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2,3-Disubstituted 6-azabicyclo[3.2.1]octanes as novel dopamine transporter inhibitors

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Abstract—A series of *cis* and *trans* 3β-aryl-2-carbomethoxy-6-azabicyclo[3.2.1]octanes, with different substitution at the *para*-position of the aryl group, were synthesized and examined for reuptake inhibition at the dopamine transporter (DAT). The potency for inhibition of DA reuptake was compared with that of cocaine to determine the significance of the replacement of the 8-azabicyclo[3.2.1]octane (tropane nucleus), displayed in cocaine, for the 6-azabicyclo[3.2.1]octane (normorphan framework). This bicyclic core structure constitutes a novel chemical scaffold in DAT inhibitor design, which may provide new insights into the 3D structure of the DAT and its interaction with cocaine and DA. Among these compounds, the *trans*-amine series **8** were the most potent ligands at the DAT. In particular, the normorphan analogue **8c** (bearing a *p*-chloro substituent at the β-aryl group, $IC_{50}=452$ nM) displayed a potency that is in the same range as cocaine ($IC_{50}=459$ nM) itself.

1. Introduction

The tropane alkaloids comprise a group of over 100 natural products occurring principally in the *Solanaceae* family[1] such as atropine, cocaine, scopolamine, anisodine and anisodamine. While some of these natural products are of pharmacological interest and, in fact, clinically useful, cocaine in particular is currently the focus of intensive studies for reasons relating to both health and social concerns.

The reinforcing (addictive) and stimulant properties of cocaine stem from the inhibition of the reuptake of serotonin (5-HT), norepinephrine (NE) and particularly dopamine (DA), into the pre-synaptic neurons.[2] Cocaine exerts this effect by binding to a specific site of the dopamine transporter (DAT).[3] Although compounds that interact with 5-HT and NE systems may modulate the pharmacological effects of cocaine, it is the DAT, controlling the uptake of the neurotransmitter DA, that is most often targeted in the development of anti-cocaine abuse medications.[4]

The strategies of designing cocaine analogues can be summarized as follows: (1) modifying the chemical structure of cocaine in such a way as to retain or reinforce its useful stimulant or antidepressant pharmacological effects and minimizing its high toxicity and dependence liability (substitute agonist approach), and (2) obtaining a competitive cocaine antagonist which can selectively inhibit cocaine binding to the DAT, but is itself devoid of transporter-inhibiting actions and is free of toxic effects (antagonist approach).

To date, most structure–activity relationships (SAR) of DAT inhibitors have been focused on a limited number of structures, including tropane analogues, GBR compounds, methylphenidate analogues, mazindol analogues, and piperidine analogues.[5] Given the urgency and complexity of the development of an effective cocaine therapy, we believe that the discovery of DAT inhibitors with novel chemical scaffolds will provide new chemical insights into DAT inhibitor design. Furthermore, DAT

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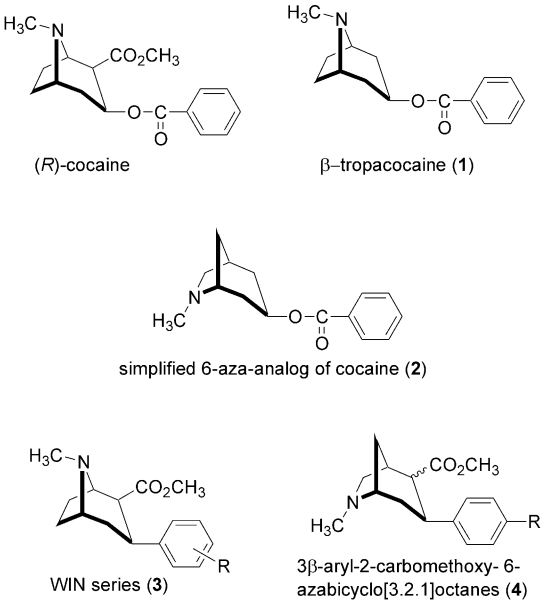


inhibitors with novel chemical scaffolds may also have pharmacological and behavioral profiles different from known DAT inhibitors.

We introduce, as a new chemical scaffold in DAT inhibitor design, the 6-azabicyclo [3.2.1]octane system (normorphan nucleus),[6] which is isomeric with the 8-azabicyclo [3.2.1]octane system (tropane nucleus), bearing an *N*-methyl group in the 6-position instead of the bridgehead *N*(8)-methyl moiety. Several natural products[7] contain the 6-azabicyclo[3.2.1]octane structure.[8] Additionally, this bicyclic system is present in pharmacologically active compounds, such as azaprophen,[9] which is a novel conformationally restricted, highly potent antimuscarinic analogue of atropine.

Support for this proposal was found in previous work by Carroll et al.[10] In order to evaluate the importance of the nitrogen position in cocaine-tropane analogues (8-azabicyclo[3.2.1]octanes), the receptor binding affinity of β-tropacocaine (**1**, lacking the 2β-carbomethoxy group of cocaine, $IC_{50} = 5.18$ μM) was compared by Carroll et al.[10] to that of the isomeric 6-methyl-6-azabicyclo[3.2.1]octan-3β-ol-benzoate[8a] (**2**, $IC_{50} = 4.95$ μM). Given that both compounds displayed similar binding affinities for the cocaine receptor, it was postulated that the 3β-(benzoyloxy)-6-methyl-6-azabicyclo[3.2.1]octan-2-carboxylic acid methyl ester, which is isomeric with cocaine, should possess binding potency similar to cocaine.

So far, the most widely studied monoamine uptake inhibitors have been the 3-aryltropane analogues of cocaine, 3β-aryl-2β-carbomethoxy-8-azabicyclo[3.2.1]-octanes (WIN analogues, **3**).[11] Since many of these derivatives are significantly more potent than cocaine itself, we selected the 3β-aryl-2-carbomethoxy-6-azabicyclo[3.2.1]octane analogues (**4**) for study. Structures **4** have as a novel scaffold the 6- azabicyclo[3.2.1]octane system (normorphan), which is isomeric with the tropane framework present in cocaine. It also bears the crucial 3-aryl substituent of its WIN analogues. For evaluating the influence of the functionality on the 3β-aryl group, different substituents (R = H, *p*-F, *p*-Cl, and *p*-Me) were introduced into the novel 6-aza aryl-tropane analogues (**4**).

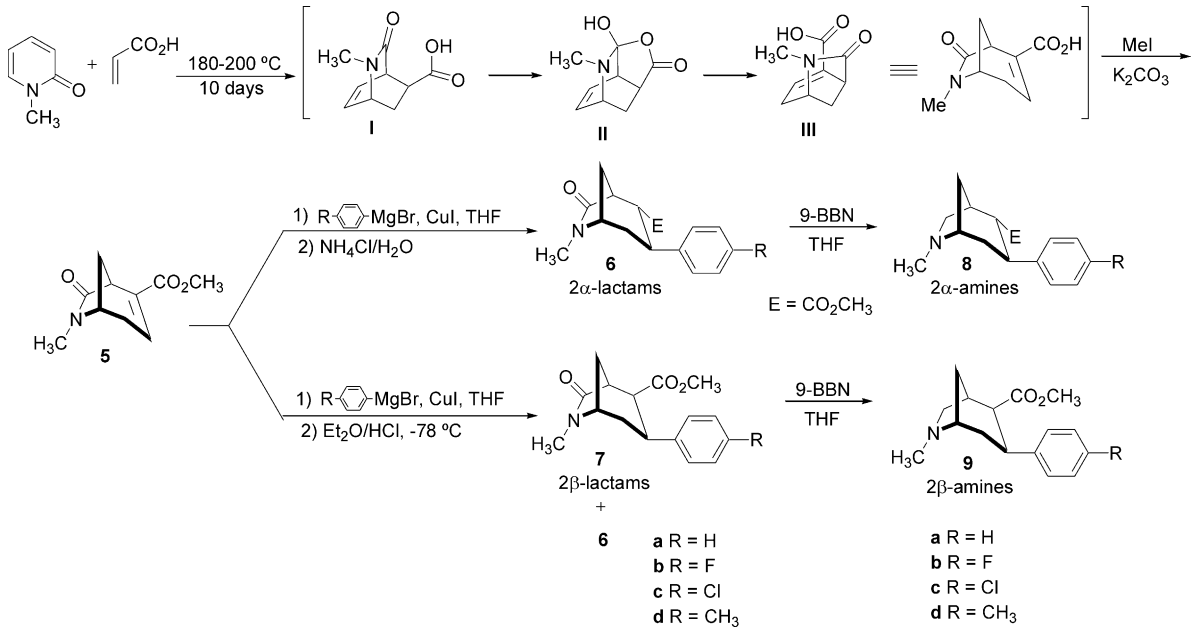
Herein we report the synthesis and the pharmacological evaluation of 3-aryl-2-carbomethoxy-6-azabicyclo[3.2.1]-octanes, as a novel class of DAT uptake inhibitors.

