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Synthesis and Structure–Activity Data of Some New Epibatidine Analogues

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Abstract—The high-pressure Diels–Alder reaction of N-carbomethoxypyrroles and phenyl vinyl sulfone affords versatile intermediates for the palladium-catalyzed preparation of new epibatidine analogues. Structure–activity relationships of new epibatidine analogues are presented. High affinities of $K_i = 0.81$ and 2.6 nM for the [^{3}H]-cytisine rat brain nicotinic acetylcholine binding sites were found for the 5-pyrimidinyl and the 5-(2-amino)-pyrimidinyl epibatidine analogues, respectively.

Introduction

Epibatidine **1**, *exo*-2-(6-chloro-3-pyridyl)-7-azabicyclo-[2.2.1]heptane, an alkaloid isolated from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, was recently reported as a novel, highly potent, nonopioid analgesic agent and a specific agonist of central nicotinic acetylcholine receptors (nAChRs).[1] Neuronal nAChRs occur as different subtypes and are widely distributed in the brain. It might be hypothesized that each subtype is involved in mediating specific functions/behaviors with a defined pharmacology that might be selectively targeted. In vitro studies have shown **1** to be a very potent activator of the nAChRs mediating cation flux, current activation, and neurotransmitter release. In vivo studies have provided converging evidence that the potent analgesic activity of this agent is accompanied by a spectrum of nAChR-mediated nonanalgesic liabilities, including motoric, thermoregulatory, and cardiovascular effects.[2a–d] Despite the fact that **1** is too toxic for clinical applications, active synthetic analogues have the potential for improved pharmacological profiles. This may open applications based on their nicotinic activity, such as the treatment of Parkinson's and Alzheimer's disease, schizophrenia, Tourette's syndrome, ulcerative colitis, cognitive disorders, and tobacco dependence.[2e] Structure–activity studies of epibatidine **1** and analogues, as reported in the literature, have shown that the chloro substituent of the pyridyl ring of epibatidine is not critical to nAChR affinity, since the deschloro analogue has slightly greater affinity than epibatidine.[2] Very recently, Daly et al.[3] reported that replacement of the chloropyridyl ring by an isoxazole ring gives epiboxidine **2**, a compound that is less toxic than epibatidine but has similar nAChR binding affinity (Fig. 1).

These data suggest that various heteroaryl groups, other than chloropyridyl, are allowed. From quantitative structure–affinity relationship (QSAR) studies of nicotinic ligands by Glennon et al.[2b] it was stated that the distance between the pyrrolidine and pyridine nitrogen atoms in epibatidine, nicotine, and its analogues is an important parameter for high binding affinity to the nicotinic receptor. Because epibatidine binds with higher affinity at nicotinic receptors than nicotine and the internitrogen distance is longer in epibatidine than in

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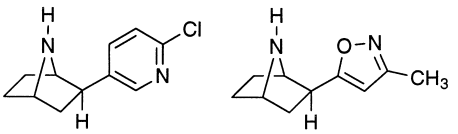


Figure 1.

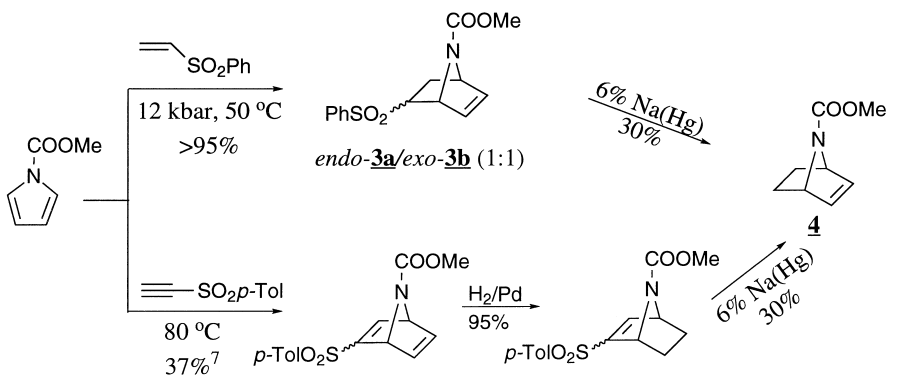
nicotine the introduction of aminoaryl groups becomes an interesting issue. Therefore, we decided to explore new epibatidine derivatives with variations in the heterocyclic system and the N-N distance.

Several approaches to the preparation of the 7-azabicyclo[2.2.1]heptane system and the total synthesis of **1** and analogues have been reported.[4,5] The Diels–Alder reaction of N-protected pyrroles with activated dienophiles is a straightforward route to prepare this ring system. Subsequent *exo*-stereoselective palladium-catalyzed hydroarylation reaction of N-protected 7-azabicyclo-[2.2.1]-hept-2-ene cycloadducts with aryl halides has proven to be an attractive, short, and efficient synthetic approach to **1**. In this article we report: 1) an efficient synthesis of the intermediate N-carbomethoxy 7-azabicyclo[2.2.1]hept-2-ene (**4**) applying the high-pressure Diels–Alder reaction of N-carbomethoxypyrrole to phenyl vinyl sulfone (Scheme 1); 2) the synthesis of new epibatidine analogues with variations in the aryl ring via palladium catalyzed hydroarylation reactions of **4** (Scheme 2); and 3) structure–activity data of these products through receptor binding studies to nAChRs in rat brain preparations.

