exo-2-(Pyridazin-4-yl)-7-azabicyclo[2.2.1]heptanes: Syntheses and Nicotinic Acetylcholine Receptor Agonist Activity of Potent Pyridazine Analogues of (±)-Epibatidine

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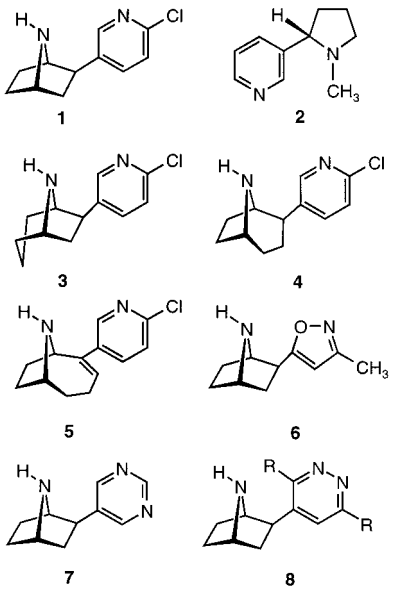
A new strategy for the straightforward synthesis of novel racemic epibatidine analogues is presented, in which the 2-chloropyridinyl moiety of epibatidine is bioisosterically replaced by differently substituted pyridazine rings. A key step of the new syntheses is the inverse type Diels−Alder reaction of the electron-rich enol ether **13** with the electron-deficient diazadiene systems of the 1,2,4,5-tetrazines **14a**−**d** to yield the novel pyridazine analogues of (±)-epibatidine **18**, **19**, **22**, and **24**. In addition preparation of the N-substituted derivatives, such as **26** and **28**, is described. The structures of the novel epibatidine analogues were assigned on the basis of spectral data, that of compound **24** being additionally verified by X-ray crystallography exhibiting two racemic solid-state conformations in the crystal lattice and representing the first X-ray structure of an unprotected 7-azabicyclo[2.2.1]heptane moiety. The nAChR agonist activity of the racemic compounds **18**, **19**, **22**, **24**, and **28** was assayed in vitro by whole-cell current recordings from *Xenopus* oocytes expressing different recombinant nicotinic receptors from the rat. Among the compounds synthesized and tested, the pyridazine analogue **24** of (±)-epibatidine and its *N*-methyl derivative **28** were found to be the most active ones retaining much of the potency of natural epibatidine but with a substantially improved selectivity ratio between the α4β2 and α3β4 subtypes.

Introduction

Epibatidine (**1**) (Scheme 1), a pyridylazabicyclo[2.2.1]-heptane, was discovered by Daly[1] as a trace alkaloid in skin extracts of an Ecuadorian frog. It was reported to be a non-opioid analgesic agent with a potency far greater than that of morphine in mice.[1] The absolute configuration of the natural product was shown to be 1*R*,2*R*,4*S*.[2] Its structural similarity to (−)-nicotine (**2**) suggested that epibatidine would have activity at nicotinic receptors. Indeed, epibatidine (**1**) was shown to exert its antinociceptive actions through neuronal nicotinic acetylcholine receptors (nAChR).[3−7] Due to its unique structure[2,8] and its remarkable pharmacological activity as a non-opioid antinociceptive agent, several approaches to the synthesis[9−22] of the alkaloid have been reported to make compound **1** available in sufficient amounts for extensive pharmacological evalutations. These have demonstrated that (+)- and (−)-epibatidine (**1**) are highly potent agonists at several nAChR subtypes yet, in contrast to the nicotines, have little enantioselectivity. In addition, (±)-epibatidine (**1**) itself is much too toxic to be a useful therapeutic agent and it was hoped that novel analogues with better selectivity between different nAChR subtypes could be of greater promise. In particular, it has been suggested[4] that an enhanced selectivity for the α4β2 receptor subtype over the α3β4 variant could lead to an improved antinociceptive effect with reduced toxic liability. Thus, based upon the approach that bioisosteric alteration in the ring systems of **1** might provide compounds with better ratios of pharmacological to toxicological activity, a series of novel neuronal nAChR ligands has been developed recently: one series involves replacement of the azabicycloheptane moiety of **1** by similar azabicy-

Scheme 1. Epibatidine (**1**), Nicotine (**2**), and Selected Novel nAChR Ligands with Replacement of the Azabicycloheptane Moiety or 2-Chloropyridinyl Unit of **1**



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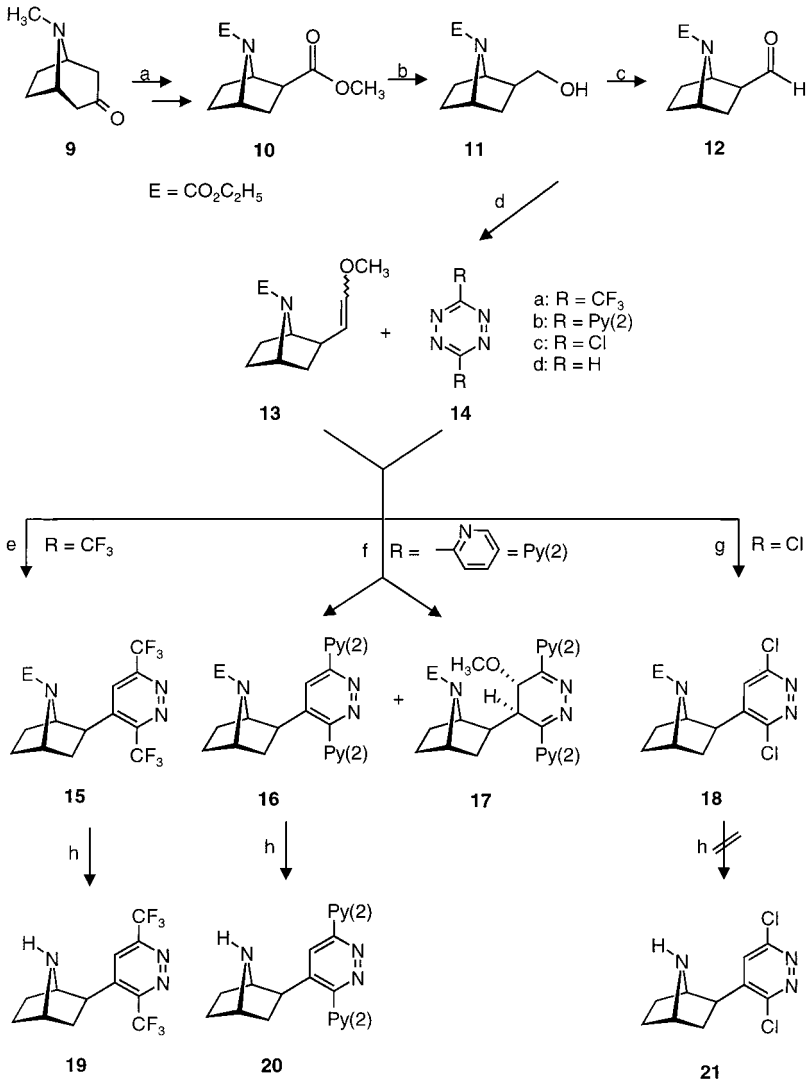
Scheme 2[a]



[a] Reagents and conditions: (a) lit. ref 25; (b) LiCl, $NaBH_4$, EtOH/THF, 12 h, rt, 96%; (c) DMSO/$(COCl_2)$ then $N(C_2H_5)_3$, 94%; (d) $[(Ph)_3PCH_2OCH_3]^+Cl^-$, LDA, toluene, 2 h, 0°C, 83%; (e) + **14a**, toluene, 12 h, reflux, 88%; (f) + **14b**, toluene, 2 days, 120 °C, pressure bottle, 32% and 59%; (g) + **14c**, toluene, 18 h, reflux, 74%; (h) $(CH_3)_3SiI$, $CHCl_3$, 4 h, reflux, then CH_3OH.

cloalkanes. Among others, (±)-homoepibatidine (**3**),[23−25] the 8-azabicyclo[3.2.1]octane derivative **4**,[26] and UB-165 (**5**)[27] have been synthesized and reported to show significant nicotinic receptor binding affinity and stimulant activity.

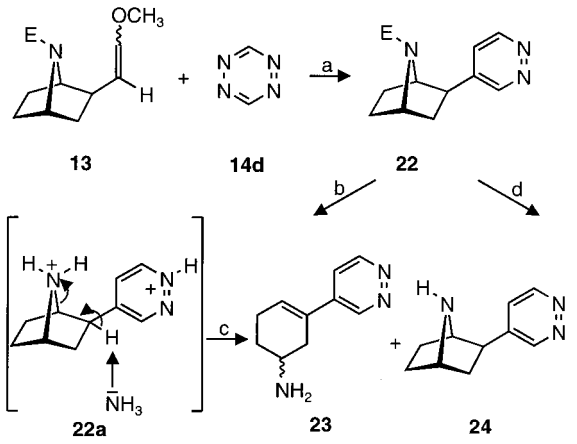
A second approach replaces the 2-chloropyridinyl unit of **1** with various heteroaryl groups, providing novel nAChR ligands with quite promising properties. Thus epiboxidine (**6**),[28] in which the 2-chloropyridinyl ring has been replaced by the methylisoxazolyl moiety, proved to be a potent antinociceptive agent with a better activity/toxicity ratio compared to epibatidine (**1**). Similar results were obtained with the 5-pyrimidinylepibatidine analogue **7**[29] exhibiting high affinities for the [^{3}H]cytisine rat brain nicotinic acetylcholine binding sites.