2. Results and discussion

2.1. Chemistry

All compounds described were prepared by the synthetic pathway outlined in Scheme 1. For the elaboration of the 6-azabicyclo[3.2.1]octane nucleus of the novel ligands, a modification of the previously reported method of Tomisawa et al.[12] ([4 + 2] cycloaddition reaction between 1-methyl-2(1*H*)-pyridone and acrylic acid) was carried out. Heating of the starting materials at 180–200 °C for 10 days provided 6-methyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid (**III**) by transformation of the initially formed Diels–Alder adduct (**I**). The postulated mechanism for this transformation is depicted in Scheme 1. The obtained carboxylic acid **III** was converted in situ to the methyl ester **5** by treatment with MeI/K_2CO_3 in acetone. This *one pot* procedure (combined yield for the two steps, 36%) constitutes a notable improvement over that previously described by Tomisawa et al.[12] for the preparation and isolation of the 6-azabicyclo-carboxylic acid derivative (**III**, 15% yield).

The synthesis of the aryl derivatives was achieved by a copper catalyzed 1,4-addition of the appropriate Grignard reagent to α,β-unsaturated ester **5**. While the initial attack of the nucleophile occurred stereoselectively from the top, or exo face, the stereocontrol of the enolate quench at C-2 was highly dependent on the reaction conditions. Using thermodynamic quenching conditions (room temperature and aqueous saturated NH_4Cl solution) equilibration could occur to give the more stable exo-protonated products (2α-lactams **6**). It is noteworthy that in the synthesis of 3β-aryltropane-2β-carboxylates **3,** by reaction of (*R*)-anhydroecgonine methyl ester (methyl 8-methyl-8-azabicyclo[3.2.1]oct-2-ene-2carboxylate) with a Grignard reagent, it is generally observed that use of both low temperatures and non-aqueous proton sources[13,14] results in higher selectivity in favor of endo protonation giving the non-thermodynamic 2β-isomer.[15,16] Under these conditions (−78 °C and ethereal HCl), copper catalyzed 1,4-addition of the appropriate Grignard reagents to the α,β-unsaturated ester **5** (lacking the bridging heteroatom β to the carbonyl) gave a mixture of 2α-(**6**) and 2β-isomers (**7**) in different ratios depending on the aryl-substituent of the Grignard reagent (a ratio of approximately 1:2 was obtained for all runs, except in the case of the *para*-fluoro derivative, in which the ratio was approximately 1:1). The pure 2α- (**6**) and 2β-isomers (**7**) were separated by column chromatography.



Scheme 1. Synthesis of *cis*- and *trans*-3-aryl-2-carbomethoxy-6-azabicyclo[3.2.1]octanes.

The relative stereochemistry of the 2α- (**6**) and 2β-lactams (**7**) was established by NMR techniques: 2D homo (COSY) and heteronuclear (HSQC) experiments. With regard to the ^{13}C data, C-2 in 2α-lactams (**6**) bearing the carbomethoxy group in an equatorial disposition, showed more deshielded signals (aprox. 3.5 ppm) than the corresponding 2β-lactams (**7**), with the carbomethoxy group located axially. Also, for 2β-lactams (**7**), C-4 and C-8 appears shielded (aprox. 7 and 6 ppm, respectively) due to a γ-gauche effect between these two carbons and the axial carbomethoxy substituent. With regard to the ^1H NMR data, for the 2α-isomers **6**, the coupling constants between H-3 and H-2 and H-4_{ax} clearly showed a *trans*-diaxial interaction between these protons, with H-3_{ax} appearing as td. For the 2β-isomers (**7**), H-3_{ax} resonates as a dt, indicating an axial disposition for the carbomethoxy group. ^1H NMR data are shown for the 2α-lactam **6a** and 2β-lactam **7a** in Table 1. The anisotropic deshielding effect of the carbomethoxy group upon H-4_{ax} (aprox. 0.8 ppm) and H-8_{ax} (aprox. 0.5 ppm) in the 2β-lactams (**7**) is noteworthy. ^1H NMR and ^{13}C NMR chemical shifts of the N-CH_3 group are fairly similar for both the 2α-(**6**) and 2β-isomers (**7**).

Next, these initially synthesized lactams (**6**, **7**) were reduced to the corresponding amines (**8**, **9**) to obtain insight into the effect of the basicity of the N(6) in inhibiting DA uptake. Chemoselective reduction of the tertiary lactams (**6**–**7**) to the corresponding cyclic tertiary amines **8**–**9** was carried out with 3 equiv of 9-borabicyclo[3.3.1]nonane (9-BBN)[17] in good yield. Analysis of the NMR spectroscopic data of the 2α-amines (**8**) and 2β-amines (**9**) strengthens the relative stereochemical assignments made previously for the 2α-(**6**) and 2β-lactams (**7**) taking into account the multiplicity and/or chemical shift of C and/or H at the 2, 3, 4 and 8 positions.

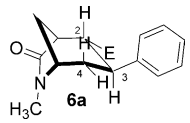
2.2. Pharmacology

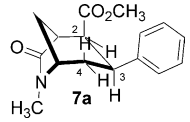
The novel ligands were tested for their ability to inhibit high-affinity reuptake of [^3H]DA into striatal nerve endings (synaptosomes) in accordance with protocols described previously.[18] The uptake data (based on IC_{50} and K_i values) of these compounds are listed in Table 2.

As shown in Table 2, several of the synthesized 3-aryl-2-carbomethoxy-6-azabicyclo[3.2.1]octanes displayed micromolar to submicromolar K_i values in inhibiting [^3H]DA uptake. We had hypothesized that compounds bearing the 2-carbomethoxy group together with a 3-benzoyloxy or 3-aryl substituent on a 6-azabicyclo[3.2.1] octane framework would exhibit a potency comparable to that of cocaine. Certainly the most potent compound (**8c**) of this series (IC_{50} = 452 nM) and cocaine (IC_{50} = 459 nM) are similar in potency.

The novel ligands exhibit an aryl group at C-3 like the WIN analogues (**3**), instead of the benzoyl group present in cocaine. However, 3-aryltropane compounds (**3**) such as WIN 35428 (*para*-F aryl substituted, K_i 22.9 nM),[11a] the *para*-Cl aryl derivative (K_i 3.68 nM),[11a] RTI-55 (*para*-I aryl substituted, K_i 1.26 nM),[11b] etc., display higher potencies in inhibiting DA uptake[5c] in comparison (see Table 2) with the most potent synthesized normorphan analogues, that is *trans*-amine series (**8**). These results may suggest that the aromatic ring of the novel ligands lie in a less favorable binding region in the cocaine receptor of the DAT, with regard to the aromatic group in the WIN analogues (**3**). Nevertheless, several structural differences between tropane and normorphan frameworks, may account for the observed differences in potency between WIN series (**3**) and 3β-aryl-2-carbomethoxy-6-azabicyclo[3.2.1]octane analogues (**4**).