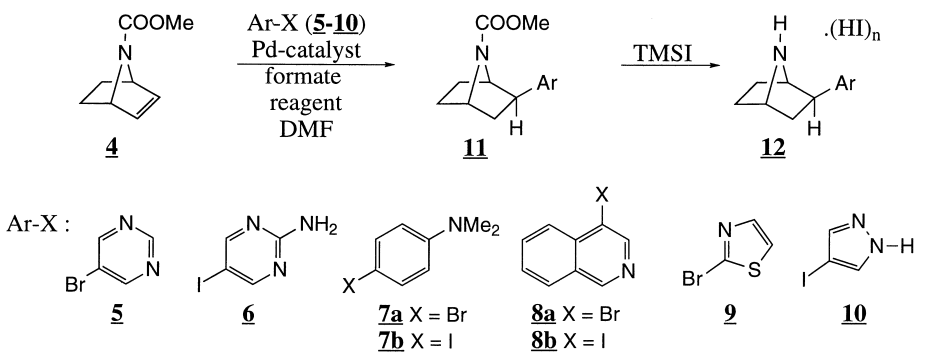
Results

The known 7-azabicyclo[2.2.1]hept-2-ene **4** is generally prepared via a thermal Diels–Alder reaction of a N-acylpyrrole to *p*-toluenesulfonylacetylene followed by two reduction steps; i.e. regioselective hydrogenation of a carbon–carbon double bond and subsequent reductive desulfonylation with sodium amalgam.[5e,7]

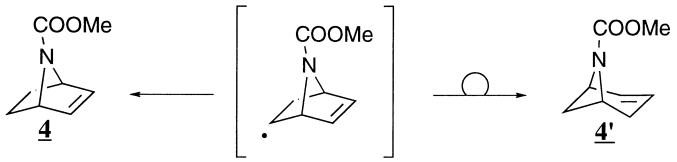
We found that N-carbomethoxypyrrole reacted readily with phenyl vinyl sulfone in acetonitrile at 12 kbar pressure and 50 °C to afford after 20 h, quantitatively, a



Scheme 1.



Scheme 2.



Scheme 3.

1:1 mixture of *endo*- and *exo*-5-phenylsulfonyl-7-methoxycarbonyl 7-azabicyclo[2.2.1]hept-2-ene (**3a** and **3b**, respectively).[9] The mixture of *endo*-**3a** and *exo*-**3b** was subsequently desulfonylated by reduction with 6% sodium amalgam to afford the desired alkene **4** in 30% isolated yield after chromatography.[10] The high-pressure promoted synthesis of **4** displays some advantages: a shorter sequence starting from commercially available phenyl vinyl sulfone and a higher overall yield of **4**. In order to find active synthetic epibatidine analogues, the presence of an external hydrogen bond acceptor atom attached to the 7-azabicycloalkane skeleton is presumed to be a prerequisite.[2] Our experiments in this field were therefore focused on the use of nitrogen-containing (hetero)aryl halides (**5–10**)[11] in the palladium(0) catalyzed hydroarylation reaction[12] with alkene **4** (Scheme 2). Three different catalytic methods have been applied: Method A uses Jeffery–Larock conditions, i.e. 1 equiv nBu$_4$N$^+$Cl$^-$, 3 equiv KOOCH, 0.05 equiv Pd(OAc)$_2$; Method B uses 2.5 equiv piperidine, 3.5 equiv HCOOH, 0.08 equiv Pd(PPh$_3$)$_4$; and Method C is similar to Method B, but applies 0.08 equiv Pd(OAc)$_2$(PPh$_3$)$_2$ as the catalyst. The experimental conditions and the results of the reactions of alkene **4** with aryl halides **5–10** are summarized in Table 1. From the results in Table 1, it follows that although aryl iodides are known to be more reactive than aryl bromides, the bromide **5** reacts well with alkene **4** in the presence of one equiv of tetrabutylammonium chloride, using Method A. A major side reaction with **8a** is the palladium-catalyzed formation of isoquinoline by a reductive mechanism.[13] Replacement of halide in the ArPdL$_2$X intermediate (L = ligand; X = halide) by formate and decomposition of the formed ArPdL$_2$OCOH to arene through deinsertion of carbon dioxide is probably faster than its oxidative addition to the double bond of alkene **4**. N-arylation of piperidine with aryl halides was another side reaction observed when using method B to give, for example, 1-piperidinyl-2-thiazole from **9**.

The *exo*-stereochemistry of the products **11** was assigned by the NMR-signal multiplicity (a doublet of doublets) for proton H-2, which is located at the *endo*-side of the molecule.[4] After treatment of the prepared N-carbomethoxy *exo*-2-aryl-7-azabicyclo[2.2.1]heptanes **11** with trimethylsilyl iodide the new epibatidine analogues **12a–12f** were isolated as their hydriodic acid salts in a nearly quantitative yield (Figure 2).

Biological data

The compounds **12a–12f** were evaluated for their binding affinities to neuronal nAChRs by measuring the displacement of [^{3}H]-cytisine from a preparation of whole rat brain according to the procedure described by Anderson et al.[14] The binding results of the test compounds have been normalized to their equilibrium dissociation constants (K_i) and are presented in Table 2. The results from Table 2 show that high binding for the nicotinic receptor is found for epibatidine **1** and the 5-pyrimidinyl and 2-amino-5-pyrimidinyl epibatidine analogues, resp. **12a** and **12b**. Although deschloro–epibatidine has a slightly greater affinity than epibatidine, the potent subnanomolar affinity of epibatidine **1** to

Table 1. Reductive Heck reactions of alkene **4** with aryl halides **5–10**

Ar-X	Prep. method[a]	Time (h)	Temp. (°C)	Product	Yield (%)[b]
5	A	24	60	**11a**	42
6	A[c]	16	60	**11b**	74
	B	24	75	**11b**	20
7a	A	20	60	**11c**	18[d]
	B	24	75	—	—
7b	A	15	60	**11c**	21
	B	24	60	**11c**	75[e]
8a	A,B,C	days	60–75	—	—
8b	B	17	70	**11d**	55
9	A	16	60	**11e**	15[f]
10	B	24	75	**11f**	30

[a] Preparation methods: (A) 1 equiv aryl halide, 0.05 equiv Pd(OAc)$_2$, 3 equiv KOOCH, 1 equiv nBu$_4$N$^+$Cl$^-$; (B) 2 equiv aryl halide, 0.08 equiv Pd(PPh$_3$)$_4$, 3.5 equiv piperidine, 2.5 equiv HCOOH; (C) 0.08 equiv Pd(OAc)$_2$(PPh$_3$)$_2$, 3.5 equiv piperidine, 2.5 equiv HCOOH.

