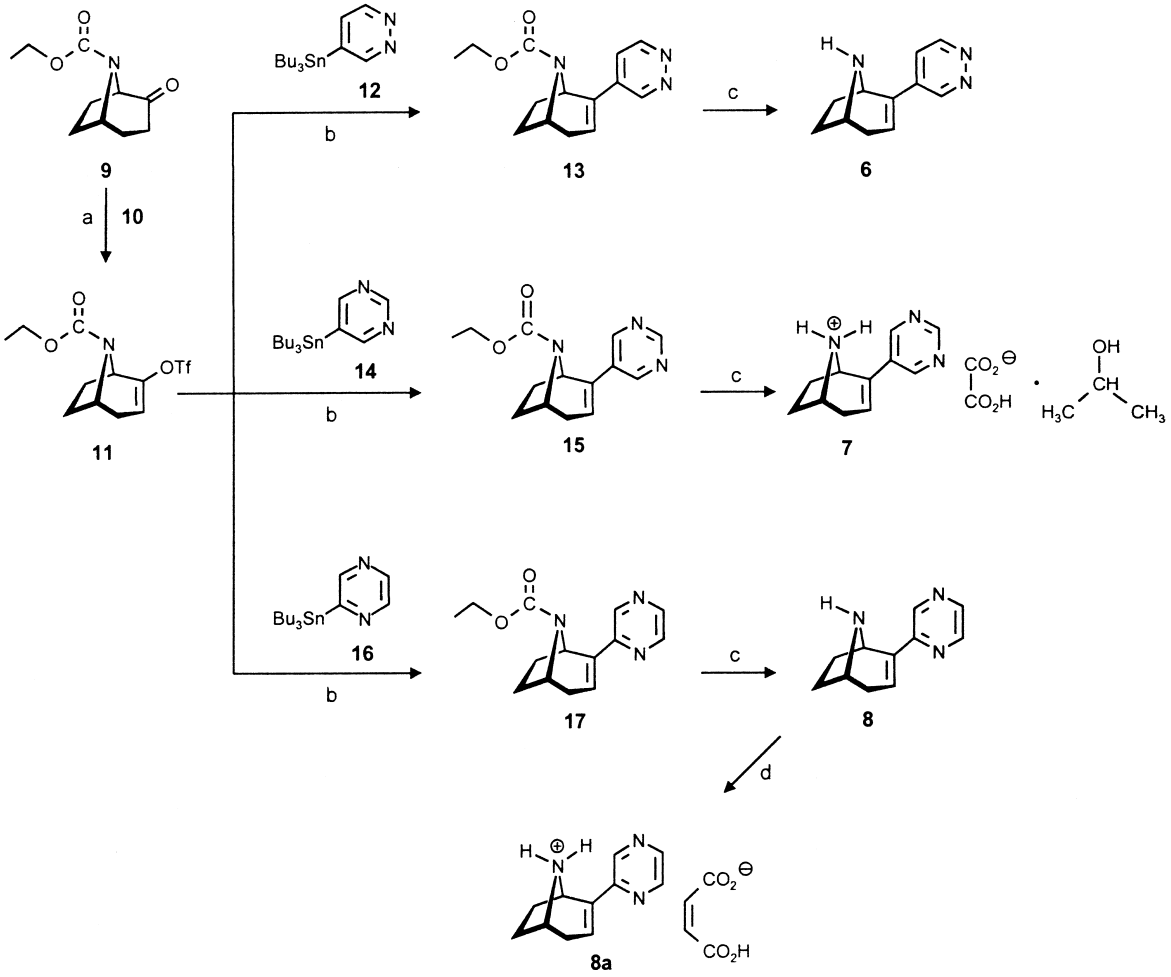
The described procedure—demonstrating an easy access to a novel enantiomerically pure ferruginine analogue such as target compound **6**, without the need to effect resolutions—encouraged further synthesis of the analogously pyrimidine coupled variant **7** of ferruginine **3**. Thus, the approved route to enantiomerically pure **6** could equally be applied to the synthesis of the pyrimidine containing bioisoster **7** by simply switching from the organostannane **12** to the 5-tributylstannyl-pyrimidine (**14**).[23] Under similar conditions used for the preparation of the pyridazine coupled compound **13**, reaction of the vinyltriflate **11** with the organostannane **14** provided the pyrimidine coupled species **15** with 81% yield. Treatment of the carbamate with concentrated aqueous hydrochloric acid (37%) or advantageously with $(CH_3)_3SiI$ in boiling $CHCl_3$ and subsequent basic work up with CH_3OH/CH_3ONa yielded the target compound **7** in satisfying yield. The base **7** could be characterized as the hydrogenoxalate, which crystallized with one molecule of 2-propanol.