Table 1. ^{1}H NMR spectral data for **6a**[a] and **7a**



Assignments[b]	δ (ppm)	multiplicity	Coupling constant (Herz)
H-4_{ax}	1.62	ddd	$J_{3ax,4ax}=11.9$, $J_{4ax,\ 4eq}=14.1$, $J_{4ax,5eq}=1.2$
H-8_{ax}	1.78	d	$J_{8ax,8eq}=11.2$
H-4_{eq}	2.19	dddd	$J_{3ax,4eq}=6.5$, $J_{4ax,\ 4eq}=14.1$, $J_{4eq,5eq}=3.9$, $J_{4eq,8eq}=2$
H-8_{eq}	2.36	dtd	$J_{1eq,8eq}=J_{5eq,8eq}=5.6$, $J_{4eq,8eq}=2$, $J_{8ax,8eq}=11.2$
H-2_{ax}	2.83	dd	$J_{2ax,3ax}=11.6$, $J_{1eq,2ax}=2.3$
H-1_{eq}	2.86	dd	$J_{1eq,2ax}=2.3$, $J_{1eq,8eq}=5.3$
NCH_3	2.91	s	
H-3_{ax}	3.15	td	$J_{2ax,3ax}=11.6$, $J_{3ax,4eq}=6.5$
OCH_3	3.55	s	
H-5_{eq}	3.66	t	$J_{4eq,5eq}=J_{5eq,8eq}=4.6$
ArH	7.15–7.30	m	
			
H-8_{eq}	2.02	dt	$J_{1eq,8eq}=J_{5eq,8eq}=5.5$, $J_{8ax,8eq}=11.1$
H-4_{eq}	2.07	dt	$J_{3ax,4eq}=4.9$, $J_{4ax,\ 4eq}=13.2$
H-8_{ax}	2.34	d	$J_{8ax,8eq}=11.5$
H-4_{ax}	2.40	t	$J_{3ax,4ax}=J_{4ax,\ 4eq}=12.9$
H-1_{eq}	2.76	t	$J_{1eq,2eq}=J_{1eq,8eq}=4.3$
NCH_3	2.85	s	
H-3_{ax}	2.90	dt	$J_{2eq,\ 3ax}=6.1$, $J_{3ax,4ax}=12.2$
H-2_{eq}	3.27	dd	$J_{2eq,\ 3ax}=6.3$, $J_{1eq,2eq}=3.6$
OCH_3	3.36	s	
H-5_{eq}	3.81	t	$J_{4eq,5eq}=J_{5eq,8eq}=4.8$
ArH	7.16–7.29	m	

[a] E = CO_2CH_3.
[b] 600 MHz.

Table 2. Inhibition of reuptake at DAT, IC_{50} and K_i ± SEM (nM)

Compd	[^{3}H]DA Uptake[a]	
	IC_{50}	K_i
(*R*)-cocaine	459 ± 159	423 ± 147
6a	> 10,000	> 10,000
6b	> 10,000	> 10,000
6c	2321 ± 342	2186 ± 324
6d	> 10,000	> 10,000
7a	> 10,000	> 10,000
7b	> 10,000	> 10,000
7c	1338 ± 56	1262 ± 53
7d	> 10,000	> 10,000
8a	4537 ± 492	4240 ± 460
8b	2254 ± 312	2107 ± 291
8c	452 ± 21.5	430 ± 23
8d	1278 ± 124	1206 ± 116
9a	> 10,000	> 10,000
9b	> 10,000	> 10,000
9c	4092 ± 482	3860 ± 451
9d	> 10,000	> 10,000

[a] Data are mean ± standard error of at least three experiments, each consisting of six drug concentrations (in triplicate).

A notable degree of stereoselectivity was observed in the efficacy of uptake inhibition at the DAT. In general, the *trans*-isomers **8** were considerably more active than the corresponding *cis*-isomers **9**. This is in apparent contradiction with SAR studies on cocaine and aryltropane analogues that show significantly greater pharmacological efficacy for the *beta*, *beta* orientation of the C-2 and C-3 substituents of the tropane nucleus.[5c] Of course, we must take into account again, the fact that we are comparing data for compounds comprised of two different structural frameworks (tropane versus normorphan nucleus). One explanation for this finding could be that the directionality (proximity) of the carbomethoxy group, which in the case of the 2β-tropane and the 2α-normorphan analogues points in the direction of the N-CH_3 bridgehead group, is crucial for inhibitory activity rather than the relative stereochemistry at C-2 and C-3.

Modifications at the tropane nitrogen in cocaine and WIN analogues have shown that a basic nitrogen is not a critical element for binding to the DAT: a series of N-sulfonamide,[19] 8-oxo[20] and 8-carbo[5b] analogues have been studied previously and found to exhibit only a modest decrease in binding and/or function. Of the new 6-azabicyclo[3.2.1]nonanes synthesized, maximum activity was observed for the *trans*-amine series (**8**). Nevertheless, significant activity was displayed for the 4-chloro aryl-substituted analogues of *trans*-lactam series (**6c**) and *cis*-lactam series (**7c**).

The *para*-position of the aryl ring may be sensitive to lipophilicity because compounds **6c**, **7c**, **8c**, and **9c** (*para*-Cl aryl substituted) had the highest inhibition

values. Considering the *trans*-amine series (**8**), the order of potency is as follows: *p*-chloro > *p*-methyl > *p*-F > H. The two most potent compounds identified in the present series are the isoelectronic *trans*-amine **8c** (*p*-chloro substituent) and *trans*-amine **8d** (*p*-methyl group). These results are in agreement with work published previously on the WIN analogues.[5b] Moreover, SAR analysis of a series of 3β-phenyltropane analogues[21] using comparative molecular field analysis (CoMFA) has revealed that the increased electron density around the 3β-phenyl ring correlates with high ligand potency at the dopamine transporter.

3. Conclusions

In summary, a convenient synthetic procedure was developed for the procurement of the *cis* and *trans* diastereomers of 3β-aryl-2-carbomethoxy-6-azabicyclo[3.2.1]octanes, namely, the *trans*- (**6**) and *cis*-lactams (**7**), and the *trans*- (**8**) and *cis*-amines (**9**). The 6-azabicyclo[3.2.1]octane (normorphan system) constitutes a novel chemical scaffold in DAT inhibitor design, and the present results provide new chemical insights into the 3-D structure of the DAT and its interaction with cocaine. The novel ligands (**6**–**9**) were evaluated for their uptake inhibition at the DAT. Among the compounds tested, the *trans*-amines **8** were the most potent ligands. In particular, compound **8c** (IC_{50} = 452 nM) and cocaine (IC_{50} = 459 nM) were of comparable potency. With regard to the substitution pattern in the 3β-aryl group of the four *trans*-amines tested, the most active compound possessed a *para*-chloro aryl-substituent, which is in agreement with work published previously.