To develop new ligands selective for distinct nAChR substypes with potent analgesic activity, reduced toxicity, and a satisfactory safety profile,[30] we have started to synthesize a new series of hitherto unknown epibatidine analogues, in which the 2-chloropyridinyl moiety is replaced by other nitrogen heterocycles such as 1,2-, 1,3-, or 1,4-diazines and 1,2,4-triazines. Herein we report a new strategy for the synthesis of novel epibatidine analogues which evokes a conceptually simple route to novel *exo*-2-(pyridazin-4-yl)-7-azabicyclo[2.2.1]-heptanes such as **8**, utilizing as the key step the inverse electron demand Diels−Alder reaction of the enol ether **13** with the π-electron-deficient 1,2,4,5-tetrazines **14a**−**d**.[31,32]

Results and Discussion

Chemistry. An attractive synthetic route to novel epibatidine analogues such as **8** originates from the commercially available 3-tropanone **9** which could easily be converted in a three-step procedure utilizing Bai's methodology[25] to the racemic ester **10** with the requisite *exo* configuration. As outlined in Scheme 2, the ester **10** could be transformed by sequences of conventional reactions to yield the desired electron-rich dienophilic enol ether **13**. This reacted with the electron-deficient diazadiene systems of the 1,2,4,5-tetrazines **14a**−**c** in a $LUMO_{diene}/HOMO_{dienophile}$-controlled Diels−Alder reaction[31,32] to yield the N-protected epibatidine analogues **15**−**18** in good yields after inverse [4+2] cycloaddition and elimination of nitrogen. Removal of the protecting

Scheme 3[a]



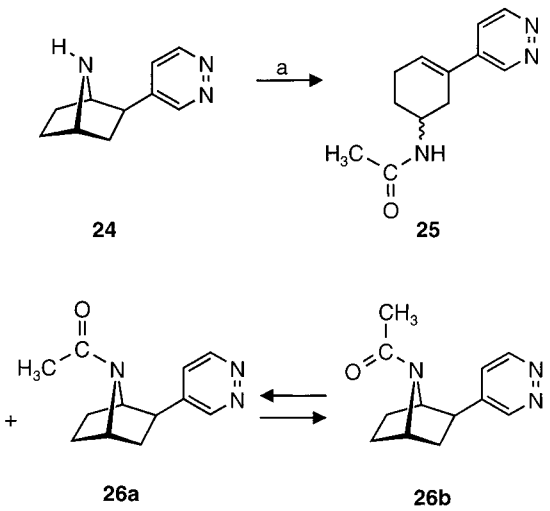
[a] Reagents and conditions: (a) toluene, 2 days, reflux, 74%; (b) $(CH_3)_3SiI$, $CHCl_3$, 4 h, 80 °C, then CH_3OH, $-CO_2$; (c) + concd aq ammonia → pH = 10; (d) dioxane/aq HCl (37%), 20 h, reflux, 28%.

groups from **15** and **16** by $(CH_3)_3SiI$ in boiling $CHCl_3$[33] afforded the desired pyridazine analogues **19** and **20** of epibatidine, which could be isolated in high yields as air-stable pale yellow oils. To our disappointment, all attempts to deprotect carbamate **18** by conventional methods furnished complex mixtures of unidentified products.

Fortunately the enol ether **13** was reactive enough to cycloadd also to the less activated parent tetrazine **14d**,[31] affording the N-protected epibatidine analogue **22** in more than 70% yield. Surprisingly, an attempt to deprotect the carbamate **22**, performed under the same conditions as described above with e.g. **15**, produced an unexpected species in fair yield, identified as the pyridazine-substituted cyclohex-3-enylamine **23** by its spectroscopic properties (MS, ^1H and ^{13}C NMR). A comprehensive and plausible mechanism for the unprecedented formation of **23** via ring opening is outlined in Scheme 3. We suppose that − in contrast to the behavior for instance of the carbamate **15** − the carbamate **22** reacts under the conditions employed (excess of trimethylsilyl iodide, refluxing in chloroform followed by methanolyses) to yield the 2-fold protonated intermediate **22a**. On treatment with concentrated aqueous ammonia, this suffers a heterolytic cleavage of the C−N linkage of the bicyclic cationic system as indicated, giving rise to the formation of the unexpected cyclohexene derivative **23** in addition to small amounts of the desired epibatidine analogue **24**. Therefore, an alternative synthetic approach was required in order to gain **24** with satisfactory yield. Treatment of carbamate **22** with dioxane/aqueous hydrochloric acid (37%) seemed to be a promising approach. Indeed the target compound **24** could be isolated in ca. 30% yield as a white solid after careful chromatography on silica gel, by which the byproduct **23** could be separated. Spectroscopic data analysis (MS, ^1H and ^{13}C NMR) conclusively proved the expected structure of **24**.

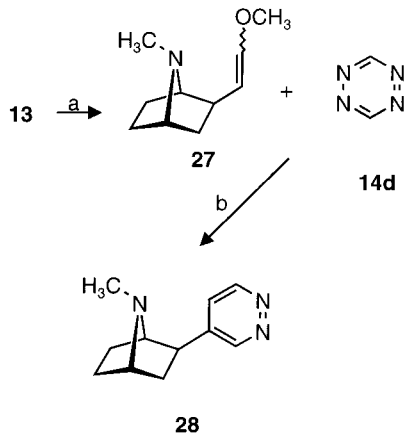
To gain greater insight into structural features important for nAChR binding[34−39] we varied the nitrogen substituents at the bicyclic system of **24**. It is well-known that in some cases introduction of an *N*-methyl group increases affinity (as with (−)-nornicotine/(−)-nicotine) whereas in other cases it has little to no effect (as with (−)-epibatidine/(−)-*N*-methylepibatidine).[35] N-

Scheme 4[a]



[a] Reagents and conditions: (a) pentafluorophenyl acetate, DMF, 14 h, rt, 13% and 69%.

Scheme 5[a]



[a] Reagents and conditions: (a) $LiAlH_4/Et_2O$, 12 h, reflux, 87%; (b) toluene, 12 h, reflux, 19%.

Methylation of pyrido[3,4-*b*]homotropane (PHT) or (−)-cytisine results in decreased affinity. With this in mind, we began to prepare the N-acetylated and N-methylated derivatives of the epibatidine analogue **24** as outlined in Schemes 4 and 5.

Because acetylation of the secondary amine **24** with acetic anhydride according to a method published for epibatidine[1] failed, the highly reactive and more selective acetylating agent pentafluorophenyl acetate[40,41] was used successfully to furnish the acetylated derivative **26a**,**b** (as a pair of rotamers about the N−CO bond) in 69% yield. The byproduct **25** (13% yield) could be separated by careful column chromatography. As with *N*-acetylepibatidine, the ^1H NMR spectrum of **26a**,**b** was recognized as a series of doubled signals, stemming from two rotamers **26a**,**b** in a 1.6:1 ratio. Because of the partial double bond character of the *N*-acetyl bond, interconversion between the rotamers is very slow, giving rise to the observed series of doubled signals.[25,42]

Our attempts to alkylate the secondary amine **24** directly with methyl iodide in solutions of various anhydrous solvents and in the presence of a variety of basic catalysts were not successful in contrast to similar attempts with (±)-epibatidine (**1**).[43] Since reductive methylation of **24** with trioxane/$NaBH_3CN$ or HCO_2H/

CH_2O also failed due to instability of the starting material, we tried an alternative procedure to obtain the *N*-methyl derivative **28**. The synthesis of **27** was accomplished utilizing the N-protected enol ether **13** as starting material. This could be transformed to the corresponding N-methylated enol ether **27** upon treatment with $LiAlH_4$/ether in good yields. **27** entered into the Diels−Alder reaction with the 1,2,4,5-tetrazine **14d** affording the desired N-methylated species **28** however in low yield. All compounds described were obtained and tested as racemic mixtures.

X-ray Crystallographic Analysis of the Target Ligand 24. Because compounds such as (±)-epibatidine (**1**),[1] (±)-epiboxidine (**6**),[28] or the 5-pyrimidinylepibatidine analogue **7**[29] with the unusual 7-azabicyclo[2.2.1]-heptane ring system as the typical pharmacophoric element exhibit such exciting biological activities, it was deemed of value to subject appropriate single crystals of the structurally similar pyridazine analogue **24** to an X-ray diffraction analysis. An advantage of having available the crystal structure of **24** was the possibility to obtain detailed information of the three-dimensional arrangement and to check the calculated geometries of epibatidine and its analogues, beneficial for the definition of relevant distances between putative pharmacophoric elements and thus for the improvement of SARs. Figure 1 shows the ORTEP diagram of the structure of two racemic solid-state conformations of **24**, solved by X-ray diffraction methods as detailed in the Experimental Section. Thus the structure of the bioisosteric variant **24** of epibatidine was unambiguously verified and represents the first X-ray structure of a N-unprotected 7-azabicyclo[2.2.1]heptane ring system, in this case attached to a 4-pyridazine substituent at C-2 in a pseudoequatorial position and in an *exo* orientation, probably crucial for biological activity (see Figure 1a). Interestingly, in the crystal lattice of the pyridazine analogue **24** two different, obviously lowest-energy conformations are fixed with the same probability.