The approved Stille-coupling could also successfully be applied for the preparation of the pyrazine containing bioisoster **17** of (−)-ferruginine (**3**) utilizing the triflate **11** and the organostannane **16** as starting materials. Compound **16** was easily accessible by direct lithiation of pyrazine and subsequent reaction with tri-*n*-butyltinchloride.[23c] The cross-coupling afforded the *N*-protected species **17** with a slightly reduced yield of 54%. This could easily be transformed to the deprotected target compound **8** upon treatment with $(CH_3)_3SiI$ in boiling $CHCl_3$ and subsequent basic methanolysis. The resulting base **8** obtained in 87% yield could be characterized as the corresponding hydrogenmaleate **8a**.

X-ray crystallographic analysis of the target ligand 7

Of all the synthesized ligands, the most potent one was the pyrimidine bioisoster **7** of ferruginine (**3**) with $K_i = 3.7$ nM ($\alpha4\beta2$). Thus it was deemed of value to subject appropriate single crystals of this compound to an X-ray diffraction analysis for several reasons. First, to the best of our knowledge, till to day no detailed information are accessible concerning the three dimensional arrangement of ligands such as **6**–**8**. Therefore, this investigation represents the first X-ray structure determination of a *N*-unprotected 8-azabicyclo[3.2.1]octene ring system combined with a 3-pyrimidine substituent attached to the bicycle at C-2.

Second, the crystal structure of ligand **7** opened the possibility to obtain for the first time greater insight into structural features important for nAChR binding thus resulting beneficial for the definition of relevant distances between the pharmacophoric elements suggested by the Sheridan model.[13b] Figure 1 shows the ORTEP diagram of the structure of two solid-state conformations of the hydrogenoxalate of **7** solved by X-ray diffraction methods as detailed in the Experimental. Thus, the structure of ligand **7** was unambiguously verified. Interestingly, in the crystal lattice of the oxalate salt of the pyrimidine bioisoster **7** of the lead **3** two different low energy conformations **7a** and **7b** are fixed with the same probability, crystallizing each with one molecule of the solvent 2-propanol. The conformational feature of **7a** differs from **7b** with respect to an approximate 24.5° rotation of the bond connecting the two pharmacophoric elements, the 8-azabicyclo[3.2.1]octene cation and the pyrimidine ring. The C-3′–C-2′–C-9′–C-10′ dihedral angle in **7a** exhibits a value of 144.6° (see atom labeling in Fig. 1) whereas the corresponding C-3–C-2–C-9–C-10 dihedral angle in **7b** is 170.1°. Both conformers display similar distances with respect to Sheridan's triangle, the well known model of the nicotinic pharmacophore. This model suggests that the essential groups in the pharmacophore are: (A) a cationic center (e.g., a protonated sp^3 nitrogen), (B) an electronegative atom capable of forming a hydrogen bond, and (C) a dummy point or an atom which defines a line along which the hydrogen bond may form. For (*S*)-nicotine, this latter point is considered to be a point toward the centroid of the pyridine ring, for **7a** and **7b** a point toward the centroid of the pyrimidine moiety. For (−)-nicotine, the optimal distances between the three points were estimated to (A–B) = 4.8 ± 0.3 Å; (A–C) = 4.0 ± 0.3 Å; (B–C) = 1.2 Å. The corresponding triangle data obtained from the X-ray structure of the two conformers



Scheme 2. Results and conditions: (a) (1) KHMDS, DME, −78 °C; (2) 2-N(Tf_2)-5-chloropyridine (**10**), $NaHCO_3/H_2O$, 85%; (b) (1) $Pd(PhCN)_2Cl_2$, CuI, LiCl, Ph_3As; (2) KF, CH_3OH; (c) (1) $(CH_3)_3SiI$, $CHCl_3$, reflux, 3.5 h; (2) CH_3ONa, CH_3OH; see Experimental; (d) maleic acid, butanone.