[b] Isolated yield of pure compounds after column chromatography.

[c] 0.35 equiv Pd(OAc)$_2$.

[d] ca. 50% conversion of **7a**.

[e] When performed 24 h at 75 °C, the yield drops to 60%.

[f] ca. 50% conversion of **4**, 1-piperidinyl-2-thiazole as by-product.

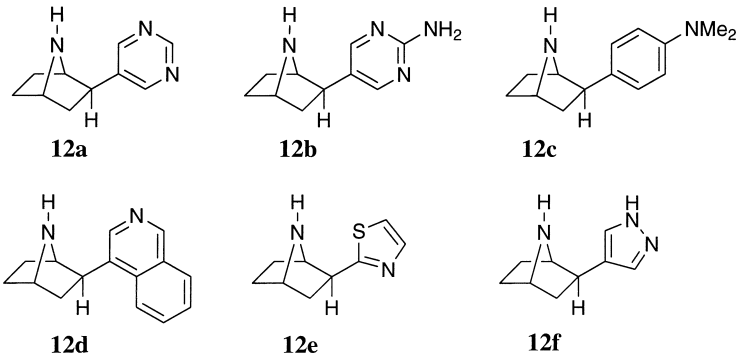


Figure 2. Prepared epibatidine analogues.

brain nAChRs is still fivefold higher than **12a** and 16-fold higher than **12b**. The lower basicity of the pyrimidinyl group in **12a** and to a lesser extent in **12b** can explain this difference. In addition, the NH_2 substituent in **12b** probably acts as a sterically demanding group which slightly decreases affinity. For comparison, substitution at the 5-position of the pyridine ring in nicotine with a bromo or a ethynyl group has led to derivatives with attractive pharmacological profiles and are evaluated as novel anti-Parkinson agents.[14] The drop in binding potency for 4-isoquinolyl analogue **12d** further indicates that any other substitution in the pyridyl ring in epibatidine significantly lowers the binding, irrespective of the internitrogen distance, which is for **12a**, **12b**, and **12d** approximately equal to epibatidine. Novel cholinergic channel activators (ChCAs) of neuronal nicotinic acetylcholine receptors (nAChRs) have been described in the literature in which a substituted isoxazole ring has been incorporated as a bioisosteric replacement for the pyridine ring found in (*S*)-nicotine, (*R*)-nornicotine and (−)-epibatidine.[16]

As compared with the recently reported high binding potency of epiboxidine **2**, an isoxazole epibatidine analogue, the moderate binding potency of the 4-pyrazole analogue **12f**, is somewhat disappointing. The presence of the N-H functionality in 4-pyrazole analogue **12f**, might hinder efficient hydrogen bond formation with the receptor. The lower potencies of N,N-dimethylanilino analogue **12c** and 2-thiazole analogue **12e** suggest that the position of the nitrogen atom in the heteroaryl ring is still very important. This distance seems to be too short in **12e** and too long in **12c**.

Table 2. Binding affinities of epibatidine analogues for [^{3}H]-cytisine-labeled nicotinic acetylcholine receptors[a]

nAChR ligand	K_i (nM)[b]
Epibatidine 1	0.16 ± 0.08 (3)
12a	0.81 ± 0.058 (3)
12b	2.6 ± 0.78 (3)
12f	18 ± 1.0 (2)
12d	53 ± 15 (3)
12e	5,800 ± 3,700 (3)
12c	29,500 ± 3,500 (2)
Nicotine	3.6 ± 0.11 (5)
Cytisine	0.82 ± 0.24 (3)

[a] Ref. 14.
[b] Mean K_i values from (x) determinations.

Experimental

DMF was distilled and dried on 4 Å molecular sieves. Piperidine was stored on potassium hydroxide pellets. Dichloromethane was dried and distilled on CaH_2 and stored over 4 Å molecular sieves. ^{1}H NMR spectra and ^{13}C NMR were recorded on a Bruker AM-100 (100 MHz, FT), AM-300 (300 MHz, FT) or AM-400 (400 MHz, FT) spectrometer with TMS as internal standard. IR spectra were run on a Perkin–Elmer 298 spectrophotometer. Mass spectra were measured with a Varian SM1-B double focusing mass spectrometer or with a VG 7070E mass spectrometer. Gas chromatography was performed on a Hewlett–Packard 5710A GC instrument equipped with a capillary HP cross-linked methyl silicone (25 m × 0.31 mm) column. Purification of products was done by normal or flash chromatography on silica gel, using Merck silica gel 60 or 60H as stationary phase. The aryl halides **5**, **7a**, **8a**, **9**, and **10** were commercially purchased. The aryl halides 5-iodo-2-aminopyrimidine **6**, 4-iodo-*N*,*N*-dimethylaniline **7b** and 4-iodoisoquinoline **8b** were prepared according to literature procedures.[11]

High pressure Diels–Alder reaction of methyl pyrrole-1-carboxylate and phenyl vinyl sulfone

A mixture of methyl pyrrole-1-carboxylate[8] (7.5 g, 60 mmol) and 1.1 equiv phenyl vinyl sulfone (9.9 g,

58.9 mmol) is dissolved in acetonitrile and kept at 12 kbar high pressure overnight at 50 °C. The pyrrole **2** is completely converted and the formed product appears to consist of an equimolar mixture of *endo*- and *exo*-5-phenylsulfonyl-N-carbomethoxy-7-azabicyclo[2.2.1]hept-2-ene (**3a** and **3b**, respectively) which can be separated by chromatography using ethyl acetate/*n*-hexane mixtures and are isolated in almost quantitative yield.