4. Experimental

4.1. Chemistry

4.1.1. General methods. Unless otherwise noted ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in a Varian gemini instrument at 300 MHz and 75.5 MHz, respectively. In ^{13}C NMR analysis (cm^{-1}) always a DEPT experiment was included. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Two-dimensional NMR experiments (COSY and HSQC) were performed in a Varian mercury 400 or in a Bruker avance 600 MHz. IR spectra were carried out in a Nicolet Avatar 320 FT-IR apparatus. Only noteworthy IR absorptions are listed. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck). The spots were located by UV light and a 1% $KMnO_4$solution or hexachloroplatinate reagent. Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–400 mesh) or Al_2O_3 (aluminium oxide 90 standardized). All reactions were carried out under an argon or nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Drying of organic extracts during the work up of reactions was performed over anhydrous $MgSO_4$. Melting points were determined in a capillary tube in a Gallenkamp apparatus and are uncorrected.

4.1.2. (1*RS*,5*RS*)-2-Carbomethoxy-6-methyl-7-oxo-6-azabicyclo[3.2.1]oct-2-ene (5). A mixture of 1-methyl-2(1*H*)-pyridone (13.6 mL, 139 mmol) and acrylic acid (4.8 mL, 69 mmol) was heated in a sealed tube at 180 °C for 10 days. The reaction mixture was dissolved in dry acetone (460 mL), K_2CO_3 (19.2 g, 139 mmol) was added and stirring was maintained for 1 h at room temperature. Then, MeI (34.6 mL, 555 mmol) was added and the reaction mixture was heated at reflux for 24 h. Filtration followed by acetone evaporation afforded a residue which was purified by chromatography (EtOAc) to give the title compound as a yellow solid (4.84 g, 36%): mp 46–48 °C. IR (NaCl) 1715, 1695; ^1H NMR δ 1.73 (d, J = 11 Hz, 1H, H-8_{ax}), 2.28–2.36 (m, 1H, H-8_{eq}), 2.42–2.48 (m, 2H, H-4), 2.83 (s, 3H, NCH_3), 3.47 (d, J = 5 Hz, 1H, H-1_{eq}), 3.75 (m, 1H, H-5_{eq}), 3.78 (s, 3H, OCH_3), 6.83 (m, 1H, H-3); ^{13}C NMR δ 26.4 (N-CH_3), 28.0 (C-4), 32.7 (C-8), 39.0 (C-1), 51.7 (OCH3), 55.1(C-5), 132.6 (C-2), 136.4 (C-3), 164.9 (CON), 175.8 (CO). Anal. calcd for $C_{16}H_{13}NO_3 \cdot 1/2H_2O$: C, 58.81; H, 6.91; N, 6.86. Found: C, 58.78; H, 7.07; N, 6.70.

4.1.3. General procedure for the synthesis of *trans*-2α-carbomethoxy-3β-aryl-6-azabicyclo[3.2.1]octanes (6). To a cooled (−5 °C) solution of the arylmagnesium bromide (4 mL, 4 mmol, 1.0 M in THF) in THF (9 mL) was added CuI (2.0 mmol) and the resulting mixture was stirred at this temperature for 10 min and then cooled to −78 °C. The α,β-unsaturated ester **5** (1.0 mmol) in THF (3 mL) was added dropwise to the mixture, which was then stirred 1 h at −78 °C and further 4 h while warming to room temperature. Saturated aqueous NH_4Cl solution (5 mL) was added to the reaction mixture, THF was evaporated in vacuo and the resulting solution was extracted with CH_2Cl_2. After evaporation of the dried organic extracts the obtained residue was purified by chromatography (SiO_2).

4.1.4. (1*RS*,2*RS*,3*RS*,5*RS*)-2α-Carbomethoxy-6-methyl-7-oxo-3β-phenyl-6-azabicyclo[3.2.1]octane (6a). Chromatography (EtOAc) followed by trituration with Et_2O gave the title compound as a white solid (45% yield): mp 129–132 °C (Et_2O). IR (KBr) 1742, 1696; ^1H NMR (600 MHz) δ 1.62 (ddd, J = 14.1, 11.9, 1.2 Hz, 1H, H-4_{ax}), 1.78 (d, J = 11.2 Hz, 1H, H-8_{ax}), 2.19 (dddd, J = 14.1, 6.5, 3.9, 2 Hz, 1H, H-4_{eq}), 2.36 (dtd, J = 11.2, 5.6, 2 Hz, 1H, H-8_{eq}), 2.83 (dd, J = 11.7, 2.3 Hz, 1H, H-2_{ax}), 2.86 (dd, J = 5.3, 2.3 Hz, 1H, H-1_{eq}), 2.91 (s, 3H, NCH_3), 3.15 (td, J = 11.7, 6.5 Hz, 1H, H-3_{ax}), 3.55 (s, 3H, OCH_3), 3.66 (t, J = 4.6 Hz, 1H, H-5_{eq}), 7.15–7.30 (m, 5H, ArH); ^{13}C NMR δ 27.5 (NCH_3), 33.3 (C-4), 36.9 (C-8), 38.7 (C-3), 43.7 (C-1), 48.7 (C-2), 51.8 (OCH_3), 57.2 (C-5), 126.7, 127.8, 128.4 (C-*o*, C-*m*, C-*p*), 142.4 (C-*ipso*), 171.5 (CON), 173.7 (CO). Anal. calcd for $C_{16}H_{19}NO_3 \cdot 1/5 \cdot H_2O$: C, 69.39; H, 7.06; N, 5.06. Found: C, 69.16; H, 6.93; N, 5.04.

4.1.5. (1*RS*,2*RS*,3*RS*,5*RS*)-2α-Carbomethoxy-6-methyl-7-oxo-3β-(4-fluorophenyl)-6-azabicyclo[3.2.1]octane (6b). Chromatography (hexane:EtOAc 2:8) followed by trituration with Et_2O gave the title compound as a white solid (58% yield): mp 179–182 °C (Et_2O). IR (KBr) 1732, 1694; ^1H NMR (400 MHz) δ 1.61 (ddd, J = 14.2,

11.8, 0.8 Hz, 1H, H-4_{ax}), 1.79 (d, $J=11.2$ Hz, 1H, H-8_{ax}), 2.20 (dddd, $J=14.1$, 6.5, 3.8, 1.9 Hz, 1H, H-4_{eq}), 2.38 (dtd, $J=11.2$, 5.6, 2 Hz, 1H, H-8_{eq}), 2.79 (dd, $J=11.4$, 2.2 Hz, 1H, H-2_{ax}), 2.87 (dd, $J=5.4$, 2.2 Hz, 1H, H-1_{eq}), 2.93 (s, 3H, NCH_3), 3.15 (td, $J=11.8$, 6.4 Hz, 1H, H-3_{ax}), 3.58 (s, 3H, OCH_3), 3.69 (t, $J=4.6$ Hz, 1H, H-5_{eq}), 6.94–7.01 (m, 2H, H-*m*), 7.19–7.25 (m, 2H, H-*o*); ^{13}C NMR δ 27.5 (NCH_3), 33.4 (C-4), 36.9 (C-8), 38.1 (C-3), 43.6 (C-1), 48.9 (C-2), 51.9 (OCH_3), 57.0 (C-5), 115.1, 115.4 (C-*m*), 129.3, 129.4 (C-*o*), 138.1, 138.2 (C-*ipso*), 159.8, 163.0 (C-*p*), 171.4 (CON), 173.5 (CO). Anal. calcd for $C_{16}H_{18}FNO_3$: C, 65.97; H, 6.23; N, 4.81. Found: C, 65.71; H, 6.31; N, 4.73.