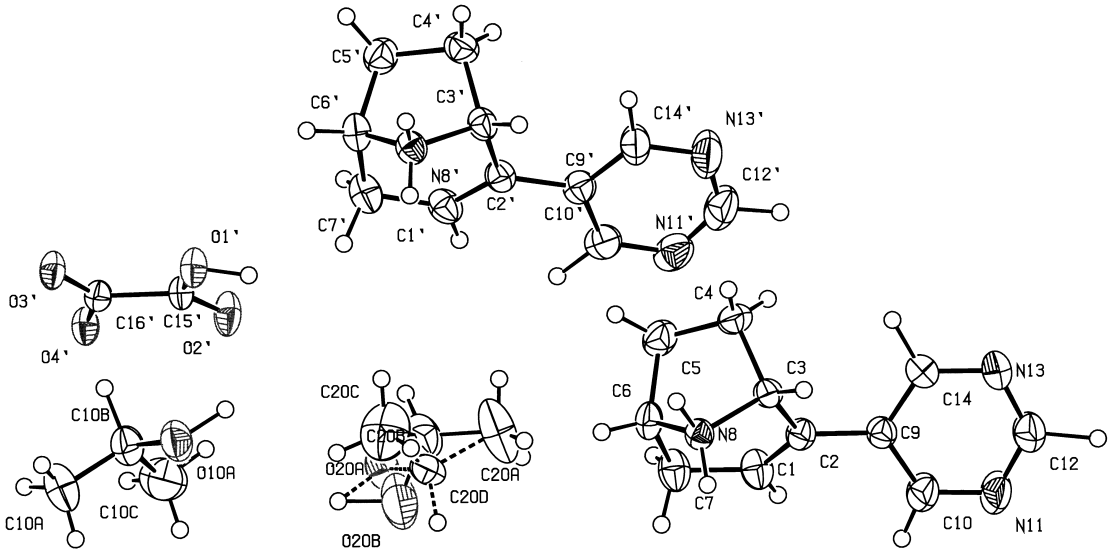


Figure 1. ORTEP plot showing the two solid-state conformations **7a** (top) and **7b** (below) of the ligand **7**.

7a and **7b** are: **7a**: (A–B) = 5.69 Å; (A–C) = 5.03 Å; (B–C) = 1.38 Å [the distance between the sp^3 nitrogen atom and the second pyrimidine ring nitrogen is (A–D) = 5.93 Å]; **7b**: (A–B) = 5.67 Å; (A–C) = 5.08 Å; (B–C) = 1.38 Å [the distance (A–D) = 6.08 Å].

These data reveal that both solid-state conformers feature spatial arrangements of the pharmacophoric elements far beyond the range proposed by the Sheridan model. The intramolecular N–N distance ranging from 5.69 Å (in **7a**) and 5.67 Å (in **7b**), a parameter believed to be crucial for high affinity binding to nAChRs, is much more comparable to that found for the lowest-energy conformation of (±)-epibatidine (5.51 Å),[13d,f] one of the most potent nAChR ligands known. This agrees well with the suggestion that the optimal inter-nitrogen distance for high-affinity binding should be closer to 5.5 Å. Like (±)-epibatidine (**1**) and the lead (−)-ferruginine (**3**) all the new ligands **6**–**8** are quite rigid molecules with a rotatable bond between the two putative pharmacophoric elements, the azabicycle and the diazine moiety. It remains uncertain, which low-energy conformation, for example of ligand **7**, is responsible for the affinity for the nAChR subtypes. It is commonly recognized that the bioactive conformation of a ligand does not necessarily correspond to the lowest-energy conformation either in vacuo, in solution, or in a crystal. However, it can be anticipated that the solid-state conformation is energetically stable and therefore not too far from the energy of the bioactive conformation.

In vitro receptor binding

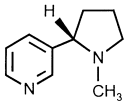
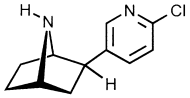
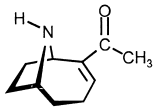
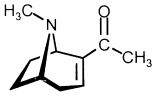
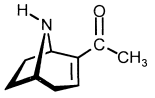
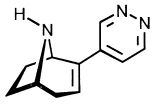
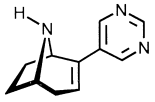
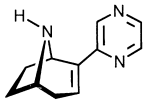
The ferruginine bioisosteres **6**–**8**, listed in Table 1 were tested for their in vitro affinity for $(\alpha4)_2(\beta2)_3$ and α7* nAChR subtypes by radioligand binding assays. To determine the affinities for the $(\alpha4)_2(\beta2)_3$ nAChR subtype[24,25] a previously described competition assay[24] was used with (±)-[^{3}H]epibatidine and P2 membrane fraction of Sprague–Dawley rat forebrain. These studies demonstrated that the specific binding of (±)-[^{3}H]epibatidine to crude synaptic membranes of rat forebrain, at concentrations up to 800 pM, is characterized by a single population of binding sites with $K_d = 8 \pm 0.3$ pM.[26] It has been previously found that the predominant receptor with high affinity for [^{3}H]nicotine, (−)-[^{3}H]cytisine, (±)-[^{3}H]epibatidine, and 5-[^{125}I]iodo-A-85380 in rat brain is composed of α4 and β2 subunits.

To characterize binding of each of the (−)-ferruginine variants to the α7* nAChR subtype, [^{3}H]MLA and membrane fractions isolated from the rat brain were used, [^{3}H]MLA bound to a single population of binding sites exhibited a K_d value of 1.2 ± 0.2 nM ($n = 3$). The affinity determined was in good agreement with previously published values[26] ($K_d = 1.86$ nM). [^{3}H]MLA bound to rat brain membranes with regional distribution characteristic of α-BTX-sensitive, putative α7* subunit-containing nAChRs.[26]