***endo*-5-Phenylsulfonyl-N-carbomethoxy-7-azabicyclo-[2.2.1]hept-2-ene (3a).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (1H, m, H-6a), 2.32 (1H, ddd, J = 4.3, 9.1, and 12.4, H-6b), 3.62 (3H, s, OCH_3), 3.74 (1H, ddd, appears as quintet, J = 4.3 and 8.6, H-5), 4.83 (1H, br s, H-4), 4.86 (1H, br s, H-1), 6.46 (1H, m, H-2), 6.54 (1H, m, H-3), 7.59 (2H, t, ArH), 7.68 (1H, t, ArH), 7.86 (2H, d, ArH); EIMS 293 (rel intensity) 168 (18), 141 (3), 125 (100); Anal. calcd for $C_{14}H_{15}NO_4S$ (Mass = 293.343): C, 57.32; H, 5.15; N, 4.77; S, 10.93. Found: C, 57.13; H, 5.01; N, 4.85; S, 10.69.

***exo*-5-Phenylsulfonyl-N-carbomethoxy-7-azabicyclo[2.2.1]-hept-2-ene (3b).** Solid; mp 127 °C; ^{1}H NMR (400 MHz, 315 K, $CDCl_3$) 1.61 (1H, dd, J = 8.4 and 11.9, H-6), 2.32 (1H, br d, J = 12.1, H-6), 3.03 (1H, dd, J = 4.3 and 8.4, H-5), 3.60 (3H, s, OCH_3), 4.79 (1H, br s, H-4), 5.07 (1H, br s, H-1), 6.32 (1H, d, J = 4.6, H-2), 6.43 (1H, d, J = 4.6, H-3), 7.55 (2H, t, ArH), 7.64 (1H, t, ArH), 7.92 (2H, d, ArH); EIMS 293 (rel, int.) 168 (20), 141 (4), 125 (100); Anal. calcd for $C_{14}H_{15}NO_4S$ (Mass = 293.343): C, 57.32; H, 5.15; N, 4.77; S, 10.93. Found: C, 57.20; H, 5.02; N, 4.87; S, 10.83.

Reduction of 3a/3b with 6% sodium amalgam. Preparation of 7-carbomethoxy-7-azabicyclo[2.2.1]hept-2-ene (4).[7] The crude cycloadduct **3a/3b** (11.05 g, 37.5 mmol) is treated with 6% sodium amalgam according to literature.[6] After column chromatography on silica gel with ethylacetate/*n*-hexane (1/8), the product was isolated and characterized as 7-carbomethoxy-7-azabicyclo-[2.2.1]heptene **4** (oil, 1.72 g, 30%). All physical data of **4** were identical[7] as reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (2H, m, H-5, H-6), 1.86 (2H, m, H-5, H-6), 3.63 (3H, s, OCH_3), 4.73 (2H, br s, H-1, H-4), 6.23 (2H, br s, H-2, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 24.1, 53.0, 59.2, 134.0, 134.9, 156.0; GC–MS (% rel intensity, ion): calcd for $C_8H_{11}NO_2$, 153; found, 153 (M^+, 3), 125 (100), 80 (50).

General procedures for reductive Heck-reaction with alkene 4

Method A. The alkene **4** (153 mg, 1 mmol) was weighed into a 10 mL vial, containing a magnetic stirrer and aryl halide **5–10** (1 mmol). Subsequently, nBu$_4$N$^+$Cl$^-$ (278 mg, 1 mmol), DMF (2 mL), KOOCH (252.4 mg, 3 mmol), and $Pd(OAc)_2$ (11.8 mg, 0.05 mmol) were added. The vial was then sealed and placed in an oil bath of 60 °C and left stirring for 16 h. The crude product was washed with 5 mL water and extracted three times with 25 mL ethyl acetate. After drying with sodium sulfate and evaporation of the solvent, the residue was subjected to silica gel chromatography using ethyl acetate/*n*-hexane mixtures as the eluent. Carbamates **11a–11f** were isolated as pure compounds and were analyzed and characterized by MS and NMR.

Method B. The alkene **4** (153 mg, 1 mmol) was weighed into a 10 mL vial, containing a magnetic stirrer and aryl halide **5–10** (1–3 mmol). Subsequently, DMF (2 mL), piperidine (2.5 mmol), $Pd(PPh_3)_4$ (0.08 mmol) and formic acid (3.5 mmol) were added. The vial was then sealed and placed in an oil bath of 70 °C and left stirring overnight for at least 16 h. The crude product was worked up as described in Method A.

Method C is essentially the same as Method B except for the fact that 8 mol% $(Ph_3P)_2Pd(OAc)_2$ was used as catalyst instead of $Pd(PPh_3)_4$.

General procedure for deprotection of carbamates 11a–11f with trimethylsilyl iodide

Carbamates **11** were dissolved in chloroform or acetonitrile (ca. 100 mg/25 mL solvent). Trimethylsilyliodide (2 mL) is added via a syringe and the mixture is refluxed for 3 h. After cooling, methanol (50 mL) is added to the brown solution and the mixture is refluxed again for 2 h. Evaporation of the solvent in vacuo gave a brown oily residue which was treated with methanol/diisopropylether mixtures (ca. 1/5–1/20). A white precipitate was formed which was subsequently filtered over a glass filter, washed with small amounts of diisopropylether and dried to give the epibatidine analogues **12** as their hydriodic acid salts.