With regard to the configuration of the three stereogenic centers (see Figure 1b) these are recognized as two racemic forms: **24a**,**b**. In addition, the conformational feature of these two preferred species can be defined with two parameters: first, the disposition of the N−H moiety, *syn* or *anti* to the pyridazine substituent, and second, as the only degree of freedom the rotation around the bond between the two putative pharmacophore elements, the 7-azabicyclo[2.2.1]heptane and the pyridazine system. Thus, ligand **24a** differs from **24b** with respect to an approximate 200° rotation of the bond connecting the two heterocyclic systems. Interestingly, the C-1a−C-2a−C-4′a−C-3′a dihedral angle in **24a** exhibits a value of 176.7° (see atom labeling in Figure 1), whereas the corresponding C-1b−C-2b−C-4′b−C-3′b dihedral angle in **24b** is −26.3°.

In compound **24a** the disposition of the N−H moiety is *anti* to the pyridazine substituent, whereas in **24b** the N−H group, pointing toward the pyridazine ring, is *syn* positioned. As the nitrogen inversion barrier of 7-azabicyclo[2.2.1]heptane has been calculated to be 11.4−12.0 kcal·mol^{-1}, *syn*/*anti* conversion can easily occur at room temperature.[34] A second interesting aspect is the inter-nitrogen distances observed for **24a**,**b**.

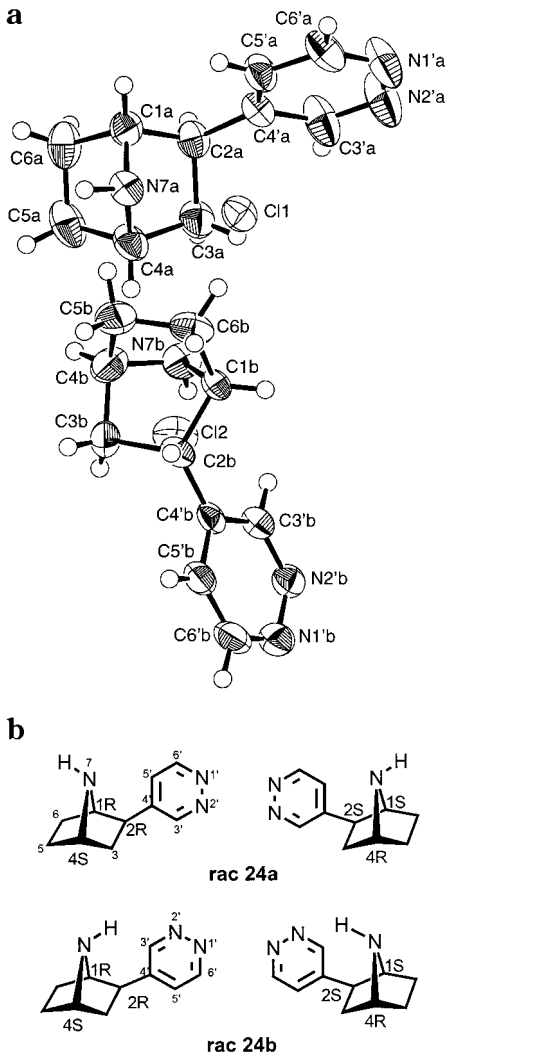


Figure 1. (a) ORTEP diagram (50% probability ellipsoids) showing the two solid-state conformations of one enantiomer of **24a** (top) and one of **24b** (below). (b) Conformational differences between the racemic species **24a**,**b** with numbering through the text.

N−N distances are used in different pharmacophoric models for various nAChR ligands due to the close relationship between nAChR affinity and inter-nitrogen distances.[35−39] In the case of (±)-epibatidine (**1**) the N−N distance showed two extreme values in the conformations obtained by molecular modeling studies of ca. 4.5 and 5.5 Å.[38]

Comparatively, in conformation **24a**, where N-7 and N-2′ are on opposite sides of the molecule, the N−N distance between N-7 and N-2′ is 5.38 Å (that between N-7 and N-1′ is 5.54 Å), similar to the calculated inter-nitrogen distance of the lowest-energy conformation of (±)-epibatidine (**1**) with 5.51 Å.[35,36,38] In contrast, for conformation **24b**, in which the pyridazine ring is rotated so that N-2′ is proximal to the sp^3 nitrogen N-7, the relevant N-7−N-2′ distance of 4.75 Å is obviously shorter (the inter-nitrogen distance N-7−N-1′ is 5.74 Å) and fits perfectly into Sheridan's nicotinic pharmacophore model,[39] similar to the calculated inter-nitrogen distance in (−)-nicotine (**2**) with 4.87 Å[35,39] and another stable conformer of (±)-epibatidine (**1**) with a relative energy of only 0.18 kcal/mol, featuring the N−N distance of 4.47 Å.[38] It is well-established that the acceptor-

Table 1. Agonist Activity of the Test Compounds at Four Representative Nicotinic Receptor Subtypes[a]

compd	activity (μM)			
	$\alpha3\beta4$	$\alpha4\beta2$	$\alpha7$	rat muscle
acetylcholine	3.2	0.32	50	0.1
(−)-nicotine bitartrate	4.0	0.1	12.6	6.3
(±)-epibatidine	0.005	0.005	0.5	0.03
18	not tested	inactive	inactive	not tested
19	inactive	inactive	inactive	not tested
22	inactive	>100	inactive	≫100
24	0.16	0.02	40.0	0.16
28	0.32	0.013	25.0	0.20

[a] To account for the different intrinsic agonist sensitivities of the receptor subtypes, a reference concentration of ACh was first defined for each subtype (first line). The activity of each test compound is expressed by giving a concentration which elicits a current signal of the same amplitude as the reference dose of ACh. All compounds were initially tested at 100 μM; thus, for inactive compounds this was the highest dose tested. Since the concentrations given in the table were read from a plot of the dose−response curve, it is not meaningful to assign statistical parameters such as SD or SEM to them; all dose−response curves were triplicates, from at least two different batches of frog oocytes.

bound conformations of ligands may not be the same as the lowest-energy conformations either in vacuo, in solution, or in a crystal. From a conformational point of view the bioisosteric analogue **24**, conformationally mobile like the parent alkaloid **1**, can be considered as a mixture of several conformational minima and some population of the intermediate structures. Thus, the small nitrogen inversion barriers and the small rotational barriers[34] indicate that ligand **24** at room temperature in solution should be a mixture of several minimum conformations with different inter-nitrogen distances more or less fit for a ligand/nAChR interaction.

In Vitro Tests. Agonist activity of the compounds was assayed in vitro by whole-cell current recordings from *Xenopus* oocytes expressing different recombinant nicotinic receptors from the rat[44] after injection with appropriate cDNA plasmids of one of the following subtypes: $\alpha3\beta4$, $\alpha4\beta2$, $\alpha7$ (all neuronal) or $\alpha1\beta1\gamma\delta$ (embryonic muscle subtype). It is common to test for the interaction of novel compounds with a designated receptor initially with competition binding assays that cannot distinguish between agonists and antagonists of the receptor. We have chosen the electrophysiological approach because it gives a direct functional measure of the activation of ligand-gated receptor currents by the test compound, which is the primary relevant parameter for biological activity. Moreover, the use of recombinant receptor subunits allows us to perform these measurements with defined molecular targets representing a set of the putative major subtypes of nAChR in the organism.

To account for the different sensitivities of the subtypes toward acetylcholine, and for the different efficiencies of ligands, the agonistic potency at each receptor subtype is expressed as the concentration found to be equipotent with a standard reference dose of acetylcholine (Table 1). [We describe these concentrations as "equipotent" rather than "equi-efficacious" because the values given were obtained as points of intersection of the measured dose−response curves with the ACh reference response rather then measured directly (see Figures 2 and 3).]

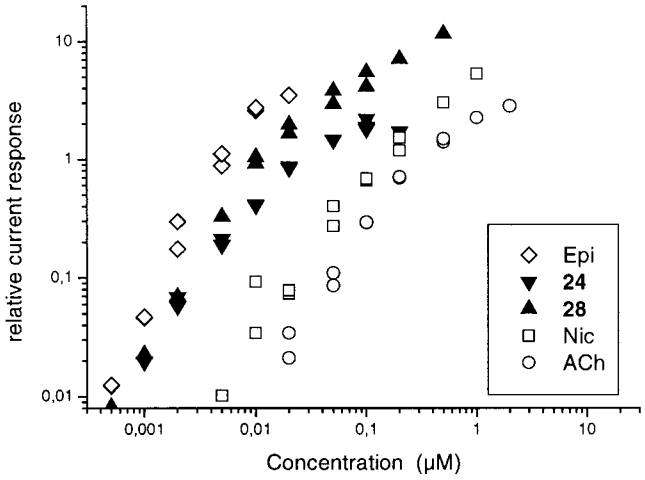


Figure 2. Current response of rat $\alpha4\beta2$ nicotinic receptors expressed in *Xenopus* oocytes plotted against the concentration of the respective agonist for epibatidine (Epi), **24**, **28**, nicotine (Nic), and acetylcholine (ACh). All current responses were normalized to the current elicited by 0,32 μM acetylcholine. The dose−response curves are plotted in a double-logarithmic fashion to emphasize the low-concentration regime. In this representation, the dose−response curve is approximately linear with a slope corresponding to the Hill coefficient.