As shown in Table 1, the above characterized competition assays yielded K_i values of 0.838 nM for (−)-nicotine (**1**) and 0.008 nM for (±)-epibatidine (**2**). These results are consistent with recently reported in vitro measurements of the natural alkaloids.[24] Compared to (±)-epibatidine (+)-anatoxin-a exhibited ca. 140-fold lower affinity ($K_i = 1.1$ nM) for the $(\alpha4)_2(\beta2)_3$ subtype and ca. 20-fold lower affinity for the α7* subtype ($K_i = 90$ nM). Changing the 9-azabicyclo[4.2.1]nonene pharmacophore in (+)-anatoxin-a to the 8-azabicyclo-[3.2.1]octene moiety of (−)-ferruginine or norferruginine caused a dramatic, 100-fold loss of affinity with K_i values dropping into the higher nanomolar range ($K_i = 120$ or 94 nM) for $(\alpha4)_2(\beta2)_3$ nAChRs, whereas the affinity for the α7* subtype is only ca. 3-fold lower in comparison with anatoxin-a.

The data of the novel ferruginine analogues **6**–**8** demonstrate that the three isomeric diazine heterocycles are suitable bioisosteres to the acetyl moiety of **3**, but that a change from a 1,2- to a 1,3- or 1,4-diazine results in compounds with significantly different affinities.

Table 1. Radioligand binding affinities of novel (−)-ferruginine (**3**) bioisosteres to $(\alpha4)_2(\beta2)_3$ and α7* nAChRs in comparison with (−)-nicotine, (±)-epibatidine, (+)-anatoxin-a[a]

Structure	Compound	$(\alpha4)_2(\beta2)_3$[b] (±)-[^{3}H]-epibatidine rat brain K_i(nM)	α7*[b] [^{3}H]MLA rat brain K_i(nM)
	(−)-Nicotine	0.838±0.132	127±5 [^{125}I] α-BTX
	(±)-Epibatidine	0.008±0.0002	4±0.5 [^{125}I] α-BTX
	(+)-Anatoxin-a	1.1±0.2	90±4
	(−)-Ferruginine	120±5	330±21
	(−)-Nor-ferruginine HCl	94±2.1	>100
	**6**	113±4.7	No effect
	**7**	3.7±0.6	5000±230
	**8**	400±17	13500±244

[a]Values represent mean±SEM obtained from *n* independent experiments where *n* = 3–5.
[b]Naturally expressed nAChRs.[24]

Substitution of the acetyl moiety of **3** to a 4-pyridazine substituent (**6**) results in approximately equal affinity for the $(\alpha4)_2(\beta2)_3$ nAChR subtype, however to a drastic reduction in affinity for the α7* subtype (see Table 1).

The most active compound of the novel diazine bioisosteres of the lead compound **3** proved to be the pyrimidine analogue **7** with $K_i = 3.7$ nM in the lower nanomolar concentrations and ca. 30-fold more active in comparison with **3**. In contrast, the pyrazine containing bioisoster **8** proved to be a significantly weaker ligand with a K_i value ca. 3-fold higher in comparison with that of **3**. Although the relevant internitrogen distances for the three bioisosteres **6**–**8** are approximately equal (because the conformational freedom in compounds containing an azabicycle, though rather limited, is given in like manner for **6**–**8** by rotation around the single bond connecting the azabicycle and the aromatic diazines) exchange of the diazine moieties obviously results in modification of the hydrogen-bond acceptor ability, crucial for nAChR affinity.

Conclusion

Following the concept that the design and synthesis of (−)-ferruginine (**3**) analogues could contribute to further understanding of the SAFIR at the nAChRs, we have studied the bioisosteric potential of three diazines, replacing the acetyl moiety as structural part of the lead **3**. A key step of our new and efficient synthetic approach to these novel diazine analogues of **3** in enantiomerically pure form was a palladium-catalyzed Stille cross-coupling of the vinyl triflate **11** of the enantiopure (+)-2-tropanone with the tributylstannyl diazines **12**, **14** and **16**. The most active ligand described was the pyrimidine bioisoster **7**, the structure of which was verified by X-ray crystallography, revealing an internitrogen distance close to that of (±)-epibatidine. Interestingly both the pyridazine bioisoster **6** and the pyrimidine bioisoster **7** proved to be more effective ligands on the α4β2 subtype compared to the leads (−)-ferruginine and (−)-norferruginine and differentiate somewhat better between α4β2 and α7* subtype.

Experimental

General procedures

Standard vacuum techniques were used in handling of air sensitive materials. Melting points were determined on a 'Leitz-Heiztischmikroskop' HM-Lux and are uncorrected. Solvents were dried and freshly distilled before use according to literature procedures. IR spectra were recorded on a Perkin–Elmer 257, 398 and a Nicolet FT-IR spectrometer 510-P; liquids were run as films, solids as KBr pellets. ^{1}H NMR and ^{13}C NMR were recorded on Jeol JNM-GX 400 and LA 500 and δ values are given in ppm relative to tetramethylsilane as internal standard (*J* values in HZ). Mass spectra were measured with a Fisons Instruments VG 70-70 E spectrometer at 70 eV ionizing voltage (EI). Column chromatography was carried out on Merck silica gel 40 (40–60 mesh, flash chromatography) or Merck silica 60, 70–230 mesh. Reactions were monitored by thin-layer chromatography (TLC) by using plates of silica gel (0.063–0.200 mm, Merck) or silicagel-60F_{254} microcards (Riedel de Haen). Optical rotations were determined on a Jasco DIP-370 polarimeter. UV–Vis spectra were recorded on a Shimadzu scanning spectrophotometer UV-2101 PC. Combustion analyses were performed internally.