***exo*-2-(Pyrimidin-5-yl)-7-carbomethoxy-7-azabicyclo[2.2.1]-heptane (11a).** The reductive Heck reaction was performed according to method A, starting from 153 mg (1.0 mmol) alkene **4** and 159 mg (1.0 mmol) 5-bromopyrimidine **5**. After 24 h at 60 °C, the reaction mixture was separated by silica gel chromatography using ethyl acetate/*n*-hexane (1/3) as the eluent to give 98 mg **11a** (42% isolated yield, R_f = 0.1) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56–1.69 (2H, m, H-5, H-6), 1.86–1.93 (3H, m, *exo* H-3, H-5, H-6), 2.06 (1H, dd, $J_{H3endo,H2endo}$ = 8.9 and J = 12.5 Hz, *endo* H-3), 2.89 (1H, dd, J = 4.7 and $J_{H2endo,H3endo}$ = 8.9 Hz, H-2), 3.68 (3H, s, OCH_3), 4.28 (1H, br s, H-4), 4.49 (1H, br s, H-1), 8.66 (2H, s, ArH), 9.08 (1H, s, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 29.5, 39.8, 43.7, 52.5, 56.1, 56.2, 61.7, 138.2, 155.5, 157.0, 213.0; Mass calcd. $C_{12}H_{15}N_3O_2$

M = 233; found GC/MS (CI, Mass, rel int.) 233 (M^+, 10), 201 (M^+ −OMe, 16), 159 (6), 127 (100).

***exo*-2-(Pyrimidin-5-yl)-7-azabicyclo[2.2.1]heptane, (12a·2HI).** Mp 215–220 °C uncor; ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$, δ 1.78–2.16 (5H, m, 2×H-5, 2×H-6, *exo* H-3), 2.59 (1H, m, *endo* H-3), 3.73 (1H, m, H-2), 4.32 (1H, br s, H-4), 4.47 (1H, br s, H-1), 9.16 (2H, s, ArH), 9.30 (1H, s, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.3, 34.6, 39.9, 40.9, 58.4, 61.3, 148.8, 152.7, 155.5; Anal. calcd for $C_{10}H_{13}N_3 \cdot 2HI$ (Mass = 431.058): C, 27.86; H, 3.51; N, 9.75. Found: C, 27.86; H, 3.48; N, 9.69.

***exo*-2-(2-Aminopyrimidin-5-yl)-7-carbomethoxy-7-azabicyclo[2.2.1]heptane (11b).** The reductive Heck reaction was performed according to method A, starting from 153 mg (1.0 mmol) **4** and 221 mg (1.0 mmol) 2-amino-5-iodopyrimidine **12** and using 0.35 equiv $Pd(OAc)_2$. After 16 h at 60 °C, the reaction mixture was separated with silica gel chromatography using dichloromethane/methanol/ammonia (80/20/1) as eluent to give 184 mg of **21c** (74% isolated yield, R_f = 0.45) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) 1.43–1.83 (5H, m, 2×H-5, 2×H-6, H-3 *exo*), 1.97 (1H, dd, $J_{H3endo,H2endo}$ = 8.9 and J = 12.5 Hz, *endo* H-3), 2.73 (1H, dd, J = 4.8 and $J_{H2endo,H3endo}$ = 8.9 Hz, H-2), 3.66 (3H, s, OCH_3), 4.16 (1H, br s, H-4), 4.44 (1H, br s, H-1), 5.49 (2H, br s, NH_2), 8.19 (2H, s, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 29.5, 39.9, 43.2, 52.6, 56.3, 59.3, 62.5, 128.6, 157.7, 162.9, 213.5; Mass calcd for $C_{12}H_{26}N_4O_2$, 248; found GC/MS (CI, Mass, rel intensity) 248 (M^+, 22), 216 (M^+ −OMe, 9), 146 (8), 127 (100).

***exo*-2-(2-Aminopyrimidin-5-yl)-7-azabicyclo[2.2.1]heptane (12b.2.2HI).** Mp 215–220 °C uncor; ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$) δ 1.91–2.17 (5H, m, 2×H-5, 2×H-6, H-3 *exo*), 2.44 (1H, m, *endo* H-3), 3.46 (1H, m, H-2), 4.38 (1H, br s, H-4), 4.58 (1H, br s, H-1), 4.87 (2H, br s, NH_2), 8.63 (2H, s, ArH); Anal. calcd for $C_{10}H_{14}N_4 \cdot 2.2$ HI (Mass = 471.66): C, 25.47; H, 3.46; N, 11.88. Found: C, 25.47; H, 3.48; N, 11.80.

***exo*-2-(4-*N*,*N*-Dimethylanilino)-7-carbomethoxy-7-azabicyclo[2.2.1]heptane (11c).** The reductive Heck reaction of **4** (223 mg, 1.46 mmol) with **7b** (2 equiv) was catalyzed by 8 mol% $Pd(PPh_3)_4$ in the presence of 3.5 equiv piperidine and 2.5 equiv formic acid at 60 °C in 2 mL DMF. After 24 h, the hydroarylated product **11c** (300 mg, 75%) was isolated as an oil by chromatography using ethyl acetate/*n*-hexane as (1/4) eluent: R_f = 0.16; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47–1.97 (6H, m, 2×H-3, 2×H-5, 2×H-6), 2.80 (1H, dd, J = 6.0 and 7.9, H-2), 2.90 (6H, s, $N(CH_3)_2$), 3.64 (3H, s, OCH_3), 4.20 (1H, br s, H-4), 4.41 (1H, br s, H-1), 6.68 (2H, d, J = 8.7, 2×ArH), 7.11 (2H, d, J = 8.7, 2×ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5, 29.6, 40.0, 40.5, 47.0, 62.1, 51.9, 55.7, 112.5, 127.3, 133.5, 148.9, 212.9; Mass calcd for $C_{16}H_{22}N_2O_2$, 274; found: GC–MS (CI, Mass, rel intensity) 274 (M^+, 20), 199 (64), 172 (100), 157 (26).

***exo*-2-(4-*N*,*N*-Dimethylanilino)-7-azabicyclo[2.2.1]heptane (12c·2HI).** From 200 mg carbamate **11c** is prepared 334 mg (97%) of **12c** as its hydriodic acid salt following the standard procedure: Mp 210–215 °C dec; ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$) δ 1.9–2.5 (6H, m, H-3, H-5 en H-6), 3.31 (6H, br s, 2×$N(CH_3)_2$), 3.48 (1H, m, H-2α), 4.39 (1H, br s, H-4), 4.52 (1H, br s, H-1), 7.60–7.73 (4H, m, Ar-H); ^{13}C NMR ($CD_3OD/CDCl_3$) δ 25.1 (CH_2, C-5), 27.1 (CH_2, C-6), 35.9 (C-2 en C-3), 43.9 (N-CH_3), 45.9 (N-CH_3), 58.5 (C-4), 62.5 (C-1), 120.3 (C-4′), 128.6 (C-3′ en C-5′); Anal. calcd for $C_{14}H_{20}N_2 \cdot 2HI$ (Mass = 472.15): C, 35.61; H, 4.70; N, 5.93. Found: C, 35.25; H, 4.67; N, 5.84.

***exo*-2-(4-Isoquinolyl)-7-carbomethoxy-7-azabicyclo[2.2.1]-heptane (11d).** The reductive Heck reaction was performed according to method B, starting from 153 mg (1.0 mmol) **4** and 638 mg (2.5 mmol) **8b**. After 17 h at 70 °C analysis by GC showed that the alkene was completely converted and the reaction products were separated by silica gel chromatography using ethyl acetate/*n*-hexane (1/2) as the eluent, to yield 155 mg of **11d** (55% isolated yield) as an oil: R_f = 0.14; Mass calcd for $C_{17}H_{18}N_2O_2$, 282; found, GC/MS (CI) (Mass, rel intensity) 282 (M^+, 28), 180 (20), 156 (100), 127 (91).

***exo*-2-(4-Isoquinolyl)-7-azabicyclo[2.2.1]heptane (12d.2HI).** Mp 220–225 °C uncor; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89–1.13 (5H, m, 2×H-5, 2×H-6, H-3), 1.73 (1H, dd, J = 9.7 and 11.8, H-3), 3.15 (1H, dd, J = 6.0 and 9.7, H-2), 3.29 (1H, br s, H-1), 3.84 (1H, br s, H-4), 6.96 (1H, t, J = 7.3, ArH), 7.19 (1H, t, J = 7.3, ArH), 7.34 (1H, d, J = 8.4, ArH), 7.44 (1H, d, J = 8.4, ArH), 7.61 (1H, s, ArH), 8.66 (1H, s, ArH); Anal. calcd for $C_{15}H_{16}N_2 \cdot 2HI$ (Mass = 480.130): C, 37.52; H, 3.78; N, 5.84. Found: C, 37.50; H, 3.73; N, 5.90.

***exo*-2-(2-Thiazolyl)-7-carbomethoxy-7-azabicyclo[2.2.1]-heptane (11e).** The reductive Heck reaction was performed according to method A, starting from 153 mg (1.0 mmol) **4** and 164 mg (1.0 mmol) **9**. After 16 h at 60 °C, analysis by GC showed that the **9** was completely converted, but ca. 50% of **4** was still present. Silica gel chromatography using ethyl acetate/*n*-hexane (1/1) as the eluent gave 36 mg of **11e** (15% isolated yield, 30% based on converted alkene): R_f = 0.20; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52–1.69 (2H, m, H-5 and H-6), 1.87 (2H, m, H-5 and H-6), 2.05 (1H, dd, $J_{H3endo,H2endo}$ = 8.8 and J = 12.6 Hz, *endo* H-3), 2.19 (1H, m, *exo* H-3), 3.43 (1H, dd, J = 4.6 and $J_{H2endo,H3endo}$ = 8.8 Hz, H-2), 3.63 (3H, s, OCH_3), 4.40–4.47 (2H, m,

H-1 and H-4), 7.21 (1H, d, $J=3.3$, ArH), 7.65 (1H, d, $J=3.3$, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 39.2, 46.9, 52.3, 55.9, 62.5, 118.5, 141.6, 156.0, 174.4, 213.8; Calculated mass for $C_{11}H_{14}N_2O_2S$, 238; found by GC/MS (Mass, rel intensity) 238 (M^+, 2), 207 (5), 136 (11), 127 (34), 112 (100).

***exo*-2-(2-Thiazolyl)-7-azabicyclo[2.2.1]heptane (12e·2HI).** Carbamate **11e** (30 mg, 0.13 mmol) was cleaved with trimethylsilyl iodide to give, after quenching with methanol and precipitation in diisopropyl ether, 49 mg **12e** (89%) as its hydriodic acid salt: Mp 215–220 °C dec; ^{1}H NMR (300 MHz, $CD_3OD/CDCl_3$) δ 1.9–2.2 (4H, m, H-5 en H-6), 2.30 (1H, m, H-3$_\beta$), 2.53 (1H, dd, H-3$_\alpha$), 3.93 (1H, dd, $J_{2\alpha,3\alpha}=12.5$ Hz, $J_{2\alpha,3\beta}=6.6$ Hz, $J_{2\alpha,1}<1$, H-2$_\alpha$), 4.44 (1H, m, H-4), 4.58 (1H, m, H-1), 7.64 (1H, d, $J=4.6$ Hz, H-3′), 7.91 (1H, d, $J=4.6$ Hz, H-4′); ^{13}C NMR ($CD_3OD/CDCl_3$) δ 25.4 (CH_2, C-5), 25.5 (CH_2, C-6), 35.8 (C-3), 41.5 (C-2), 58.0 (C-4), 63.2 (C-1), 119.9 (C-3′), 139.8 (C-4′); Anal. calcd for $C_9H_{12}N_2S{\cdot}2HI$ (Mass = 436.098): C, 24.79; H, 3.24; N, 6.42; S, 7.35. Found: C, 24.86; H, 3.17; N, 6.57; S, 7.18.

***exo*-2-(4-Pyrazolyl)-7-azabicyclo[2.2.1]heptane (12f·2.25HI).** The reductive Heck reaction was performed according to method B, starting from 153 mg (1.0 mmol) **4** and 388 mg (2.0 mmol) of **10**. After 24 h at 75 °C, the reaction mixture was worked up and purification silica gel chromatography gave 66 mg *exo*-2-(4-pyrazolyl)-7-carbomethoxy-7-azabicyclo[2.2.1] heptane **11f** (30% isolated yield). Deprotection of the carbamate **11f** with trimethylsilyl iodide afforded **12f** as its hydriodic acid salt: Mp 220–225 °C uncor; ^{1}H NMR (400 MHz, CD_3OD) δ 1.84 (1H, m, H-6$_\alpha$), 2.0–2.2 (2H, m, H-5$_\beta$ en H-6$_\beta$), 2.25 (1H, m, H-3$_\beta$), 2.41 (1H, dd, $J_{3\alpha,2\alpha}=9.3$, $J_{3\alpha,3\beta}=13.6$, H-3$_\alpha$), 3.41 (1H, dd, $J_{2\alpha,3\alpha}=9.3$ Hz, $J_{2\alpha,3\beta}=5.4$, $J_{2\alpha,1}<1$, H-2$_\alpha$), 4.41 (2H, t, $J_{4,3\beta}\approx J_{4,5\beta}\approx J_{1,6\beta}\approx 4.4$, $J_{4,3\alpha}\approx J_{1,2\alpha}<1$, H-1 en H-4), 8.11 (2H, br s, H-3′ en H-5′); ^{13}C NMR (75 MHz, CD_3OD) δ 25.6 (CH_2, C-5), 26.9 (CH_2, C-6), 35.7 (C-2), 36.0 (CH_2, C-3), 58.7 (C-4), 64.3 (C-1), 122.5 (C-4′), 132.4 (C-3′ en C-5′); Anal calcd for $C_9H_{13}N_3{\cdot}2.25HI$ (Mass = 451.02): C, 23.97; H, 3.41; N, 9.32. Found: C, 23.97; H, 3.37; N, 9.30.

Binding assay

Briefly, binding assays have been carried out as follows: drug solutions were prepared manually, and consequently diluted by a Tecan dilution robot, which transferred the proper dilution series in triplicate in individual incubation tubes. Those were placed in a Filterprep-101 (Ismatec, Zürich, Switzerland) which was programmed to add [^{3}H]-cytisine solutions and tissue suspensions to the test tubes, and to perform the actual binding experiment automatically. Finally, the resulting samples were counted for [^{3}H] in a Liquid Scintillation Counter (Packard). Concentrations of the unlabelled drug, causing 50% displacement of the specific binding of a labeled compound (IC_{50} values), were obtained by computerized log-probit linear regression analysis of data obtained in experiments in which four to six different concentrations of the test compound were used. Inhibition constant (K_i) values were calculated using the Cheng–Prusoff equation; $K_i = IC_{50}/(1 + S/K_d)$ in which S represents the concentration of the label. Mean K_i values were calculated from at least three values obtained from independent experiments, that is, in experiments performed on different days with different membrane preparations. All incubations were done in triplicate. Results are shown in Table 2.

References and Notes

1. (a) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475; (b) Badio, B.; Daly, J. W. *Mol. Pharmacol.* **1994**, *45*, 563.

2. (a) Bai, D.; Xu, R.; Zhu, X. *Drugs of the Future* **1997**, *22*, 1210. (b) For a review about pharmacological properties of epibatidine, see: Sullivan, J. P.; Bannon, A. W. *CNS Drug Rev.* **1996**, *2*, 21. (c) For QSAR studies see: Glennon, R. A.; Herndon, J. L.; Dukat, M. *Med. Chem. Res.* **1994**, *4*, 461. (d) Holladay, M.; Lebold, S. A.; Lin, N.-H. *Drug Dev. Res.* **1995**, *35*, 191. (e) For pharmacological properties of nicotine see: Benowitz, N. L. *Annu. Rev. Pharmacol. Toxicol.* **1996**, *36*, 597.

3. Badio, B.; Garraffo, H. M.; Plummer, C. V.; Padgett, W. L.; Daly, J. W. *Eur. J. Pharmacol.* **1997**, *321*, 189.

4. (a) For reviews on the total synthesis of epibatidine, see: Broka, C. A. *Med. Chem. Res.* **1994**, *4*, 449. Dehmlow, E. V. *J. Prakt. Chem.* **1995**, *167*; Szántay, C.; Kardos-Balogh, Z.; Szántay, Jr. *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1995; Vol. 46, 95; (b) For a review on the synthesis of the 7-azabicyclo[2.2.1]heptane system, see: Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179.