In addition, the agonistic potencies of the newly synthesized ligands were compared with those of (−)-nicotine and (±)-epibatidine. The different standard concentrations of acetylcholine were empirically fixed to give a robust, nonsaturating current response for that respective receptor subtype. Due to the different intrinsic sensitivities of the subtypes to agonists, these values are necessarily also different for each one. The concentration values given in Table 1 are not the same as the EC_{50} values. However, when comparing the activity of different compounds they fulfill a similar role. Indeed, it is one of the main advantage of our "relative concentration" parameters that they avoid many of the difficulties and pitfalls of determining EC_{50} values correctly. To determine an EC_{50} value from a dose−response curve, obviously one first needs the correct value of the maximum current that can be elicited. This can be surprisingly difficult to determine for a variety of reasons, including partial agonism, receptor desensitization, open-channel block by the agonist itself, kinetic parameters, and, in the case of the oocytes, the simple fact that the maximum current is often much too big to measure with the available recording electronics. By concentrating our measurements on the low-dose regime of the dose−response curve, we effectively avoid all of these problems and obtain results which reflect the intrinsic activity of the compound at the receptor much more reliably than the more commonly used EC_{50} values.

As shown in Table 1, replacement of the chloropyridine moiety in epibatidine with an *unsubstituted* pyridazine ring providing **24** led to a potent and highly effective agonist on neuronal and muscle nAChRs, especially on the $\alpha4\beta2$ subtype. Thus much of the biological activity of the most potent natural compound (±)-epibatidine was retained. This could be anticipated for a bioisosteric analogue, in which the inter-nitrogen distances, crucial for a highly potent ligand, are nearly equivalent to those of the parent alkaloid. Indeed **24** turned out to be the most active compound. The drastic

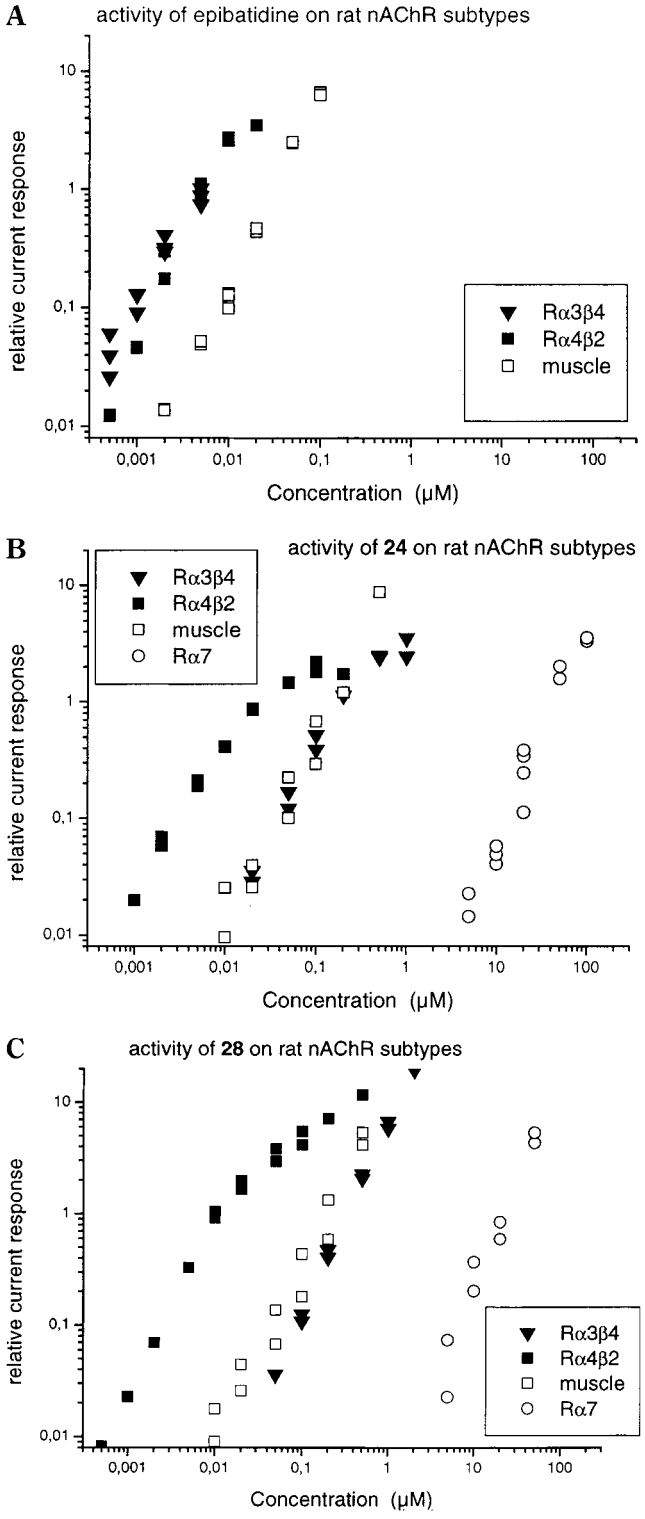


Figure 3. Dose-dependent current responses evoked by epibatidine (A), **24** (B), and **28** (C) on different subunit combinations of rat nicotinic receptors. The responses are normalized to the signal elicited by a reference concentration of ACh which, for each receptor subtype, was chosen to give a robust activation of current. Note that there is a clear preference for the α4*β*2 over the α3*β*4 subtype with compounds **24** and **28**, whereas epibatidine is about equipotent at these receptor subtypes.

drop in agonistic potency for the 2-fold trifluoromethyl-substituted pyridazine analogue such as **19** indicates that 3,6-substitution in the pyridazine ring significantly lowers the potency, mainly for steric reasons, irrespective of the inter-nitrogen distance, which remains approximately equal to that of (±)-epibatidine. A similar significant loss of potency is also observed with the structurally varied ligands **18** and **22**, characterized by a carbamate group at N-7 of the bicyclic moiety. In comparison, **28**, the N-7-methylated bioisostere of (±)-epibatidine, just like **24**, exhibited significant agonistic potencies, whereas the corresponding carbamate **22** revealed complete loss of activity.

Most probably due to the different basicity of the pyridazine ring, **24** proved to be about 4-fold less potent at the α4*β*2 subtype and ca. 30-fold less potent at the α3*β*4 subtype than (±)-epibatidine but about 5- and 25-fold, respectively, more potent than (−)-nicotine. At the α1*β*1*γδ* subtype **24** was about 5-fold less potent than the frog poison but nearly 40-fold more potent than (−)-nicotine. Remarkably, **24** and its *N*-7-methyl derivative **28** both differentiate somewhat better between nAChR subtypes than (±)-epibatidine, in particular between α3*β*4 and α4*β*2. While (±)-epibatidine in our system is equipotent on both receptors, **28** is 25-fold selective toward the α4*β*2 subtype, which is more comparable to (−)-nicotine (40-fold).

Conclusion

Bioisosterism is an important concept in medicinal chemistry and serves as a valuable aid in SAR studies and new drug design. Following the idea that bioisosteric alterations in the ring systems of (±)-epibatidine might provide compounds with better ratios of pharmacological to toxicological activity, we successfully replaced the chloropyridinyl pharmacophore of (±)-epibatidine by differently substituted pyridazines. A key step of our new and efficient synthetic approach to novel pyridazine analogues of (±)-epibatidine was the inverse type Diels−Alder reaction of the electron-rich enol ether **13** with the electron-deficient diazadiene system of various 1,2,4,5-tetrazines. The most active compound described was **24**, the structure of which could be verified by X-ray crystallography revealing a N−N distance close to that of (±)-epibatidine. Though somewhat less potent, **24** was found to retain much of the agonist activity of the most potent frog poison (±)-epibatidine and proved to be a highly effective agonist on neuronal and muscle nAChRs, especially on the α4*β*2 subtype. Interestingly **24** as well as its *N*-7-methyl derivative **28** both differentiate somewhat better between nAChR subtypes, in particular between α3*β*4 and α4*β*2.

Experimental Section

General Procedures. Standard vacuum techniques were used in handling of air-sensitive materials. Melting points are uncorrected: "Leitz-Heiztischmikroskop" HM-Lux. Solvents were dried and freshly distilled before use according to literature procedures. IR: Perkin-Elmer 257, 398 and FT-IR spectrometer 510-P (Nicolet). Liquids were run as films, solids as KBr pellets. ^{1}H and ^{13}C NMR: JEOL JNM-GX 400 and LA 500; δ/ppm = 0 for tetramethylsilane, 7.26 for chloroform. MS: Vacuum Generators 7070 (70 eV; ^{11}B). Column chromatography: purifications were carried out on Merck silica gel 60 [70−260 (flash chromatography) or (200−400 mesh)]. Reactions were monitored by thin-layer chromatography (TLC) using plates of silica gel (0.063−0.200 mm; Merck) or silica gel 60-F_{254} microcards (Riedel de Haen).