(1*R*)2-(Trifluoromethanesulfonyloxy)-8-azabicyclo[3.2.1]-oct-2-ene-8-carboxylic acid ethyl ester (11). To a stirred solution of potassium hexamethyldisilazide (KHMDS, 1.0 g, 5.0 mmol or 10 mL of a 0.5 M solution in toluene) in dry dimethoxyethane (DME, 25 mL), cooled to −78 °C under Ar, was added drop-wise (ca. 1 mL/min) a solution of the ketone **9** (788 mg, 4.00 mmol) in dry tetrahydrofurane (5 mL). After stirring for 40 min at −78 °C, a solution of **10** (1.9 g, 4.8 mmol) in dry DME (5 mL) was added in one portion. The resulting solution was stirred at −78 °C for 2 h and then allowed to warm to 0 °C. Ether (40 mL) and then a solution of saturated aqueous $NaHCO_3$ (15 mL) were added. The aqueous phase was separated and re-extracted with ether (2×25 mL) and the combined organic phase dried with K_2CO_3. After filtration the solvent was evaporated in vacuo and the resulting yellow oil purified by column chromatography on silica gel (column 15×2 cm, with *n*-hexane/ethyl acetate 3:1) to provide **11** as a colourless oil (1.12 g, 85%); R_f = 0.39 (*n*-hexane/ethyl acetate 4:1); $[\alpha]_D^{20}$ −29.7 (*c* 1.1, $CHCl_3$); IR (film) 2987, 1712, 1421 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.0 Hz, 3H), 1.63 (s, broad, 1H), 1.90 (d, broad, *J* = 17.4 Hz, 1H), 2.04 (s, broad, 1.5H), 2.18 (dt, *J* = 2.5 Hz, *J* = 10.8 Hz, 2H), 2.82 (s, broad, 0.5H), 4.08 (q, *J* = 7.0 Hz, 2H), 4.24–4.39 (m, 2H), 5.49 (t, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 29.1, 31.9, 34.4, 51.5, 55.6, 61.5, 113.9, 118.4 (q, *J* = 320.0 Hz, CF_3), 151.1, 154.3; MS (70 eV) *m*/*z* (%) 329 (15, M^+), 154 (100); HRMS calcd for $C_{11}H_{14}F_3NO_5S$: 329.0541, found 329.0544.

(1*R*)-2-(4-Pyridazinyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid ethyl ester (13). Bis(benzonitrile)-palladium(II)chloride (15.5 mg, 30.0 μmol), CuI (11.4 mg, 60.0 μmol), Ph_3As (19 mg, 60.0 μmol), LiCl (38 mg, 0.9 mmol) and triflate **11** (110 mg, 0.3 mmol) were placed in an argon-flushed flask and dissolved in dry NMP (0.5 mL). The flask with the resulting solution was immersed in an oil bath maintained at a temperature of 90 °C and a solution of 4-pyridazinyltributyltin (**12**) (118 mg, 0.32 mmol) in dry NMP (0.5 mL) was added. After stirring at 90 °C for 3 h the black slurry was allowed to cool to room temperature, then a solution of KF (300 mg) in CH_3OH (10 mL) was added and the mixture stirred for 12 h. After evaporation of the solvent purification of the residue by flash chromatography on silica gel (column 15×2 cm, ethyl acetate) afforded **13** as colourless oil (64 mg, 82%). R_f = 0.26 (ethyl acetate); $[\alpha]_D^{20}$ = −16.0 (*c* 0.1, CH_3OH); IR (film) 2957, 1686, 1425 cm^{-1}; UV (CH_3OH): λ_{max} (lgε) = 255 nm (3.08), 355 (2.45); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 6.9 Hz, 3H), 1.70 (s, broad, 1H), 1.85–1.97 (m, 1H), 2.03 (dd, *J* = 15.9, 4.0 Hz, 1H), 2.08–2.29 (m, 2H), 2.90 (s, broad, 1H), 4.06 (q, *J* = 6.9 Hz, 2H), 4.41 (s, broad, 1H), 4.77 (s, broad, 1H), 6.15 (t, *J* = 3.5 Hz, 1H), 7.31 (s, broad, 1H), 9.09 (d, *J* = 5.5 Hz, 1H), 9.12–9.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, two rotamers, ratio 1:1) δ 14.6, 26.8 and 27.8, 29.7 and 30.7, 34.2 and 35.2, 51.9, 54.2, 61.2, 120.9, 127.2, 132.1, 136.0, 148.1, 151.2, 154.5; MS (70 eV) *m*/*z* (%) 259 (100, M^+); HRMS calcd for $C_{14}H_{17}N_3O_2$: 259.1321, found 259.1320.