5. Synthesis of epibatidine and analogues via cycloaddition to pyrrole derivatives: (a) Huang, D. F.; Shen, T. Y. *Tetrahedron Lett.* **1993**, *34*, 4477; (b) Okabe, K.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1432; (c) Kotian, P. L.; Carroll, F. I. *Synth. Commun.* **1995**, *25*, 63; (d) Gonzalez, J.; Koontz, J. I.; Hodges, L. M.; Nilsson, K. R.; Neely, L. K.; Myers, W. H.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **1995**, *117*, 3405; palladium-catalyzed hydroarylations: (e) Clayton, S. C.; Regan, A. C. *Tetrahedron Lett.* **1993**, *34*, 7493; (f) Xu, R.; Chu, G.; Bai, D. *Tetrahedron Lett.* **1996**, *37*, 1463; (g) Xu, R.; Bai, D.; Chu, G.; Tao, J.; Zhu, X. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 279; (h) Bai, D.; Xu, R.; Chu, G.; Zhu, X. *J. Org. Chem.* **1996**, *37*, 4600; (i) Malpass, J. R.; Hemmings, D. A.; Wallis, A. L. *Tetrahedron Lett.* **1996**, *37*, 3911; (j) Larock, R. C. U.S. Patent 5,565,573, 1996; *Chem Abstr.* 125, 301303; (k) Akasaka, K.; Kimura, T.; Senaga, M.; Machida, Y. Jpn. Patent Kokai Tokkyo, JP 070 61,940, 1995, *Chem. Abstr.* 123, 132885; Akasaka, K.; Kimura, T.; Senaga, M.; Machida, Y. Jpn. Patent Kokai Tokkyo JP 070 10,878, 1995; *Chem. Abstr.* 122, 291257; (l) Shen, T. Y.; Harman, W.; Dean, W.; Huang, D. F.; Gonzalez,

F. PCT Int. Appl., WO 9422868, 1995; *Chem. Abstr.* 123, 131780 and PCT Int. Appl. WO 9606093, 1996: *Chem. Abstr.*, *125*, 58831; (m) Giblin, G. M. P.; Jones, C. D.; Simpkins, N. S. *Synlett* **1997**, 589; (n) Qian, C.; Li, T.; Biftu, T.; Shen, T.-Y. PCT Int. Appl., WO 9507078, 1995; *Chem. Abstr.* 123, 25683.

6. For a recent review about high-pressure synthesis see: Ciobanu, M., Matsumoto, K. *Liebigs Ann./Recueil* **1997**, *4*, 623.

7. Altenbach, H. J.; Constant, D.; Martin, H.-D.; Mayer, B.; Müller, M.; Vogel, E. *Chem. Ber.* **1991**, *124*, 791.

8. Wang, N.-C.; Anderson, H. J. *Can. J. Chem.* **1977**, *67*, 4103.

9. Similarly, N-carbomethoxy 2,4-dimethylpyrrole gave a high-pressure Diels–Alder reaction with phenyl vinyl sulfone in chloroform at 12 kbar and 50 °C to yield the crude sulfonyl compound after 48 h. Subsequent reductive desulfonylation with 6% sodium amalgam gave 1,3-dimethyl-7-carbomethoxy-7-azabicyclo[2.2.1]hept-2-ene in ca. 35% isolated yield.

10. The sodium amalgam reduction of the phenylsulfonyl group in **3a/3b** gave a side product in 7% isolated yield which was tentatively characterized as N-carbomethoxy-6-azabicyclo[3.1.1]hept-2-ene **4′** (based on NMR and mass spectra), which probably arises from of a rearrangement of the intermediate radical (Scheme 3). ^{1}H NMR δ 1.58 (2H, br s), 2.65 (1H, m), 3.12 (1H, br s), 3.36 (1H, br d), 3.66 (3H, s, OMe), 4.70 (1H, d), 6.29 (2H, br d). Formation of 6-azabicyclo[3.1.1]hept-2-ane derivatives have been described before in literature, see for example: Corey, E. J.; Loh, T.-P.; AchyuthaRao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600. Structure elucidation and application of **4′** towards epibatidine-type compounds will be described in a forthcoming paper.

11. For preparation of some aryl halides see: (a) 5-iodo-2-aminopyrimidine **6** from 2-aminopyrimidine: Shepherd, R. G.; Fellows, C. E. *Am. Soc.* **1948**, *70*, 157; (b) 4-iodo-dimethylaniline **7b** from 4-bromo-dimethylaniline **7a**: Gilman, H.; Summers, L. *Am. Soc.* **1950**, *72*, 2767; (c) 4-iodo-isoquinoline **8b** from 4-bromo-isoquinoline **8a** via iododestannation of 4-trimethylstannylisoquinoline: Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 1731.

12. (a) For a recent review on Heck reactions, see: de Meijere, A.; Meyer, F. E. *Angew. Chem.* **1994**, *106*, 2473; (b) Arcadi, A.; Marinelli, F.; Bernochi, E.; Cacchi, S.; Ortar, G. *J. Organomet. Chem.* **1989**, *368*, 249; (c) Larock, R. C.; Johnson, P. L. *J. Chem. Soc., Chem. Commun.* **1989**, 1368.

13. (a) Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3491; (b) Cacchi, S.; Arcadi, A. *J. Org. Chem.* **1983**, *48*, 4236.

14. Anderson, D.; Arneric, S. *Eur. J. Pharm.* **1994**, *253*, 261.

15. Cosford, N. D. P.; Bleicher, L.; Herbaut, A.; McCallum, J. S.; Vernier, J.-M.; Dawson, H.; Whitten, J. P.; Adams, P.; Chavez-Noriega, L.; Correa, L. D.; Crona, J. H.; Mahaffy, L. S.; Menzaghi, F.; Rao, T. S.; Reid, R.; Sacaan, A. I.; Santori, E.; Stauderman, K. A.; Whelan, K.; Lloyd, G. K.; McDonald, I. A. J. *Med. Chem.* **1996**, *39*, 3235.

16. Garvey, D. S.; Wasicak, J. T.; Elliot, R. L.; Lebold, S. A.; Hettinger, A.-M.; Carrera, G. M.; Lin, N.-H.; He, Y.; Holladay, M. W.; Anderson, D. J.; Cadman, E. D.; Raszkiewicsz, J. L; Sullivan, J. P.; Arneric, S. P. *J. Med. Chem.* **1994**, *37*, 4455.