***exo*-2-Hydroxymethyl-7-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (11)**. To a solution of 2.27 g (10.0

mmol) of ester **10** in 30 mL of dry tetrahydrofuran and 50 mL of dry ethanol were added 0.86 g (20 mmol) of LiCl and 0.76 g (20 mmol) of $NaBH_4$. The reaction mixture was stirred for 12 h at room temperature then a solution of citric acid was added until pH = 4 was reached. After evaporation of the solvent in vacuo, 50 mL of water were added and the resulting mixture extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$ and filtered. After removal of solvent in vacuo the residue was purified by flash chromatography over silica gel eluting with ethyl acetate:*n*-hexane = 2:1, to give **11** (1.96 g, 98%, R_f = 0.43) as a colorless oil. IR (film): ν (cm^{-1}) = 3439, 2954, 2876, 1700, 1380, 1317, 1270, 1196, 1170, 1140, 1105, 1019, 918, 855. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.1 Hz, 3H, 9-H), 1.28 (m, 1H, 6-H), 1.41 (m, 2H, 5-H and 6-H), 1.51 (dd, J = 12.1 Hz, J = 8.5 Hz, 1H, 3α-H), 1.75 (m, 2H, 5-H and 3β-H), 1.92 (m, 1H, 2-H), 3.32−3.43 (m, 2H, 10-H), 4.08 (q, J = 7.1 Hz, 2H, 8-H), 4.24 (m, 2H, 1-H and 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (C-9), 29.1 (C-5), 29.3 (C-6), 33.4 (C-3), 45.6 (C-2), 55.9 (C-4), 57.5 (C-1), 61.1 (C-8), 65.1 (C-10), 156.1 (C-7). MS (70 eV): *m*/*z* (%) 199 (23, M^+). HRMS: calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1207.

***exo*-2-Formyl-7-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (12).** To a solution of 1.0 mL (11 mmol) of oxalyl chloride in 30 mL of dry CH_2Cl_2 was slowly added a solution of 1.7 mL (24 mmol) of DMSO in 5 mL of dry CH_2Cl_2 at −78 °C. After 5 min a solution of 1.59 g (8.0 mmol) of **11** in 10 mL of dry CH_2Cl_2 was added. The reaction mixture was stirred for 30 min at −78 °C, than 9 mL of triethylamine was added. After the mixture was warmed to room temperature 100 mL of water was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic layers washed with saturated aqueous $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$ and filtered. After removal of solvent in vacuo the residue was purified by flash chromatography over silica gel eluting with ethyl acetate:petroleum ether (40/60) = 3:1 to give 1.56 g (98%, R_f = 0.54) **12** as a colorless oil. IR (film): ν (cm^{-1}) = 2980, 1699, 1412, 1379, 1345, 1315, 1271, 1194, 1171, 1102, 1010, 958, 778. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, J = 7.1 Hz, 3H, 9-H), 1.42−1.58 (m, 3H, 6α-H and 5-H), 1.72−1.88 (m, 2H, 6β-H and 3α-H), 2.16−2.22 (m, 1H, 3β-H), 2.49 (ddd, J = 8.8 Hz, J = 4.6 Hz, J = 1.7 Hz, 1H, 2-H), 4.04 (q, J = 7.1 Hz, 2H, 8-H), 4.34 (t, J = J = 4.5 Hz, 1H, 4-H), 4.55 (d, J = 4.5 Hz, 1H, 1-H), 9.58 (d, 1H, J = 1.7 Hz, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (C-9), 29.1 (C-5), 29.3 (C-6), 30.4 (C-3), 55.1 (C-2), 56.0 (C-4), 57.0 (C-1), 61.2 (C-8), 155.4 (C-7), 200.8 (C-10). MS (70 eV): *m*/*z* (%) 197 (6, M^+), 140 (100). HRMS: calcd for $C_{10}H_{15}NO_3$ 197.1052, found 197.1046.

***exo*-2-(2-Methoxyethenyl)-7-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (13)**. To a suspension of 5.15 g (15.0 mmol) of methoxymethyltriphenylphosphonium chloride in 30 mL of dry toluene was added dropwise at 0 °C under argon 7.5 mL of a freshly prepared LDA solution (2 M in THF). The deep red reaction mixture was stirred at 0 °C for 15 min and then a solution of 0.99 g (5 mmol) of **12** in 8 mL of dry toluene was added slowly. After 2 h at 0 °C the reaction mixture was partitioned between 50 mL of ice−water and 100 mL of Et_2O and stirred for 30 min. The organic layer was separated, the aqueous layer extracted with Et_2O (3 × 30 mL), the combined organic layers washed with 100 mL of saturated aqueous $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the oily residue was purified by flash chromatography over silica gel eluting with petroleum ether (40/60):Et_2O = 1:1 to give 0.89 g (78%, R_f = 0.70) enol ether **13** as colorless oil. IR (film): ν (cm^{-1}) = 2955, 2875, 2836, 1699, 1376, 1345, 1311, 1252, 1208, 1176, 1104, 1014, 977, 936, 902, 875, 780. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21−1.27 (m, overlapped by t, 3H, 9-H), 1.33−1.51 (m, 3H, 5-H and 6-H), 1.68−1.78 (m, 3H, 6-H and 3-H), 2.21−2.28 (m, 0.52H, 2-H), 2.71−2.78 (m, 0.48H, 2-H), 3.48 (s, 1.56H, 12-H), 3.58 (s, 1.44H, 12-H), 3.96−4.03 (br s, 1H, 4-H), 4.08−4.16 (m, overlapped by q, 2H, 8-H), 4.26−4.34 (br s, overlapping of 1-H and 10-H, 1.48H, 1-H and 10-H), 4.59−4.71 (m, 0.52H, 10-H), 5.57 (d, J = 6.0 Hz, 0.48H, 11-H, Z-isomer), 6.31 (d, J = 12.6 Hz, 0.52H, 11-H, E-isomer). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (C-9), 29.0 (C-5), 38.2 (C-6), 39.4 (C-3), 42.3 (C-2), 55.8 and 56.0 (C-4), 59.6 (C-1), 60.9 (C-12), 61.8 (C-1), 62.3 (C-8), 107.3 and 111.4 (C-10), 145.0 and 146.6 (C-11), 156.1 (C-7). MS (70 eV): *m*/*z* (%) = 225 (63, M^+), 141 (100). HRMS: calcd for $C_{12}H_{19}NO_3$ 225.1365, found 225.1365.

***exo*-2-(3,6-Bistrifluoromethylpyridazin-4-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (15).** To a solution of 0.45 g (2.0 mmol) of the enol ether **13** in 15 mL of dry toluene was added dropwise a solution of 0.43 g (2.0 mmol) of the tetrazine **14a** in 10 mL of dry toluene at room temperature. After stirring for 30 min at room temperature the mixture was refluxed under argon for 12 h and cooled to room temperature. The solvent was evaporated in vacuo and the residue purified by flash chromatography over silica gel eluting with diethyl ether:petroleum ether (40/60) 1:1 (column 20 × 1 cm) to give **15** (0.67 g, 88%) as a colorless oil, which crystallized after storing at 4 °C for 3 days; mp 61−63 °C (*n*-hexane). IR (film): ν (cm^{-1}) = 2975, 2896, 1703, 1632, 1619, 1546, 1501, 1288, 1174, 1054. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 3H, 9-H), 1.62−1.71 (m, 2H, 5-H and 6-H), 1.79−1.85 (m, 1H, 5-H), 1.88−1.94 (m, 2H, 6-H and 3β-H), 2.12 (dd, J = 12.6 Hz, J = 9.1 Hz, 1H, 3α-H), 3.32 (d, 1H, J = 9.0 Hz, J = 5.2 Hz, 2-H), 4.15 (q, J = 7.1 Hz, 2H, 8-H), 4.35 (s, br, 1H, 4-H), 4.50 (s, br, 1H, 1-H), 8.15 (s, 1H, 11-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (C-9), 28.7 (C-5), 29.7 (C-6), 40.3 (C-3), 41.8 (C-2), 56.1 (C-4), 61.5 (C-1), 61.8 (C-8), 120.9 (q, $J_{C,F}$ = 275.3 Hz, C-14), 121.6 (q, $J_{C,F}$ = 276.8 Hz, C-12), 123.3 (C-15), 146.2 (C-10), 150.7 (q, $J_{C,F}$ = 33.0 Hz, C-13), 153.9 (q, $J_{C,F}$ = 35.3 Hz, C-11), 155.3 (C-7). MS (70 eV): *m*/*z* (%) 383 (41), 141 (100). Anal. ($C_{15}H_{15}F_6N_3O_2$) C, H, N.

***exo*-2-(3,6-Dipyridin-2-ylpyridazin-4-yl)-7-azabicyclo-[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (16) and *exo*-2-(5-Methoxy-3,6-dipyridin-2-yl-4,5-dihydropyridazin-4-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (17).** A solution of 0.47 g (2.0 mmol) of the vinyl ether **13** and 0.35 g (1.5 mmol) of the tetrazine **14b** in 15 mL of dry toluene was heated for 2 days at 120 °C in a pressure bottle. After cooling to room temperature the solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel, column 30 × 2 cm), eluting with ethyl acetate: petroleum ether (40/60) 6:1. Fraction 1 contained 0.38 g (59%, R_f = 0.48) of compound **17** as yellow crystals; fraction 2 contained 0.19 g (32%, R_f = 0.45) of compound **16** as colorless crystals. **16**: mp 154−156 °C. IR (KBr): ν (cm^{-1}) = 2979, 2921, 1706, 1568, 1466, 1386, 1089, 822, 743. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, 3H, J = 7.1 Hz, 9-H), 1.49−1.53 (m, 1H, 5-H), 1.60−1.64 (m, 1H, 6-H), 1.83−1.87 (m, 4H, 4-H, 5-H and 6-H), 3.73 (dd, 1H, J = 8.8 Hz, J = 5.2 Hz, 2-H), 4.10 (q, 2H, J = 7.1 Hz, 8-H), 4.49−4.50 (m, 2H, 1-H and 4-H, overlapped), 7.35−7.40 (m, 2H, 20-H and 15-H), 7.84−7.92 (m, 2H, 22-H and 13-H), 8.14−8.16 (m, 1H, 23-H), 8.68−8.71 (m, 4H, 14-H, 16-H, 19-H and 21-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (C-9), 28.8 (C-5), 29.7 (C-6), 38.8 (C-3), 43.2 (C-2), 56.4 (C-4), 61.2 (C-1), 62.0 (C-8), 121.7, 122.6, 123.5, 124.5, 125.5, 136.9, 144.5, 148.5, 149.4, 155.6, 156.6, 157.8, 158.4, 153.7 (C-7). MS (70 eV): *m*/*z* (%) 401 (M^+, 45), 261 (100). Anal. ($C_{23}H_{23}N_5O_2$), C, H, N.

17: IR (KBr): ν (cm^{-1}) = 2988, 2941, 1696, 1585, 1463, 1376, 1088, 802, 746. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.1 Hz, 3H, 9-H), 1.19−1.28 (m, 3H, 5-H and 6-H), 1.39 (m, 3H, 3-H and 6-H), 1.71−1.78 (m, 1H, 2-H), 3.32 (s, 3H, 24-H), 3.75 (d, 1H, J = 7.0 Hz, 10-H), 4.01 (q, 2H, J = 7.1 Hz, 8-H), 4.24 (s, br, 1H, 4-H), 4.27 (s, br, 1H, 1-H), 5.13 (s, 1H, 23-H), 7.36 (m, 2H, 20-H and 15-H), 7.82 (m, 2H, 22-H and 13-H), 8.44 (m, 2H, 21-H and 14-H), 8.70 (m, 2H, 19-H and 16-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C-9), 28.6 (C-5), 29.2 (C-6), 36.5 (C-3), 36.9 (C-2), 40.6 (C-10), 56.1 (C-4), 57.2 (C-1), 58.5 (C-24), 60.8 (C-8), 64.4 (C-23), 122.5−164.5, 153.8 (C-7). MS (70 eV): *m*/*z* (%) 433 (M^+, 0.1), 401 (28, $M^+ - CH_3OH$), 265 (100). Anal. ($C_{24}H_{27}N_5O_3$), C, H, N.

***exo*-2-(3,6-Dichloropyridazin-4-yl)-7-azabicyclo[2.2.1]-heptane-7-carboxylic Acid Ethyl Ester (18).** To a solution of 302 mg (1.35 mmol) of the enol ether **13** in 10 mL of dry toluene was added a solution of 204 mg (1.35 mmol) of 3,6-dichlorotetrazine **14c** in 5 mL of dry toluene. The mixture was refluxed under an atmosphere of Ar for 60 h, cooled to room temperature and the solvent evaporated in vacuo. The residue was purified by flash chromatography over silica gel eluting with ethyl acetate:*n*-hexane 1:2 (column 15 × 2.5 cm) to give **18** (331 mg, 78%, $R_f = 0.27$) as a colorless oil. IR (film): ν (cm^{-1}) = 2979, 1704, 1562, 1377, 1326, 1134, 1102. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 3H, 9-H), 1.58−1.78 (m, 4H, 5-H and 6-H), 1.86 (m, 1H, 3β-H), 2.11 (dd, J = 12.6 Hz, J = 9.4 Hz, 1H, 3α-H), 3.17 (dd, J = 5.0 Hz, J = 9.4 Hz, 1H, 2-H), 4.11 (d, J = 7.1 Hz, 2H, 8-H), 4.38 (br s, 1H, 4-H), 4.45 (br s, 1H, 1-H), 7.55 (s, 1H, 11-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6 (C-9), 28.9 (C-5), 29.3 (C-6), 38.2 (C-3), 44.1 (C-2), 56.2 (C-4), 60.0 (C-1), 61.6 (C-8), 127.1 (C-11), 146.3 (C-10), 155.2 (C-7), 156.2 (C-12), 156.3 (C-13). MS (70 eV): m/z (%) = 315 (21, M^+), 141 (100). HRMS: calcd for $C_{13}H_{15}Cl_2N_3O_2$ 315.0541, found 315.0530.

***exo*-2-(3,6-Bistrifluoromethylpyridazin-4-yl)-7-azabicyclo[2.2.1]heptane (19).** To a solution of 308 mg (0.80 mmol) of the carbamate **15** in 4 mL of dry chloroform was added dropwise under argon at room temperature a solution of 0.33 mL (2.41 mmol) of trimethylsilyl iodide and the reaction mixture refluxed for 4 h. After cooling 1.5 mL of methanol was added dropwise and the mixture kept at room temperature for 30 min, the solvent was removed in vacuo and the residue resolved in 8 mL of water. Concentrated aqueous ammonia was added until pH = 10 was reached. The resulting mixture was extracted with chloroform (3 × 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$ and filtered. After removal of solvent in vacuo the residue was purified by flash chromatography over silica gel eluting with CH_2Cl_2:CH_3OH: concentrated aqueous ammonia 97:3:1, to give 206 mg (91%) **19** as a pale yellow oil. IR (film): ν (cm^{-1}) = 3412, 2956, 1569, 1412, 1367, 1291, 1109. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48−1.70 (m, 5H, 5-H, 6-H and 3-H), 1.97 (dd, J = 12.4 Hz, J = 9.0 Hz, 1H, 3α-H), 3.10 (m, 1H, 2-H), 3.64 (s, br, 1H, 4-H), 3.87 (s, br, 1H, 1-H), 8.72 (s, 1H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.8 (C-5), 31.8 (C-6), 40.7 (C-3), 40.9 (C-2), 56.2 (C-4), 62.7 (C-1), 121.0 (q, $J_{C,F}$ = 275.3 Hz, C-9), 121.9 (q, $J_{C,F}$ = 276.0 Hz, C-11), 124.8 (C-7), 148.3 (C-12), 150.4 (q, $J_{C,F}$ = 32.2 Hz, C-8), 153.7 (q, $J_{C,F}$ = 35.3 Hz, C-10). MS (70 eV): m/z (%) 311 (100, M). HRMS: calcd for $C_{12}H_{11}F_6N_3$ 311.0895, found 311.0879.

The free base (180 mg, 0.58 mmol) was converted to the corresponding hydrogen oxalate monohydrate salt in acetone (6 mL) by reaction with oxalic acid monohydrate (64 mg, 0.59 mmol) to yield colorless crystals (209 mg, 90%), mp 167−168 °C (acetone). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.75−1.84 (m, 2H, 5-H), 1.85−1.98 (m, 2H, 6-H), 2.01−2.10 (m, 1H, 3β-H), 2.25 (dd, ^2J = 12.4 Hz, ^3J = 9 Hz, 1H, 3α-H), 3.49 (m, 1H, 2-H), 4.19−4.21 (m, 1H, 1-H), 4.43 (s, broad, 1H, 4-H), 8.64 (s, 1H, 12H). MS (70 eV): m/z (%) = 311 (M^+ − oxalic acid, 100). Anal. ($C_{14}H_{15}F_6N_3O_5$) C, H, N.

***exo*-2-(3,6-Dipyridin-2-ylpyridazin-4-yl)-7-azabicyclo-[2.2.1]heptane (20).** Using the same procedure as described for **19** 87 mg (88%) **20** was obtained from 0.12 g (0.30 mmol) of **16**, which was characterized as the corresponding hydrogen oxalate: to a solution of the obtained free base **16** in 3 mL of acetone was added a solution of 30 mg (0.28 mmol) of the monohydrate of oxalic acid in 2 mL of acetone. The mixture was refluxed for 10 min, filtered and the filtrate stored for 12 h at 4 °C to give, after drying in vacuo, 98 mg (90%, related to the free base) of colorless crystals, mp 177−178 °C. IR (film): ν (cm^{-1}) = 3346, 2946, 1639, 1438. ^{1}H NMR (400 MHz, CD_3O-(D): δ = 1.64−1.70 (m, 1H, 5-H), 1.75−1.82 (m, 1H, 6-H), 1.86−1.93 (m, 2H, 6-H and 5-H), 1.96 (dd, J = 13.3 Hz, J = 9.5 Hz, 3α-H), 2.07−2.16 (m, 1H, 3β-H), 3.93 (dd, J = 9.3 Hz, J = 6.6 Hz, 2-H), 4.10 (br s, 2H, NH_2), 4.20 (t, 1H, J = 4.3 Hz, 4-H), 4.60 (d, 1H, J = 4.4 Hz, 1-H). ^{13}C NMR (100 MHz, CD_3O-(D): δ = 25.5 (C-5), 27.8 (C-6), 34.9 (C-3), 41.5 (C-2), 58.6 (C-4), 62.8 (C-1), 121.8, 123.3, 124.4, 125.3, 125.5, 137.8, 137.9, 140.9, 148.9, 153.4, 156.0, 157.5, 158.8, 164.9. MS (70 eV): m/z (%) 329 (M^+ − oxalic acid, 20), 261 (100). Anal. ($C_{23}H_{23}N_5O_2$) C, H, N.

***exo*-2-(Pyridazin-4-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (22)**. Following the procedure described for the preparation of carbamate **15** 0.36 g (74%) of **22** was obtained as a colorless oil ($R_f = 0.47$) from 0.45 g (2.0 mmol) of the enol ether **13** and 0.12 g (2.0 mmol) of the tetrazine **14d**. IR (film): ν (cm^{-1}) = 2978, 2912, 1705, 1584, 1374. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, 3H, J = 7.1 Hz, 9-H), 1.50−1.62 (m, 2H, 5-H), 1.73−1.91 (m, 3H, 6-H and 3-H), 2.01−2.07 (m, 1H, 3-H), 2.86 (dd, 1H, J = 9.0 Hz, J = 4.8 Hz, 2-H), 4.10 (q, 2H, J = 7.1 Hz, 8-H), 4.30 (br s, 1H, 1-H), 4.45 (br s, 1H, 4-H), 7.37 (br s, 1H, J not determinable, 13-H), 9.03 (dd, 1H, J = 5.5 Hz, J = 1.1 Hz, 12-H), 9.06 (pseudo-t, overlapped by dd, J = 1.2 Hz, 11-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (C-9), 28.8 (C-5), 29.6 (C-6), 39.5 (C-3), 45.2 (C-2), 56.1 (C-1), 61.2 (C-4), 61.4 (C-8), 124.0 (C-13), 144.3 (C-10), 151.2 (C-12), 151.7 (C-11), 155.5 (C-7). MS (70 eV): m/z (%) 247 (M^+, 41), 141 (100). HRMS: calcd for $C_{13}H_{17}N_3O_2$ 247.1312, found 247.1320.

3-Pyridazin-4-ylcyclohex-3-enylamine (23). To a solution of 272 mg (1.10 mmol) of the carbamate **22** in 5 mL of dry chloroform was added dropwise under argon at room temperature a solution of 0.45 mL (3.31 mmol) of trimethylsilyl iodide. The reaction mixture was heated for 4 h under argon to 75−80 °C (pressure bottle), cooled to room temperature and 1.8 mL of methanol added. After gas evolution has ceased, the solvent was evaporated in vacuo. The residue dissolved in 8 mL of water and concentrated aqueous ammonia added until pH = 12 was reached. The resulting reaction mixture was extracted with chloroform (3 × 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$ and filtered. After removal of solvent in vacuo the residue was purified by flash chromatography over silica gel (column 20 × 2 cm) eluting with CH_2Cl_2:CH_3OH:concentrated aqueous ammonia 85:15:1, to give **23**, 148 mg (77%), as a pale yellow oil. IR (Film): ν (cm^{-1}) = 3397, 2973, 2911, 1602, 1587. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (m, 1H, 6α-H), 1.61 (br s, 2H, NH_2), 1.82−1.89 (m, 1H, 6β-H), 2.07−2.16 (m, 1H, 5α-H), 2.23−2.32 (m, 1H, 5β-H), 2.33−2.42 (m, 1H, 2α-H), 2.52−2.61 (m, 1H, 2β-H), 3.13 (br s, 1H, 1-H), 6.45 (br s, 1H, 4-H), 7.29 (dd, 1H, J = 5.5 Hz, J = 2.5 Hz, 8-H), 9.01 (dd, 1H, J = 5.5 Hz, J = 1.1 Hz, 9-H), 9.17 (dd, 1H, J = 2.5 Hz, J = 1.1 Hz, 10-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0 (C-6), 31.1 (C-5), 35.6 (C-2), 46.5 (C-1), 120.9 (C-4), 130.1 (C-3), 130.5 (C-8), 138.6 (C-7), 148.3 (C-9), 151.1 (C-10). MS (70 eV): m/z (%) 175 (M^+, 54), 133 (100). HRMS: calcd for $C_{10}H_{13}N_3$ 175.1109, found 175.1102.

***exo*-2-(Pyridazin-4-yl)-7-azabicyclo[2.2.1]heptane (24).** To a solution of 198 mg (0.80 mmol) of compound **22** in 0.5 mL of dioxane was added 2 mL of aqueous hydrochloric acid (37%) and argon was bubbled through the solution for 10 min. The mixture was refluxed for 20 h under argon, and cooled to room temperature before 2 mL of water was added. The solvent was evaporated in vacuo, the residue dissolved in 1 mL of water and concentrated aqueous ammonia was added until pH = 12 was reached. After removal of the solvent in vacuo the residue was purified by column chromatography (silica gel, column 30 × 1.5 cm, eluting with CH_2Cl_2:MeOH:concentrated aqueous ammonia = 95:15:0.1). Fraction 1 contained 9 mg (7%, $R_f = 0.16$) of **23** as colorless oil; fraction 2 contained compound **24**: yield 39 mg (28%, $R_f = 0.09$) as colorless crystals, mp 158 °C. IR (KBr): ν (cm^{-1}) = 3389, 2924, 1606, 1467, 1369. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.50−1.72 (m, 5H, 3β-H, 5-H and 6-H), 1.93 (dd, J = 12.4 Hz, J = 9.1 Hz, 1H, 3α-H), 2.75 (dd, J = 9.1 Hz, J = 5.0 Hz, 1H, 2-H), 3.66 (m, 1H, 4-H), 3.85 (m, 1H, 1-H), 7.53 (dd, J = 5.2 Hz, J = 2.3 Hz, 1H, 8-H), 9.02 (dd, J = 5.2 Hz, J = 1.1 Hz, 1H, 9-H), 9.14 (dd, J = 2.3 Hz, J = 1.1 Hz, 1H, 10-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.2 (C-5), 31.3 (C-6), 39.5 (C-3), 44.8 (C-2), 56.4 (C-4), 62.2 (C-1), 124.5 (C-8), 145.7 (C-7), 151.0 (C-9), 152.2 (C-10). MS (70 eV): m/z (%) =

176 (4, $M^+ + 1$), 175 (25, M^+), 69 (100). HRMS: calcd for $C_{10}H_{13}N_3$ 175.1128, found 175.1110.

Crystal Structure Determination of 24. A brownish crystal (ca. 0.25 × 0.25 × 0.10 mm^3), obtained by recrystallization from dichloromethane, was mounted on a glass fiber and investigated on a Rigaku AFC5R diffractometer with graphite monochromated Cu Kα radiation and a rotating anode generator (Rigaku). Empirical formula $C_{20}H_{12}N_3Cl$, molecular mass 209.68 au. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of **25** carefully centered reflections in the range 41.18° < 2Θ < 57.13°, corresponded to a primitive orthorhombic cell with dimensions: a = 22.634(3) Å, b = 20.097(5) Å, c = 9.418(5) Å, V = 4284(4) $Å^3$. For Z = 16, the calculated density is 1.30 g/cm^3. The systematic absences of 0kl: $k \neq 2n$, $h0l$: $l \neq 2n$, $hk0$: $h \neq 2n$ uniquely determine the space group to be *Pbca* (No. 61). The data were collected at a temperature of 23 ± 1 °C using the $\omega-2\Theta$ scan technique to a maximum 2Θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.30° with a takeoff angle of 6.0°. Scans of (1.10 ± 0.30 tan Θ)° were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm, the crystal to detector distance was 400 mm, and the detector aperture was 9.0 × 13.0 mm (horizontal × vertical). A total of 3624 reflections was collected. The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied. The linear absorption coefficient, μ, for Cu Kα radiation is 28.6 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.79−1.00. The data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods[45] and expanded using Fourier techniques.[46] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 1917 observed reflections ($I > 3.00\sigma(I)$) and 253 variable parameters and converged (largest parameter shift was 0.01× its ESD) with unweighted and weighted agreement factors of: $R = \sum||F_o| - |F_c||/\sum|F_o| = 0.054$; $R_w = \sqrt{(\sum\varpi(|F_o| - |F_c|)^2/\sum\varpi F_o^2)} = 0.064$. The standard deviation of an observation of unit weight was 1.80. The weighting scheme was based on counting statistics and included a factor (p = 0.029) to downweight the insense reflections. Plots of $\sum\varpi(|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.48 and −0.36 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[47] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[48] All calculations were performed using the teXsan[49] crystallographic software package of Molecular Structure Corp.

***N*-(3-Pyridazin-4-ylcyclohex-3-enyl)acetamide (25) and *exo*-7-Acetyl-2-(pyridazin-4-yl)-7-azabicyclo[2.2.1]heptane (26a,b).** To a solution of 35 mg (0.20 mmol) of amine **22** in 1 mL of dry DMF was added 68 mg (0.30 mmol) of pentafluorophenyl acetate. The mixture was stirred under an atmosphere of argon for 14 h at room temperature, then the solvent was evaporated in vacuo at room temperature and the residue purified by flash chromatography over silica gel eluting with ethyl acetate: CH_3OH = 19:1 (column 25 × 1.5 cm). Fraction 1 contained 6 mg (13%, R_f = 0.14) of compound **25** as a colorless oil; fraction 2 contained 30 mg (68%, R_f = 0.09) **26a**,**b** as a colorless oil. **25**: IR (film): ν (cm^{-1}) = 3278, 3070, 2933, 1649, 1558, 1374, 919, 836, 733. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.59−1.72 (m, 1H, 6α-H), 1.73−1.84 (m, 1H, 6β-H), 1.89−1.99 (m, 1H, 5α-H), 2.01 (s, 3H, 8-H), 2.19−2.28 (m, 1H, 5β-H), 2.41−2.47 (m, 1H, 2α-H), 2.78−2.84 (m, 1H, 2β-H), 4.21−4.32 (m, 1H, 1-H), 5.72 (br d, 1H, NH), 6.52 (dd, J = 4.9 Hz, J = 3.1 Hz, 1H, 4-H), 7.32 (d, J = 5.4 Hz, 1H, 12-H), 9.07 (d, J = 5.4 Hz, 1H, 11-H), 9.21 (br s, 1H, 10-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.6 (C-8), 27.1 (C-6), 29.7 (C-5), 32.3 (C-2), 44.7 (C-1), 121.0 (C-4), 129.8 (C-3), 130.4 (C-12), 138.2 (C-9), 148.2 (C-11), 151.1 (C-10), 169.6 (C-7). MS (70 eV): m/z (%) = 217 (M^+, 16), 158 (100). HRMS: calcd for $C_{12}H_{15}N_3O$ 217.1215 found, 217.1186.

26a,b (rotamers): IR (film): ν (cm^{-1}) = 2965, 1634, 1420, 1052, 885. ^1H NMR (500 MHz, $CDCl_3$) 2 rotamers (ratio 1.6:1): δ = 1.51−1.77 (m, 2H, 5α-H and 6α-H), 1.77−1.93 (m, 3H, 3β-H, 5β-H and 6β-H), 1.83 (s, 1.14H, 8-H), 1.97−2.05 (0.38 H, 3α-H), 2.03 (s, 1.86H, 8-H), 2.16 (dd, J = 9.3 Hz, J = 12.2 Hz, 0.62H, 3α-H), 2.91 (dd, J = 4.9 Hz, J = 9.0 Hz, 0.62H, 2-H), 2.95 (dd, J = 4.5 Hz, J = 9.0 Hz, 0.38H, 2-H), 3.95 (d, J = 4.2 Hz, 0.38H, 1-H), 4.27 (t, J = 4.6 Hz, 0.62H, 4-H), 4.73 (d, J = 4.6 Hz, 0.62H, 1-H), 4.82 (t, J = J = 4.8 Hz, 0.38 H, 4-H), 7.24 (br s, 0.62H, 12-H), 7.39 (br s, 0.38 H, 12-H), 8.94−9.13 (m, 2H, 10-H and 11-H). ^{13}C NMR (125 MHz, $CDCl_3$): 2 rotamers, δ = 21.3 and 22.9 (C-8), 28.2 and 28.9 (C-5), 29.8 and 31.1 (C-6), 37.7 and 40.9 (C-3), 43.1 and 44.4 (C-2), 53.2 and 57.1 (C-1), 56.7 and 62.9 (C-4), 123.5 and 123.8 (C-12), 143.7 and 144.0 (C-9), 150.9 and 151.0 (C-11), 151.3 and 151.5 (C-10), 167.1 and 167.8 (C-7). MS (70 eV): m/z (%) = 217 (M^+, 38), 106 (100). HRMS: calcd for $C_{12}H_{15}N_3O$ 217.1215, found 217.1214.

***exo*-2-(Methoxyethenyl)-7-methyl-7-azabicyclo[2.2.1]heptane (27).** To a suspension of $LiAlH_4$ (380 mg, 10.0 mmol) in dry diethyl ether (40 mL) was added dropwise a solution of enol ether **13** (525 mg, 2.33 mmol). The reaction mixture was refluxed under an atmosphere of Ar for 12 h and after cooling to 0 °C a saturated aqueous solution of potassium sodium tartrate tetrahydrate (20 mL) was slowly added at 0 °C. The suspension was vigorously stirred for 30 min at 10 °C, then the aqueous phase was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (10 mL) dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the oily residue was purified by flash chromatography over silica gel eluting with CH_2Cl_2:MeOH:diethylamine = 95:15:0.2 (column 25 × 1.5 cm) to give **27** (390 mg, 87%, R_f = 0.26) as a colorless oil. IR (film): ν (cm^{-1}) = 2958, 2872, 2792, 1685, 1652, 1464, 1129, 1106. ^1H NMR (400 MHz, $CDCl_3$, *E*/*Z*-isomers, ratio 3:2): δ = 1.15−1.42 (m, 3H, 5-H, 6-H), 1.71−1.90 (m, 3H, 6-H, 3-H), 1.92−2.00 (m, 0.6H, 2-H, *E*-isomer), 2.17 (s, 1.2H, N−CH_3, *Z*-isomer), 2.23 (s, 1.8H, N−CH_3, *E*-Isomer), 2.42−2.50 (m, 0.4H, 2-H, *Z*-isomer), 3.07−3.15 (m, 2H, 1-H, 4-H, *E*-isomer), 3.12−3.17 (0.8H, 1-H, 4-H, *Z*-isomer), 3.46 (s, 1.8H, OCH_3, *E*-isomer), 3.50 (s, 1.2H, OCH_3, *Z*-isomer), 4.42 (dd, J = 9.0 Hz, J = 6.2 Hz, 0.4H, 8-H, *Z*-isomer), 4.76 (dd, J = 9.1, J = 12.6 Hz, 0.6H, 8-H, *E*-isomer), 5.70 (d, J = 6.2 Hz, 0.4H, 9-H, *Z*-isomer), 6.22 (d, J = 12.6 Hz, 0.6H, 9-H, *E*-isomer). ^{13}C NMR (100 MHz, $CDCl_3$, *E*/*Z*-isomers): δ = 29.7 (C-5), 31.5 (C-6), 35.1 (N−CH_3), 35.5 (C-3), 40.6 (C-2), 59.3 and 59.5 (C-4, *E*/*Z*), 61.1 and 61.5 (OCH_3, *E*/*Z*), 67.6 and 68.1 (C-1, *E*/*Z*), 108.6 and 113.2 (C-8, *E*/*Z*), 144.3 and 145.9 (C-9, *E*/*Z*). MS (70 eV): m/z = 167 (31, M^+), 83 (100). HRMS: calcd for $C_{10}H_{17}NO$ 167.1310, found 167.1298.

***exo*-7-Methyl-2-(pyridazin-4-yl)-7-azabicyclo[2.2.1]heptane (28).** To a solution of the enol ether **27** (380 mg, 2.28 mmol) in dry toluene (30 mL) was added dropwise a solution of the tetrazine **14d** in dry toluene (20 mL) at room temperature under an argon atmosphere. The mixture was heated at reflux and stirred under Argon for 16 h and cooled to room temperature. The solvent was evaporated in vacuo and the residue purified twice by flash chromatography over silica gel (eluting with CH_2Cl_2:MeOH:diethylamine = 95:15:0.2, column 25 × 1,5 cm) to give **28** (82 mg, 19%, R_f = 0.23) as a slightly brownish-yellow oil. IR (film): ν (cm^{-1}) = 2961, 2882, 2804, 1586. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.41−1.44 (m, 2H, 5-H), 1.62−1.69 (m, 1H, 3β-H), 1.83 (dd, J = 12.0 Hz, J = 9.2 Hz, 1H, 3α-H), 1.89−1.99 (m, 2H, 6-H), 2.23 (s, 3H, N−CH_3), 2.60 (dd, J = 9.2 Hz, J = 4.9 Hz, 1H, 2α-H), 3.17 (d, J = 4.0 Hz, 1H, 1-H), 3.32−3.33 (m, 1H, 4H), 7.56−7.57 (dd, J = 2.3 Hz,

J = 5.2 Hz, 1H, 5′−H), 8.99 (dd, J = 5.2 Hz, J = 1.1 Hz, 1H, 6′−H), 9.17 (dd, J = 2.3 Hz, J = 1.1 Hz, 1H, 3′−H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5 (C-5), 26.4 (C-6), 34.5 (N-CH_3), 40.7 (C-3), 45.8 (C-2), 61.2 (C-4), 67.0 (C-1), 124.8 (C-5″), 146.3 (C-4′), 151.0 (C-6′), 152.3 (C-3′). MS (70 eV): m/z (%) = 189 (24, M^+), 83 (100). HRMS: calcd for $C_{11}H_{15}N_3$ 189.1266, found 189.1257.

Biological Characterization. Whole-cell current recording from *Xenopus* oocytes expressing recombinant nAChR from the rat was performed as described elsewhere.[44] Oocytes were injected with appropriate cDNA plasmids to express one of the following nAChR subypes: $\alpha 3\beta 4$, $\alpha 4\beta 2$, $\alpha 7$ (all neuronal) or $\alpha 1\beta 1\gamma\delta$ (embryonic muscle subtype). Oocytes were voltage-clamped to −80 mV membrane potential and total membrane currents were recorded with a GeneClamp 500 Amplifier (Axon Instruments). For initial testing, compounds were applied by superfusion at a concentration of 100 μM in frog Ringer solution (in mM: 115 NaCl, 2.5 KCl, 1.8 $CaCl_2$, 10 HEPE, pH 7.2). If a current response indicating the activation of receptors resulted, then the compounds were further characterized by the determination of a dose−response curve. The agonistic potency of the active compounds at each receptor subtype is expressed as the concentration which was found to be equipotent with a standard reference dose of acetylcholine (Table 1).

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Supporting Information Available: Elemental analysis for compounds **15**−**17**, **19**, and **20** (Table 2); ^{1}H and ^{13}C NMR spectra of compounds **18**, **22**, **24**, and **28**; crystal data, final atomic positional parameters, atomic thermal parameters, and bond distances and angles for compound **24** (Tables 3−7). This material is available free of charge via the Internet at http://pubs.acs.org.

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