(1*R*)-2-(4-Pyridazinyl)-8-azabicyclo[3.2.1]oct-2-ene (6). To a solution of carbamate **13** (20 mg, 73 μmol) in degassed $CHCl_3$ (1 mL) was added freshly distilled TMSI (19 mg, 95 μmol) and the resulting pale brown solution was heated in a sealed flask at 80 °C for 3.5 h. After cooling to ambient temperature the solvent was evaporated in vacuo, then a solution of sodium methoxide (11 mg, 0.2 mmol) in dry CH_3OH (1 mL) was added and the reaction mixture stirred at room temperature for 15 min. The volatile components were removed in vacuo and the residue purified by column chromatography on reversed-phase silica gel (ICN RP C-18, column 8×1 cm, eluting with *n*-hexane/CH_3OH = 100:0⇒1:1.) The purification by column chromatography was repeated for two times and afforded **6** (11 mg, 75%) as a pale yellow oil. R_f = 0.20 (CH_2Cl_2/CH_3OH/concd aq NH_3 = 95:15:0.1); $[\alpha]_D^{20}$ −18.5 (*c* 0.1, CH_3OH); IR (film) 3218, 2964, 1589, 1405 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.93–2.0 (m, 1H), 2.24–2.31 (m, 1H), 2.37–2.45 (m, 2H), 2.48–2.52 (m, 1H), 3.04 (d, ^3J = 20.4 Hz, 1H), 4.26 (t, ^3J = 5.9 Hz, 1H), 4.81 (d, ^3J = 5.3 Hz, 1H), 6.62 (t, ^3J = 5.3 Hz, 1H), 7.75 (dd, ^3J = 5.5 Hz, ^4J = 3.4 Hz, 1H), 9.14 (dd, ^3J = 5.5 Hz, ^5J = 1.1 Hz, 1H), 9.34 (dd, ^4J = 2.5 Hz, ^{5}J = 1.1 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ 30.46, 35.84, 36.34, 52.44, 54.74, 120.52, 126.91, 136.47, 139.72, 148.01, 151.19; MS (70 eV) *m*/*z* (%) 187 (70, M^+), 158 (100); HRMS calcd for $C_{11}H_{14}N_3$ [M^+ + H]: 188.1108, found 188.1160.

(1*R*)-2-(5-Pyrimidinyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid ethyl ester (15). Bis(benzonitrile)-palladium(II)-chloride (32 mg, 0.1 mmol), CuI (12 mg, 0.1 mmol), Ph_3As (32 mg, 0.1 mmol), LiCl (120 mg, 2.9 mmol) and triflate **11** (220 mg, 0.66 mmol) were placed in an argon-flushed flask and dissolved in dry

DMF (0.7 mL). After addition of tributyltinpyrimidine (**14**) the mixture was heated in an oil bath at 80 °C for 1.5 h, cooled to ambient temperature and KF (200 mg), dissolved in CH_3OH (10 mL), was added. The mixture was stirred for 40 min, then diluted with ethyl acetate (25 mL), filtered and the filtrate evaporated in vacuo. Purification of the residue by column chromatography on silica gel (column 3×20 cm, ethyl acetate) afforded **15** as a pale yellow oil (140 mg, 81%). R_f (ethyl acetate) 0.44. $[\alpha]_D^{20}$ −100.1 (*c* 0.35, CH_2Cl_2); IR (film) 2983, 1697, 1418 cm^{-1}; UV (CH_2Cl_2): λ_{max} (lgε) = 244 nm (3.76); ^1H NMR (500 MHz, $CDCl_3$): δ 1.22 (bs, 3H), 1.73 (bs, 1H), 1.93–2.03 (m, 2H), 2.12–2.17 (m, 1H), 2.26 (bs, 1H), 2.81–2.97 (m, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 4.44 (bs, 1H), 4.74 (bd, 1H), 5.89 (s, 1H), 8.69 (s, 2H), 9.08 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.8, 29.9, 34.5, 35.0, 52.2, 55.2, 61.4, 124.8, 132.5, 138.7, 153.6 (2 C), 154.8, 157.6; MS (70 eV) *m*/*z* (%) 259 (100, M^+); HR-MS calcd for $C_{14}H_{17}N_3O_2$: 259.1321, found 259.1344.