4.1.6. (1*RS*,2*RS*,3*RS*,5*RS*)-2α-Carbomethoxy-6-methyl-7-oxo-3β-(4-chlorophenyl)-6-azabicyclo[3.2.1]octane (6c). Chromatography (hexane:EtOAc 2:8) followed by trituration with Et_2O gave the title compound as a white solid (56% yield): mp 156 °C (Et_2O). IR (KBr) 1729, 1688; ^{1}H NMR (400 MHz) δ 1.60 (ddd, $J=14$, 11.6, 2 Hz, 1H, H-4_{ax}), 1.79 (d, $J=11.2$ Hz, 1H, H-8_{ax}), 2.19 (dddd, $J=14$, 6.4, 4, 2 Hz, 1H, H-4_{eq}), 2.38 (dtd, $J=11.2$, 5.5, 2 Hz, 1H, H-8_{eq}), 2.80 (dd, $J=11.6$, 2.4 Hz, 1H, H-2_{ax}), 2.88 (dd, $J=5.2$, 2.4 Hz, 1H, H-1_{eq}), 2.92 (s, 3H, NCH_3), 3.14 (td, $J=11.6$, 6.4 Hz, 1H, H-3_{ax}), 3.59 (s, 3H, OCH_3), 3.69 (t, $J=4.6$ Hz, 1H, H-5_{eq}), 7.17–7.21 (m, 2H, ArH), 7.23–7.28 (m, 2H, ArH); ^{13}C NMR δ 27.5 (NCH_3), 33.3 (C-4), 36.9 (C-8), 38.2 (C-3), 43.6 (C-1), 48.7 (C-2), 51.9 (OCH_3), 57.0 (C-5), 128.6, 129.3, 132,5 (C-*o*, C-*m,* C-*p*), 141.1 (C-*ipso*), 171.4 (CON), 173.6 (CO). Anal. calcd for $C_{16}H_{18}ClNO_3\cdot 1/5H_2O$: C, 61.72; H, 5.96; N, 4.50. Found: C, 61.91; H, 5.95; N, 4.43.

4.1.7. (1*RS*,2*RS*,3*RS*,5*RS*)-2α-Carbomethoxy-6-methyl-7-oxo-3β-(4-tolyl)-6-azabicyclo[3.2.1]octane (6d). Chromatography (EtOAc) followed by trituration with Et_2O gave the title compound as a white solid (62% yield): mp 149–150 °C (Et_2O). IR (KBr) 1748, 1689; ^{1}H NMR (300 MHz) δ 1.62 (ddd, $J=14.1$, 11.9, 1.4 Hz, 1H, H-4_{ax}), 1.79 (d, $J=11.1$ Hz, 1H, H-8_{ax}), 2.19 (dddd, $J=14.1$, 6.5, 4.1, 2 Hz, 1H, H-4_{eq}), 2.37 (dtd, $J=11.1$, 5.5, 2 Hz, 1H, H-8_{eq}), 2.30 (s, 3H, CH_3), 2.79 (dd, $J=11.4$, 2.1 Hz, 1H, H-2_{ax}), 2.86 (dd, $J=5.1$, 2.1 Hz, 1H, H-1_{eq}), 2.92 (s, 3H, NCH_3), 3.13 (td, $J=11.6$, 6.4 Hz, 1H, H-3_{ax}), 3.58 (s, 3H, OCH_3), 3.68 (t, $J=4.7$ Hz, 1H, H-5_{eq}), 7.00–7.20 (m, 4H, ArH); ^{13}C NMR δ 21.0 (CH_3), 27.5 (NCH_3), 33.4 (C-4), 36.9 (C-8), 38.3 (C-3), 43.7 (C-1), 48.8 (C-2), 51.8 (OCH_3), 57.1 (C-5), 127.6, 129.1, 136.2 (C-*o*, C-*m*, C-*p*), 139.4 (C-*ipso*), 171.6 (CON), 173.6 (CO). Anal. calcd for $C_{17}H_{21}NO_3\cdot 2/3H_2O$: C, 68.23; H, 7.52; N, 4.68. Found: C, 68.42; H, 7.17; N, 4.60.

4.1.8. General procedure for the synthesis of *cis*-2β-carbomethoxy-3β-aryl)-6-azabicyclo[3.2.1]octanes (7). To a cooled (−5 °C) solution of the arylmagnesium bromide (4 mL, 4 equiv, 1.0 M in THF) in THF (9 mL) was added CuI (2,0 equiv) and the resulting mixture was stirred at this temperature for 10 min and then cooled to −78 °C. The α,β-unsaturated ester **5** (1.0 equiv) in THF (3 mL) was added dropwise to the mixture, which was then stirred 1 h at −78 °C and further 4 h while warming to room temperature. The reaction mixture was cooled again to −78 °C, a 1 M solution of HCl in Et_2O (8 mL, 8 equiv) was added and allowed to warm to room temperature. Then, THF was evaporated in vacuo and the resulting solution was taken up in CH_2Cl_2 and washed with water. After evaporation of the dried organic extracts the obtained residue was purified by chromatography (SiO_2).

4.1.9. (1*RS*,2*SR*,3*RS*,5*RS*)-2β-Carbomethoxy-6-methyl-7-oxo-3β-phenyl-6-azabicyclo[3.2.1]octane (7a). Chromatography (hexane:EtOAc 1:1) gave *trans*-normorphan **6a** (16%) as a white solid and the title *cis*-normorphan (41% yield) as a brown solid: mp 94–96 °C. IR (KBr) 1735, 1686; ^{1}H NMR (600 MHz) δ 2.02 (dt, $J=11.1$, 5.5 Hz, 1H, H-8_{eq}), 2.07 (dt, $J=13.2$, 4.9, Hz, 1H, H-4_{eq}), 2.34 (d, $J=11.5$ Hz, 1H, H-8_{ax}), 2.40 (t, $J=12.9$ Hz, 1H, H-4_{ax}), 2.76 (t, $J=4.3$ Hz, 1H, H-1_{eq}), 2.85 (s, 3H, NCH_3), 2.90 (dt, $J=12.2$, 6.1 Hz, 1H, H-3_{ax}), 3.27 (dd, $J=6.3$, 3.6 Hz, 1H, H-2_{eq}), 3.36 (s, 3H, OCH_3), 3.81 (t, $J=4.8$ Hz, 1H, H-5_{eq}), 7.16–7.29 (m, 5H, ArH); ^{13}C NMR δ 26.0 (C-4), 27.7 (NCH_3), 30.9 (C-8), 37.0 (C-3), 43.5 (C-1), 45.2 (C-2), 51.2 (OCH_3), 57.5 (C-5), 126.5, 127.5, 128.0 (C-*o*, C-*m*, C-*p*), 140.5 (C-*ipso*), 172.2 (CON), 175.2 (CO). Anal. calcd for: $C_{16}H_{19}NO_3\cdot 1/4H_2O$: C, 69.17; H, 7.07; N, 5.04. Found: C, 69.57; H, 6.93; N, 4.84.

4.1.10. (1*RS*,2*SR*,3*RS*,5*RS*)-2β-Carbomethoxy-6-methyl-7-oxo-3β-(4-fluorophenyl)-6-azabicyclo[3.2.1]octane (7b). Chromatography (hexane:EtOAc 1:1) gave *trans*-normorphan **6b** (31%) as a white solid and the title *cis*-normorphane (29% yield) as an orange solid: mp 68–69 °C. IR (NaCl) 1731, 1697; ^{1}H NMR (600 MHz) δ 1.99–2.07 (m, 2H, H-4_{eq}, H-8_{eq}), 2.31 (d, $J=11.3$ Hz, 1H, H-8_{ax}), 2.36 (t, $J=12.7$ Hz, 1H, H-4_{ax}), 2.75 (t, $J=4.4$ Hz, 1H, H-1_{eq}), 2.85 (s, 3H, NCH_3), 2.87 (dt, $J=12$, 5.5 Hz, 1H, H-3_{ax}), 3.22 (dd, $J=6.1$, 3.6 Hz, 1H, H-2_{eq}), 3.39 (s, 3H, OCH_3), 3.80 (t, $J=4.7$ Hz, 1H, H-5_{eq}), 6.90–7.00 (m, 2H, ArH), 7.10–7.20 (m, 2H, ArH); ^{13}C NMR δ 26.2 (C-4), 27.7 (NCH_3), 30.8 (C-8), 36.4 (C-3), 43.4 (C-1), 45.2 (C-2), 51.3 (OCH_3), 57.3 (C-5), 114.6, 114.9 (C-*m*), 129.0, 129.1 (C-*o*), 136.16, 136.20 (C-*ipso*), 159.6, 162.9 (C-*p*), 172.0 (CON), 175.0 (CO). Anal. calcd for $C_{16}H_{19}NO_3\cdot 1/2H_2O$: C, 63.99; H, 6.38; N, 4.66. Found: C, 64.21; H, 6.13; N, 4.39.

4.1.11. (1*RS*,2*SR*,3*RS*,5*RS*)-2β-Carbomethoxy-6-methyl-7-oxo-3β-(4-chlorophenyl)-6-azabicyclo[3.2.1]octane (7c). Chromatography (EtOAc:hexane 1:1) gave *trans*-normorphan **6c** (21%) as a white solid and the title *cis*-normorphan (37% yield) as a yellow solid: mp 105–106 °C. IR (KBr) 1718, 1693; ^{1}H NMR (600 MHz) δ 2.00–2.08 (m, 1H, H-4_{eq}, H-8_{eq}), 2.27 (d, $J=11.2$ Hz, 1H, H-8_{ax}), 2.36 (t, $J=12.4$ Hz, 1H, H-4_{ax}), 2.76 (t, $J=4.3$ Hz, 1H, H-1_{eq}), 2.85 (s, 3H, NCH_3), 2.83–2.89 (m, 1H, H-3_{ax}), 3.24 (dd, $J=6.2$, 3.7 Hz, 1H, H-2_{eq}), 3.40 (s, 3H, OCH_3), 3.80 (t, $J=4.8$ Hz, 1H, H-5_{eq}), 7.16 (d, $J=8.3$ Hz, 2H, ArH), 7.23 (d, $J=8.2$ Hz, 2H, ArH); ^{13}C NMR δ 25.9 (C-4), 27.6 (NCH_3), 30.7 (C-8), 36.3 (C-3), 43.3 (C-1), 45.0 (C-2), 51.2 (OCH_3), 57.2 (C-5), 128.0, 128.8, 132.0 (C-*o*, C*m*, C-*p*), 139.0 (C-*ipso*), 171.8 (CON), 174.7 (CO). Anal. calcd for $C_{16}H_{18}ClNO_3\cdot 3/$

$4H_2O$: C, 59.81; H, 6.12; N, 4.36. Found: C, 60.11; H, 6.01; N, 4.11.

4.1.12. (1*RS*,2*SR*,3*RS*,5*RS*)-2β-Carbomethoxy-6-methyl-7-oxo-3β-(4-tolyl)-6-azabicyclo[3.2.1]octane (7d). Chromatography (EtOAc:hexane 1:1) gave *trans*-normorphan **6d** (20%) as a white solid and the title *cis*-normorphan (44% yield) as a white solid: mp 82–84 °C. IR (KBr) 1730, 1702; ^{1}H NMR (600 MHz) δ 1.98–2.08 (m, 2H, H-4_{eq}, H-8_{eq}), 2.28 (s, 3H, CH_3), 2.32 (d, J = 11.3 Hz, 1H, H-8_{ax}), 2.37 (t, J = 12.7 Hz, 1H, H-4_{ax}), 2.75 (t, J = 4.3 Hz, 1H, H-1_{eq}), 2.84 (s, 3H, NCH_3), 2.86 (dt, J = 12.4, 6.1 Hz, 1H, H-3_{ax}), 3.25 (dd, J = 6.1, 3.6 Hz, 1H, H-2_{eq}), 3.38 (s, 3H, OCH_3), 3.79 (t, J = 4.8 Hz, 1H, H-5_{eq}), 7.07 (d, J = 8 Hz, 2H, ArH), 7.11 (d, J = 8 Hz, 2H, ArH); ^{13}C NMR δ 20.8 (CH_3), 26.0 (C-4), 27.6 (NCH_3), 30.8 (C-8), 36.6 (C-3), 43.5 (C-1), 45.2 (C-2), 51.1 (OCH_3), 57.4 (C-5), 127.3, 128.6, 135.9 (C-*o*, C-*m*, C-*p*), 137.4 (C-*ipso*), 172.1 (CON), 175.1 (CO). Anal. calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.77; H, 7.52; N, 4.70.

4.1.13. General procedure for the preparation of amines 8–9. To a solution of lactames **6–7** (1 equiv) in anhydrous THF (4.4 mL) was added 9-borabicyclo [3.3.1]nonane (6 mL, 3 equiv, 0.5 M solution in THF). The reaction mixture was heated at reflux for 24 h. The solution was cooled to room temperature, EtOAc was added and the mixture was extracted with aqueous 1 M HCl solution. The aqueous phase was basified with solid K_2CO_3 and extracted with CH_2Cl_2. After evaporation of the dried organic extracts the residue was purified by chromatography (Al_2O_3).

4.1.14. (1*RS*,2*RS*,3*RS*,5*RS*)-2α-Carbomethoxy-6-methyl-3β-phenyl-6-azabicyclo[3.2.1]octane (8a). Chromatography (CH_2Cl_2) gave the desired amine (65% yield) as a white solid: mp 46–48 °C. IR (KBr) 1729; ^{1}H NMR (600 MHz) δ 1.45 (ddd, J = 13.6, 12.2, 1.4 Hz, 1H, H-4_{ax}), 1.59 (d, J = 11.3 Hz, 1H, H-8_{ax}), 1.98–2.07 (m, 2H, H-4_{eq}, H-8_{eq}), 2.51 (s, 3H, NCH_3), 2.61–2.68 (m, 2H, H-7_{exo}, H-1_{eq}), 2.75 (d, J = 11.5 Hz, 1H, H-2_{ax}), 3.10 (t, J = 4.4 Hz, 1H, H-5_{eq}), 3.25 (d, J = 9.3 Hz, 1H, H-7_{endo}), 3.28 (td, J = 12, 5.9 Hz, 1H, H-3_{ax}), 3.45 (s, 3H, OCH_3), 7.10–7.30 (m, 5H, ArH); ^{13}C NMR δ 35.9 (C-8), 39.4 (C-4), 39.5 (C-3), 40.0 (C-1), 42.4 (NCH_3), 51.2 (OCH_3), 51.9 (C-2), 56.2 (C-7), 60.9 (C-5), 126.2, 127.5, 128.2 (C-*o*, C-*m*, C-*p*), 143.6 (C-*ipso*), 173.8 (CO). Anal. calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.20; H, 8.24; N, 5.31.

4.1.15. (1*RS*,2*RS*,3*RS*,5*RS*)-2α-Carbomethoxy-6-methyl-3β-(4-fluorophenyl)-6-azabicyclo[3.2.1]octane (8b). Chromatography (CH_2Cl_2) gave the desired amine (65% yield) as a white solid: mp 67–68 °C (CH_2Cl_2). IR (KBr) 1730; ^{1}H NMR (600 MHz) δ 1.40 (m, 1H, H-4_{ax}), 1.56 (d, J = 11.3 Hz, 1H, H-8_{ax}), 1.97–2.03 (m, 2H, H-4_{eq}, H-8_{eq}), 2.49 (s, 3H, NCH_3), 2.59–2.65 (m, 2H, H-7_{exo}, H-1_{eq}), 2.68 (dd, J = 1.6, 11.7 Hz, 1H, H-2_{ax}), 3.08 (t, J = 4.4 Hz, 1H, H-5_{eq}), 3.23 (d, J = 9.5 Hz, 1H, H-7_{endo}), 3.26 (td, J = 5.8, 11.9 Hz, 1H, H-3_{ax}), 3.46 (s, 3H, OCH_3), 6.85–6.95 (m, 5H, H-*m*), 7.10–7.20 (m, 2H, H-*o*); ^{13}C NMR δ 35.7 (C-8), 38.9 (C-3), 39.6 (C-4), 40.0 (C-1), 42.6 (NCH_3), 51.3 (OCH_3), 52.1 (C-2), 56.3 (C-7), 61.0 (C-5), 114.8, 115.1 (C-*m*), 128.8, 129.0 (C-*o*), 139.2, 139.3 (C-*ipso*), 159.5, 162.8 (C-*p*), 173.7 (CO). Anal. calcd for $C_{16}H_{20}FNO_2 \cdot 1/5H_2O$: C, 68.40; H, 7.32; N, 4.99. Found: C, 68.28; H, 7.36; N, 4.73.

4.1.16. (1*RS*,2*RS*,3*RS*,5*RS*)-2α-Carbomethoxy-6-methyl-3β-(4-chlorophenyl)-6-azabicyclo[3.2.1]octane (8c). Chromatography (CH_2Cl_2) gave the desired amine (63% yield) as a white solid: mp 52–54 °C (CH_2Cl_2). IR (KBr) 1722; ^{1}H NMR (600 MHz) δ 1.40 (ddd, J = 13.5, 12.2, 1.3 Hz, 1H, H-4_{ax}), 1.56 (d, J = 11.3 Hz, 1H, H-8_{ax}), 1.97–2.03 (m, 2H, H-4_{eq}, H-8_{eq}), 2.49 (s, 3H, NCH_3), 2.61 (t, J = 5.2 Hz, 1H, H-1_{eq}), 2.61–2.66 (m, 1H, H-7_{exo}), 2.68 (dd, J = 11.7, 1.8 Hz, 1H, H-2_{ax}), 3.09 (t, J = 4.2 Hz, 1H, H-5_{eq}), 3.22 (d, J = 10.5 Hz, 1H, H-7_{endo}), 3.27 (td, J = 12.1, 6 Hz, 1H, H-3_{ax}), 3.47 (s, 3H, OCH_3), 7.10–7.25 (m, 4H, ArH); ^{13}C NMR δ 35.8 (C-8), 39.0 (C-3), 39.5 (C-4), 40.0 (C-1), 42.7 (NCH_3), 51.4 (OCH_3), 51.9 (C-2), 56.3 (C-7), 61.0 (C-5), 128.3, 129.0, 131.8, (C-*o*, C-*m*, C-*p*), 142.2 (C-*ipso*), 173.6 (CO). Anal. calcd for $C_{16}H_{20}ClNO_2$: C, 65.41; H, 6.86; N, 4.77. Found: C, 65.11; H, 7.21; N, 4.60.

4.1.17. (1*RS*,2*RS*,3*RS*,5*RS*)-2α-Carbomethoxy-6-methyl-3β-(4-tolyl)-6-azabicyclo[3.2.1]octane (8d). Chromatography (CH_2Cl_2) gave the desired amine (62% yield) as a yellow oil. IR (KBr) 1733; ^{1}H NMR (600 MHz) δ 1.44 (td, J = 13.6, 1.4 Hz, 1H, H-4_{ax}), 1.59 (d, J = 11.5 Hz, 1H, H-8_{ax}), 1.98–2.06 (m, 2H, H-4_{eq}, H-8_{eq}), 2.29 (s, 3H, CH_3), 2.54 (s, 3H, NCH_3), 2.63 (t, J = 4.4 Hz, 1H, H-1_{eq}), 2.66 (dd, J = 10.3, 5.4 Hz, 1H, H-7_{exo}), 2.73 (dd, J = 11.9, 1.8 Hz, 1H, H-2_{ax}), 3.11 (m, 1H, H-5_{eq}), 3.21–3.28 (m, 2H, H-7_{endo}, H-3_{ax}), 3.46 (s, 3H, OCH_3), 7.05 (d, J = 7.7 Hz, 2H, ArH), 7.11 (d, J = 8.1 Hz, 2H, ArH); ^{13}C NMR δ 21.0 (CH_3), 36.0 (C-8), 39.1 (C-3), 39.2 (C-4), 40.0 (C-1), 42.2 (NCH_3), 51.4 (OCH_3), 52.0 (C-2), 56.2 (C-7), 61.1 (C-5), 127.4, 129.0, 135.8 (C-*o*, C-*m*, C-*p*), 140.5 (C-*ipso*), 174.0 (CO). Anal. calcd for $C_{17}H_{23}NO_2 \cdot 1/2H_2O$: C, 72.31; H, 8.57; N, 4.96. Found: C, 72.36; H, 8.30; N, 4.89.

4.1.18. (1*RS*,2*SR*,3*RS*,5*RS*)-2β-Carbomethoxy-6-methyl-3β-phenyl-6-azabicyclo[3.2.1]octane (9a). Chromatography (CH_2Cl_2) gave the desired amine (58% yield) as a yellow oil. IR (NaCl) 1732; ^{1}H NMR (600 MHz) δ 1.68 (dt, J = 11, 5.1 Hz, 1H, H-8_{eq}), 1.94 (dt, J = 12.8, 4.8 Hz, 1H, H-4_{eq}), 2.07 (d, J = 11.6 Hz, 1H, H-8_{ax}), 2.23 (td, J = 12.8, 1 Hz, 1H, H-4_{ax}), 2.50 (s, 3H, NCH_3), 2.68 (q, J = 4.6 Hz, 1H, H-1_{eq}), 2.83 (dd, J = 10.9, 5.6 Hz, 1H, H-7_{exo}), 2.94 (dd, J = 5.9, 3.6 Hz, 1H, H-2_{eq}), 3.03 (d, J = 10.7 Hz, 1H, H-7_{endo}), 3.22 (t, J = 5.3 Hz, 1H, H-5_{eq}), 3.25 (dt, J = 12, 6.2 Hz, 1H, H-3_{ax}), 3.36 (s, 3H, OCH_3), 7.10–7.30 (m, 5H, ArH); ^{13}C NMR δ 29.5 (C-8), 32.7 (C-4), 37.3 (C-3), 39.9 (C-1), 43.0 (NCH_3), 50.9 (OCH_3, C-2), 60.4 (C-7), 61.4 (C-5), 125.9, 127.5, 127.8 (C-*o*, C-*m*, C-*p*), 142.5 (C-*ipso*), 173.4 (CO). Anal. calcd for $C_{16}H_{21}NO_2 \cdot 1/2H_2CO_3$: C, 68.26; H, 7.64; N, 4.82. Found: C, 68.57; H, 7.65; N, 4.87.

4.1.19. (1*RS*,2*SR*,3*RS*,5*RS*)-2β-Carbomethoxy-6-methyl-3β-(4-fluorophenyl)-6-azabicyclo[3.2.1]octane (9b). Chromatography (CH_2Cl_2) gave the desired amine (62%

yield) as a yellow oil. IR (NaCl) 1733; ^{1}H NMR (600 MHz) δ 1.67 (dt, J = 11.5, 5.1 Hz, 1H, H-8_{eq}), 1.90 (dt, J = 12.9, 5 Hz, 1H, H-4_{eq}), 2.04 (d, J = 11.4 Hz, 1H, H-8_{ax}), 2.20 (td, J = 12.6, 1.3 Hz, 1H, H-4_{ax}), 2.50 (s, 3H, NCH_3), 2.69 (q, J = 4.5 Hz, 1H, H-1_{eq}), 2.79 (dd, J = 10.5, 5.7 Hz, 1H, H-7_{exo}), 2.91 (dd, J = 6, 3.6 Hz, 1H, H-2_{eq}), 3.03 (d, J = 9.9 Hz, 1H, H-7_{endo}), 3.2 (t, J = 3.3 Hz, 1H, H-5_{eq}), 3.23 (dt, J = 11.1, 5.3 Hz, 1H, H-3_{ax}), 3.40 (s, 3H, OCH_3), 6.94 (t, J = 8.7 Hz, 2H, H-*m*), 7.20 (dd, J = 8.3, 5.6 Hz, 2H, H-*o*); ^{13}C NMR δ 29.4 (C-8), 33.2 (C-4), 36.9 (C-3), 40.0 (C-1), 43.4 (NCH_3), 51.0 (OCH_3, C-2), 60.6 (C-7), 61.6 (C-5), 114.5, 114.8 (C-*m*), 128.9, 129.0 (C-*o*), 138.15, 138.18 (C-*ipso*), 159.5, 162.7 (C-*p*), 173.3 (CO). Anal. calcd for $C_{16}H_{20}FNO_2 \cdot 1/2H_2O$: C, 67.11; H, 7.39; N, 6.63. Found: C, 69.29; H, 7.27; N, 5.05.

4.1.20. (1*RS*,2*SR*,3*RS*,5*RS*)-2β-Carbomethoxy-6-methyl-3β-(4-chlorophenyl)-6-azabicyclo[3.2.1]octane (9c). Chromatography (CH_2Cl_2) gave the desired amine (65% yield) as a yellow solid: mp 39–41 °C. IR (NaCl) 1732; ^{1}H NMR (600 MHz) δ 1.66 (dt, J = 11.1, 5.4 Hz, 1H, H-8_{eq}), 1.89 (dt, J = 12.6, 4.5 Hz, 1H, H-4_{eq}), 1.99 (d, J = 11.6 Hz, 1H, H-8_{ax}), 2.17 (td, J = 1, 12.8 Hz, 1H, H-4_{ax}), 2.48 (s, 3H, NCH_3), 2.68 (q, J = 4.6 Hz, 1H, H-1_{eq}), 2.77 (dd, J = 10.7, 5.5 Hz, 1H, H-7_{exo}), 2.90 (t, J = 4.7 Hz, 1H, H-2_{eq}), 3.02 (d, J = 10.7 Hz, 1H, H-7_{endo}), 3,19 (t, J = 5.5 Hz, 1H, H-5_{eq}), 3.22 (dt, J = 11.9, 5.9 Hz, 1H, H-3_{ax}), 3.39 (s, 3H, OCH_3), 7.10–7.20 (m, 5H, ArH); ^{13}C NMR δ 29.3 (C-8), 33.1 (C-4), 36.9 (C-3), 40.0 (C-1), 43.5 (NCH_3), 50.8 (C-2), 51.0 (OCH_3), 60.5 (C-7), 61.5 (C-5), 127.9, 128.9, 131.6 (C-*o*, C-*m*, C-*p*), 141.2 (C-*ipso*), 173.2 (CO). Anal. calcd for $C_{16}H_{20}ClNO_2$: C, 65.41; H, 6.86; N, 4.77. Found: C, 65.02; H, 6.90; N, 4.58.

4.1.21. (1*RS*,2*SR*,3*RS*,5*RS*)-2β-Carbomethoxy-6-methyl-3β-(4-tolyl)-6-azabicyclo[3.2.1]octane (9d). Chromatography (CH_2Cl_2) gave the desired amine (61% yield) as a yellow oil. IR (NaCl) 1732; ^{1}H NMR (600 MHz) δ 1.69 (dt, J = 11.1, 5.4 Hz, 1H, H-8_{eq}), 1.92 (dt, J = 12.8, 4.7 Hz, 1H, H-4_{eq}), 2.06 (d, J = 11.6 Hz, 1H, H-8_{ax}), 2.20 (td, J = 12.8, 1 Hz, 1H, H-4_{ax}), 2.28 (s, 3H, CH_3), 2.50 (s, 3H, NCH_3), 2.66 (q, J = 4.6 Hz, 1H, H-1_{eq}), 2.82 (dd, J = 10.7, 5.8 Hz, 1H, H-7_{exo}), 2.91 (dd, J = 5.9, 3.6, Hz, 1H, H-2_{eq}), 3.01 (d, J = 10.4 Hz, 1H, H-7_{endo}), 3.19 (t, J = 5.8 Hz, 1H, H-5_{eq}), 3.19–3.23 (m, 1H, H-3_{ax}), 3.38 (s, 3H, OCH_3), 7.00–7.15 (m, 5H, ArH); ^{13}C NMR δ 20.9 (CH_3), 29.5 (C-8), 32.9 (C-4), 37.0 (C-3), 39.9 (C-1), 43.0 (NCH_3), 50.86 (OCH_3), 50.92 (C-2), 60.4 (C-7), 61.4 (C-5), 127.3, 128.5, 135.2 (C-*o*, C-*m*, C-*p*), 139.4 (C-*ipso*), 173.4 (CO). Anal. calcd for $C_{17}H_{23}NO_2 \cdot 1/2H_2O$: C, 72.31; H, 8.57; N, 4.96. Found: C, 72.68; H, 8.19; N, 4.97.

4.2. Pharmacology

Synaptosomal Uptake of [^{3}H] Dopamine. Compounds were tested as the free base, and cocaine as the hydrochloride salt. The effect of candidate compounds in antagonizing [^{3}H] DA high-affinity uptake was determined essentially as previously described.[18] Male Sprague Dawley rats were killed by decapitation and the striatum was dissected and used as a source of rat DAT. The striatum was homogenized with a teflon-glass pestle in ice-cold 0.32 M sucrose and centrifuged for 10 min at 1000*g*. The supernatant was centrifuged at 17,500*g* for 20 min. This P_2 synaptosomal pellet was resuspended in 30 volumes of ice-cold modified KRH buffer consisting of (in mM) NaCl (125), KCl (4.8), $MgSO_4$ (1.2), $CaCl_2$ (1.3), KH_2PO_4 (1.2), glucose (5.6), nialamide (0.01), and HEPES (25) (pH 7.4). An aliquot of the synaptosomal suspension was preincubated with the buffer and drug for 30 min at 4 °C and then for 15 min at 37 °C before uptake was initiated by the addition of ~5 nM for [^{3}H]DA. After 5 min, uptake was terminated by adding 5 mL of cold buffer containing glucosamine as a substitute for NaCl and then finally by rapid vacuum filtration over GF/C glass-fiber filters, followed by washing with two 5 mL volumes of ice-cold, sodium-free buffer. The bound and free [^{3}H] DA was separated by rapid vacuum filtration over Whatman GF/C filters, using a Brandel M24R cell harvester, followed by two washes with 5 mL of cold buffer. Radioactivity on the filters was then extracted by allowing the filters to sit overnight with 5 mL of scintillation fluid. The vials were vortexed and counted. Specific uptake of [^{3}H]DA was defined as that which is sensitive to inhibition by 30 μM cocaine. This definition was virtually identical to that calculated by subtracting the mean of identical tubes incubated at 0 °C. IC_{50} values were determined using the computer program LIGAND. The Cheng-Prusoff equation for classic, competitive inhibition was used for calculating K_i from IC_{50} values in uptake experiments, in which 67 nM was used as the K_m for [^{3}H]DA. Even though uptake is a non-equilibrium process, K_i determinations are thought to be appropriate estimates of affinity between these compounds and the biogenic amine transporters because it is likely that the relatively long (45 min) period of incubation of the drug before addition of the [^{3}H] amine is adequate time for equilibrium between the test compound and the biogenic amine transporter to occur.

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