(1*R*)-2-(5-Pyrimidinyl)-8-azabicyclo[3.2.1]oct-2-ene (7). A solution of the carbamate **15** (80 mg, 0.31 mmol) in aqueous hydrochloric acid (0.8 mL, 37%) was heated at reflux for 4 h. The solvent was removed in vacuo, the residue dissolved in acetone (2 mL) and the solution slightly warmed until a precipitate was formed which showed to be extremely hygroscopic. It was dissolved in water (1 mL) and aqueous ammonia added until a basic pH was reached. The aqueous phase was extracted with CH_2Cl_2 (2×2 mL) the combined organic phase dried with Na_2SO_4, filtered and the solvent removed to afford **7** (17 mg, 30%). This was dissolved in butanone/2-propanol (2 mL, 1:1) and a saturated solution of oxalic acid (8.2 mg, 0.09 mmol) was added affording a precipitate (16 mg, 53%) of a colourless, hygroscopic salt, which crystallizes with one molecule of 2-propanol. Use of the same deprotection procedure as described for **6** yielded 62% of the free base **7** as a pale yellow oil. R_f = 0.39 (eluent CH_2Cl_2/MeOH/NH_3 = 95:5:1); $[\alpha]_D^{20}$ −50.4° (*c* 1.65×10^{-3}, MeOH pa); IR (KBr) 2924, 1620, 1560, 1414 cm^{-1}; UV (CH_3OH): λ_{max} (lgε) = 244 nm (3.17) (*c* 3.8×10^{-4}, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 1.02–1.04 (m, 6H), 1.87–1.92, 2.18–2.35 (2m, 5H), 2.86–2.93 (m, 1H), 3.78–3.83 (m, 1H), 4.15 (m, 1H), 4.67 (d, *J* = 3 Hz, 1H), 6.19 (t, *J* = 3.4 Hz, 1H), 8.77 (s, 2H), 8.98 (s, 1H); ^{13}C NMR (500 MHz, CD_3OD) δ 25.5, 29.5, 34.4, 34.9, 54.9, 56.6, 65.0, 126.2, 132.7, 134.7, 155.4, 158.8, 167.0; MS (70 eV) *m*/*z* (%) 187 (41, M^+), 41 (100); HRMS calcd for $C_{11}H_{13}N_3$: 187.1108, found 187.1109.

Crystal structure determination of 7

To gain single crystals of **7** for X-ray analysis compound **7** (10 mg) was dissolved in butanone/2-propanol (1 mL, 1:1) and filtered through a folded filterpaper in such a way that the filtrate directly went into a test tube (bore ca. 1 cm). Then *n*-hexane (3 mL) chosen as suitable precipitant was layered carefully down the side of the tube on to the solution. The tube was then corked and left to stand undisturbed for 12 h under exclusion of moisture, furnishing colourless crystals suitable for X-ray crystallographic analysis.

A crystal plate of approximate dimensions 0.52×0.33×0.12 mm was mounted on a glass fiber. All measurements were made on a Nonius CAD4 diffractometer using Cu-K_α on a sealed tube generator. Empirical formula ($C_{11}H_{14}N_3 + C_3H_8O + C_2HO_4$, molecular mass 337.37 au, Z = 4. Unit cell parameters: *a* = 10.8874(7) Å, *b* = 11.2061(9) Å, *c* = 14.4504(12) Å, α = γ = 90°, β = 108.246(6)°; calculated density 1.3383(2) g/cm^3; space group $P2_1$ (#4); Cu-K_α radiation, λ = 1.5418 Å. A total of 6315 reflections were collected [5046 > 4σ(F)] with R(int) = 0.0284. Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of 25 carefully centered high angle reflections. The data were collected at a temperature of −80 °C using the ω-2θ scan technique to a maximum 2θ value of 140°. Omega scans of (0.85 + 0.23 tanθ)° were collected up to a maximum of 30 s. A total of 6315 reflections (−12 < h < 13, −13 < k < 13, −17 < l < 0) was collected. The intensities of two representative reflections were measured every 60 min, and the orientation checked after every 150 reflections. No decay correction was applied. The linear absorption coefficient, μ, for Cu-K_α radiation is 8.34 cm^{-1}. Data were reduced using XCAD4[27] and the structure solved using SIR92.[28] Refinement was carried out with SHELX97.[29] Two molecules of **7** were identified in the asymmetric unit, together with two solvent molecules each of oxalic acid and 2-propanol; one of the 2-propanol molecules exhibited two distinct conformations of roughly equal occupancy.

The final cycle of full-matrix least-squares refinement was based on 5046 observed reflections ($F_o > 4.00\sigma(F_o)$] and 587 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of: R1 = 0.0562 (0.0753 for all 6315 reflections), wR2 = 0.1419 for all 6315 reflections. Weight = $1/[\sigma^2(F_o^2) + (0.0603*P)^2 + 0.77*P]$ where $P = (Max(F_o^2, 0) + 2 * F_c^2)/3$. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.22 and −0.20 $e^-/Å^3$, respectively (1σ level 0.049). Torsion angles of special interest: C1–C2–C9–C10 −36.09 (0.56)°, C1′–C2′–C9′–C10′ −13.50 (0.55)°.[30]

(1*R*)-2-(2-Pyrazinyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid ethyl ester (17). Bis(benzonitrile)-palladium(II)-chloride (28 mg, 0.07 mmol), CuI (30 mg, 0.25 mmol), LiCl (135 mg, 3.2 mmol), Ph_3As (45 mg, 0.14 mmol) and triflate **11** (306 mg, 0.93 mmol) were placed in an argon-flushed flask and dry DMF (0.7 mL) was added. The flask was dipped into a preheated oil bath (85 °C) and the organostannane **16** (390 mg, 1 mmol) added. The resulting mixture was heated at 85 °C under argon for 12 h, cooled to room temperature and a solution of KF (200 mg) in dry CH_3OH (10 mL) was added. The mixture was stirred for 40 min, diluted with ethyl acetate (25 mL), filtered and the filtrate concentrated in vacuo. Purification of the residue by column chromatography on silica gel (column 2×18 cm, eluent: (1) *n*-hexane/ethylacetate = 3:1; (2) *n*-hexane/ethylacetate = 2:1) afforded **17** (130 mg, 54%) as a pale yellow syrup. R_f = 0.34 (*n*-hexane/ethylacetate = 2:1);

$[\alpha]_D^{20}$ −131.2 (*c* 0.36, CH_2Cl_2); IR (film): ν = 2978, 1700, 1518, 1468, 1416 cm^{-1}; UV (CH_2Cl_2): λ_{max} (lgε) = 229 nm (4.27), 286 (4.01); ^1H NMR (400 MHz, $CDCl_3$) δ 1.21–1.28 (m, 3H), 1.70–2.09, 2.14–2.19 (2m, 5H), 2.93 (bs, 1H), 4.08–4.14 (m, 2H), 4.48 (bs, 1H), 5.18 (s, 1H), 6.41 (t, *J* = 44 Hz, 1H), 8.36 (s, 1H), 8.47 (s, 1H), 8.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 29.6, 34.5, 34.9, 52.0, 53.5, 61.0, 125.9, 126.3, 140.9, 142.4, 143.5, 151.3, 154.4; MS (70 eV) *m*/*z* (%) 259 (100, M^+); HRMS calcd for $C_{14}H_{17}N_3O_2$: 259.1321, found 259.1323.

(1*R*)-2-(2-Pyrazinyl)-8-azabicylo[3.2.1]oct-2-ene maleate (8a). To a solution of the carbamate **17** (105 mg, 0.4 mmol) in dry $CHCl_3$ (4 mL) was added TMSI (113 μL, 0.8 mmol) and the mixture heated under reflux and an atmosphere of argon in a sealed flask for 3 h. The mixture was cooled to room temperature, the volatile components removed in vacuo, then dry CH_3OH (2 mL) and a solution of HCl in diethyl ether (2 M, 0.3 mL) were added and the solvent removed again. Water (1 mL) and aqueous NH_3 were added until a basic pH was reached. The aqueous phase was extracted with CH_2Cl_2 (3×2 mL), the combined organic phase dried with $MgSO_4$, filtered and the solvent removed in vacuo to afford the free base **8** (80 mg, 87%) as a pale yellow oil. One part of the base **8** (29 mg, 0.16 mmol) was dissolved in butanone (1 mL), the solution heated to 70 °C and a solution of maleic acid (15 mg, 0.12 mmol) added to afford the salt **8a** as a white, very hygroscopic solid. R_f = 0.33 (CH_2Cl_2/CH_3OH/aq NH_3 = 90:10:1); $[\alpha]_D^{20}$ −35.9 (*c* 0.2, CH_3OH); IR (KBr): ν = 2962, 2610, 1952, 1700, 1685, 1653, 1558 cm^{-1}; UV (CH_3OH): λ_{max} (lgε) = 286 nm (3.71), 240 (3.84); ^1H NMR (400 MHz, CD_3OD) δ 1.77–1.82, 1.98–2.20 (2m, 4H), 2.28 (dd, *J* = 4.6 Hz, *J* = 19.6 Hz, 1H), 2.83 (bd, *J* = 19.8 Hz, 1H), 4.04–4.08 (m, 1H), 4.91 (d, *J* = 4.8 Hz, 1H), 6.05 (s, 2H), 6.56 (t, *J* = 3.4 Hz, 1H), 8.30 (d, ^3J = 2.6 Hz, 1H), 8.41 (dd, ^3J = 2.6 Hz, ^4J = 1.6 Hz, 1H), 8.75 (d, ^4J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 29.7, 34.8, 35.2, 55.0, 55.3, 127.1, 136.8, 138.5, 142.6, 144.3, 145.2, 151.8, 171.3; MS (70 eV) *m*/*z* (%) 187 (62, M^+), 159 (100); HRMS calcd for $C_{11}H_{13}N_3$: 187.1109, found 187.1114.

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30. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications nos. CCDC 163387. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk).