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Novel Pyridylmethylamines as Highly Selective 5-HT$_{1A}$ Superagonists

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To further improve the maximal serotonergic efficacy and better understand the configurational requirements for 5-HT$_{1A}$ binding and activation, we generated and biologically investigated structural variants of the lead structure befiradol. For a bioisosteric replacement of the 3-chloro-4-fluoro moiety, a focused library of 63 compounds by solution phase parallel synthesis was developed. Target binding of our compound collection was investigated, and their affinities for 5-HT$_2$, α_1, and α_2-adrenergic as well as D$_1$−D$_4$ dopamine receptors were compared. For particularly interesting test compounds, intrinsic activities at 5-HT$_{1A}$ were examined in vitro employing a GTPγS assay. The investigation guided us to highly selective 5HT$_{1A}$ superagonists. The benzothiophene-3-carboxamide **8bt** revealed almost exclusive 5HT$_{1A}$ recognition with a K_i value of 2.7 nM and a maximal efficacy of 124%. To get insights into the bioactive conformation of our compound collection, we synthesized conformationally constrained bicyclic scaffolds when SAR data indicated a chair-type geometry and an equatorially dispositioned aminomethyl substituent for the 4,4-disubstituted piperidine moiety.

Introduction

Serotonin (5-HT[a]) is the endogenous ligand of a ligand-gated ion channel (5-HT$_3$) and 14 serotonergic G-protein-coupled receptors (GPCRs) grouped into six subfamilies (5-HT$_{1-2}$, 5-HT$_{4-7}$).[1] The serotonin receptor 5-HT$_{1A}$ has been investigated intensively and was the first subtype to be cloned.[2] Showing a fast onset of action and high intrinsic activity, the 5-HT$_{1A}$ receptor can be activated to produce maximally effective antidepressant-like activity, opening new perspectives for the treatment of depressive disorders.[3−8] There is strong evidence that the target protein 5-HT$_{1A}$ can be also addressed for the treatment of further central nervous system (CNS) disorders including tardive dyskinesia and neuropathic pain.[9,10] Within the family of aminergic GPCR ligands, 1,4-disubstituted aromatic piperidines and piperazines (1,4-DAPs, Figure 1)[11] are known as privileged structural moieties simulating endogenous neurotransmitters including dopamine, serotonin, and (nor)epinephrine. Representative examples of this huge family of bioactive compounds are the CNS active drug haloperidol, the drug candidates WAY-100635,[12] BP 897,[13] and the recently discovered 2-pyridinylmethylamine derivative befiradol (F-13640), a highly selective 5-HT$_{1A}$ receptor agonist that shows remarkable effects and is currently undergoing clinical trials for the treatment of severe, chronic pain.[10,14−16] Befiradol shows high binding affinity and selectivity as well as strong partial agonist properties in vitro. As an example, subtype selectivity over 5-HT$_{1B}$ was shown to be greater than 10 000.[17] Efforts to advance ligand efficacy have been performed recently.[18]

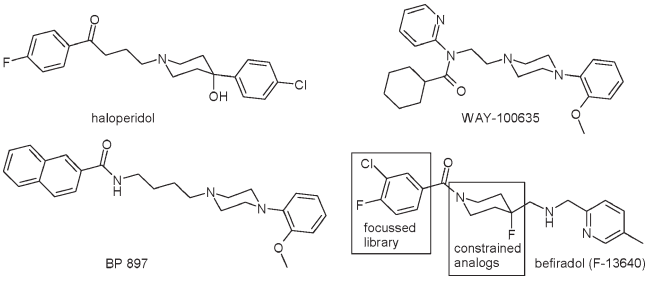

Figure 1. CNS active 1,4-disubstituted aromatic piperidines and piperazines (1,4-DAPs).

To further improve the maximal serotonergic efficacy and better understand the configurational requirements for 5-HT$_{1A}$ binding and activation, we aimed to generate and biologically investigate structural variants of the lead structure befiradol. Intending a bioisosteric replacement of the

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[a]Abbreviations: 5-HT, serotonin (5-hydroxytryptamine); 5-HT$_{1A}$, serotonin 1A receptor; GPCR, G-protein-coupled receptor; K_i, inhibition constant; *t*-BuOK, potassium *tert*-butoxide; CHO, Chinese hamster ovary; comp, compound; 1,4-DAPs, 1,4-disubstituted aromatic piperidines and piperazines; DIPEA, diisopropylethylamine; DMEA, dimethylethylamine; DMF, dimethylformamide; DMSO, dimethylsulfoxide; GTPγS, guanosine 5′-*O*-[γ-thio]triphosphate; HF·Pyr, poly(hydrogen fluoride)pyridine; HSQC, heteronuclear single quantum coherence; HPLC, high performance liquid chromatography; *m*-CPBA, *m*-chloroperbenzoic acid; MHz, megahertz; MS, mass spectrometry; NBS, *N*-bromosuccinimide; NOE, nuclear Overhauser effect; PPh$_3$, triphenylphosphine; mp, melting point; t_R, retention time; TBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluorborate; Tf, trifluoromethylsulfonyl; CNS, central nervous system; TMS, trimethylsilyl; THF, tetrahydrofuran; Ph, phenyl; RT, room temperature; Ms, methanesulfonyl; Pr, propyl; SAR, structure−activity relationship; SEM, standard error of the mean; TM, transmembrane helix; (HR-)EIMS, (high resolution) electron ionization based mass spectrometry; FTIR, Fourier transform infrared spectroscopy; TFA, trifluoroacetic acid.

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3-chloro-4-fluoro moiety, we developed a focused library of 63 compounds by solution phase parallel synthesis. Inspired by the 4-hydroxypiperidine partial structure of haloperidol, we further envisioned increasing hydrophilicity of some final products by a fluoride to hydroxyl exchange. Our program involved the investigation of target binding of our compound collection and comparison to the affinities for 5-HT_2, α_1- and α_2-adrenergic, and D_1-D_4-dopaminergic receptors. For particularly interesting test compounds, intrinsic activities at 5-HT_{1A} should be examined in vitro employing a guanosine 5′-*O*-[γ-thio]triphosphate (GTPγS) assay. To get insights into the bioactive conformation of our compound collection, we planned to synthesize bicyclic scaffolds in which the geometry of the central piperidine moiety was conformationally restrained by a bridge of two or three CH_2 units. Whereas azabicyclo-[3.2.1]octanes were chosen to simulate equatorially and axially substituted chair conformations of the piperidine unit, *endo*-substituted azabicyclo[3.3.1]nonanes should represent boat-type analogues.

Results and Discussion

Chemistry. For the development of a focused library based on befiradol, the central intermediate **7**[7,8] was synthesized employing *N*-benzoyl protection (Scheme 1). In detail, Corey−Chaykovsky methenylation[19−21] of the piperidone **1** led to the oxirane **2** which was subsequently subjected to ring-opening by poly(hydrogen fluoride)pyridine[22−25] to afford the fluoro alcohol **3**, regioselectively. Activation of the alcohol function and substitution of the thus formed triflate **4** with sodium azide followed by a one pot reaction in which the azide function was first reduced under Staudinger conditions[26] and then reductively alkylated with 5-methylpyridine-2-carbaldehyde gave the pyridylmethylamine **6**. The central intermediate **7** was accessed as the corresponding trihydrochloride by removal of the benzoyl protective group with hydrochloric acid.[27,28] For the envisioned structural variations of the benzamide moiety, we selected commercially available biphenyl, (tetrahydro)naphthyl, paracyclophanyl, ferrocenyl, and (nor)adamantyl carboxylic acid derivatives as representatives for saturated and unsaturated carbocyclic and heterocyclic analogues. Moreover, monocyclic and fused heteroarene carboxylic acids and analogous heterobiarenes were employed. Thus, activation of a collection of 63 carboxylic acids with *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluroniumtetrafluorborate (TBTU) and subsequent amide formation with the central building block **7** was performed in parallel to afford the target compounds **8aa−cj** (Scheme 1). The synthesis of the *N*-methyl derivative **9** was done by N-acylation and subsequent reductive methylation with paraformaldehyde.

To study the influence of the 4-fluoro substituent of the piperidine ring onto receptor binding, 4-hydroxy analogues were synthesized (Scheme 2). Thus, the oxirane **2** was subjected to ring-opening with a saturated solution of ammonia in methanol to afford the respective aminomethylpiperidine. Subsequent reductive alkylation with the methylpyridine-2-carbaldehyde led to the test compound **10**, which was deprotected and acylated with thienyl-3-carboxylic acid and 3-chloro-4-fluorobenzoic acid to yield the final products **11** and **12**, respectively.

For the preparation of the conformationally restrained 4-fluoropiperidine derivatives incorporating an ethylene bridge (**24** and **25**), nortropinone (**13**) was N-acylated to give the carboxamides **14** and **15** (Scheme 3). Subsequent methenylation gave the epoxides **16** and **17**. Ring-opening with poly-(hydrogen fluoride)pyridine[22−25] stereospecifically produced the isomers **18** and **19** displaying an *endo* positioned hydroxymethyl group. The relative stereochemistry was unambiguously determined by NMR spectroscopy when a combination of heteronuclear single quantum coherence (HSQC) and nuclear Overhauser effect (NOE) experiments displayed proximity between the hydroxymethyl group and the methylene bridge. O-Activation gave the mesylates **20** and **21** which were transformed into the azides **22** and **23**, respectively, and subsequently reduced and alkylated to yield the test compounds **24** and **25**.

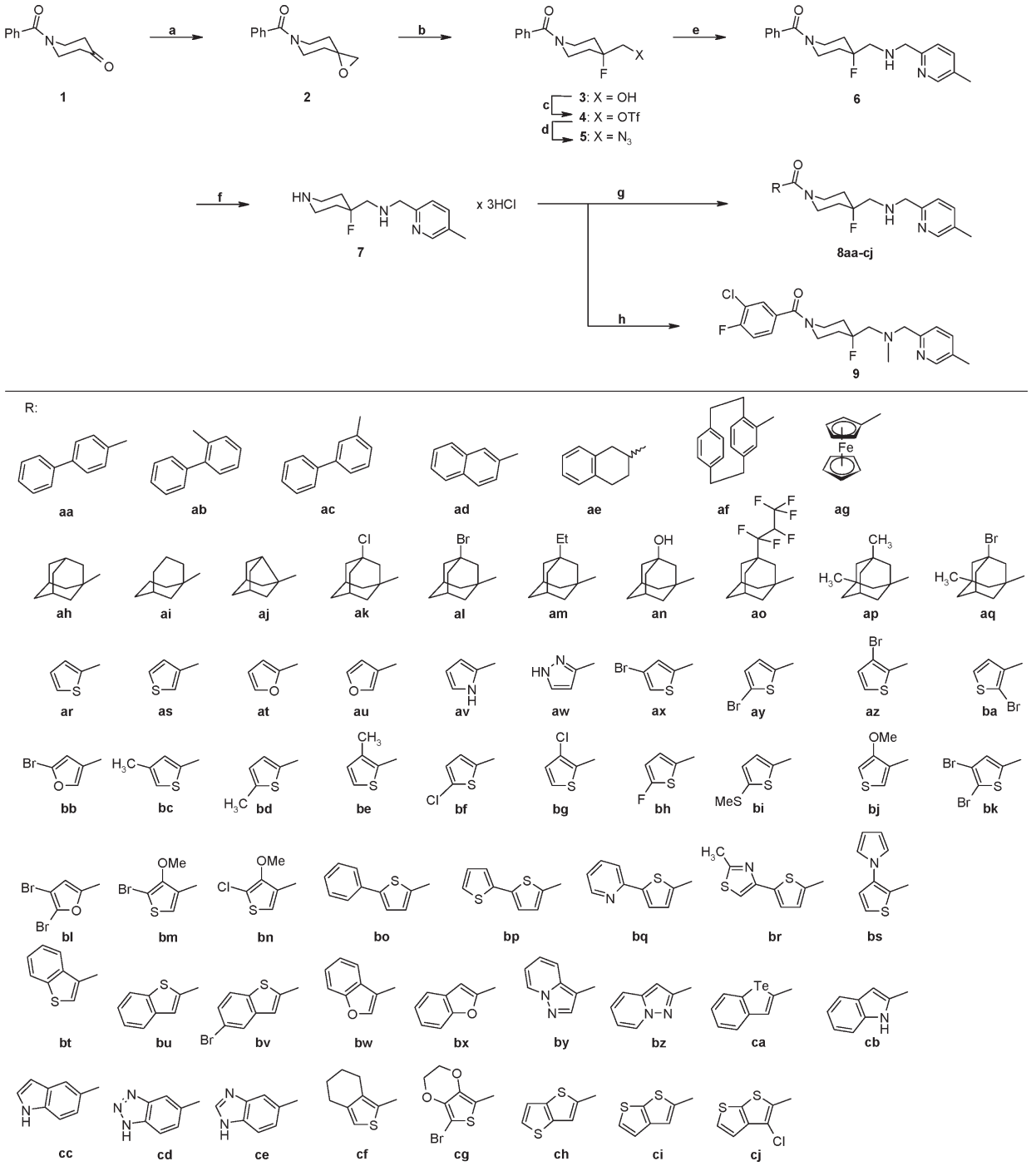
For the preparation of the 3-chloro-4-fluorobenzamide **30**, we evaluated an alternative synthetic approach by initially treating the piperidone **26** (Scheme 4) with methyltriphenylphosphonium bromide. The thus formed olefin **27** was subjected to a bromofluorination[29,30] reaction to give the *endo* bromomethyl derivative **28** diastereoselectively. Subsequent conversion into the azidomethyl derivative **29**, Staudinger reduction,[26] and reductive alkylation yielded the conformationally restrained befiradol analogue **30**.

In the course of our preparation of the conformationally restrained bicyclic 4-hydroxypiperidine derivatives (Scheme 5), we intended to approach the *endo* alcohols **34**, **35**, and **36** and the *exo* alcohol **38**. Thus, Corey−Chaykovsky methenylation[19,20] of the tropinones **14**, **15**, and **26** led to selective oxirane formation with an *endo* positioned oxygen, whereas epoxidation of the corresponding olefins led to a 2:3 mixture of oxiranes with *endo* and *exo* oxygens, respectively. The isomers could be separated by column chromatography. The *endo* alcohols **31−33** were prepared from the epoxides with *endo* oxygen according to the synthesis of the 4-hydroxypiperidines **10−12**. For the synthesis of the phenyl substituted derivative **34**, oxirane ring-opening of **31** was done with sodium azide, followed by a one pot synthesis leading to the target compound **34**, whereas the ring-opening for the synthesis of the 3-chloro-4-fluorophenyl substituted derivative **36** was achieved by heating the precursor **33** in ammonia in methanol. This modification was necessary because of the tendency of the aromatic fluoro substituent to be substituted by an azide group. Starting from the 3-thienylcarboxamide **32**, the heterocyclic test compound **35** was prepared analogously. The *exo* alcohol **38** was synthesized from **15** via a ring-opening reaction of an *exo*-epoxide intermediate with sodium azide resulting in formation of the azidoalcohol **37**. The relative stereochemistry was determinded on the stage of the ring-opening products employing a combination of HSQC and NOE experiments.

To modify the structural properties of our bicyclic scaffold, we also synthesized a pair of homologous diastereomers incorporating a propylene bridge (Scheme 6). Starting with *N*-Boc azabicyclo[3.3.1]nonane-3-one (**39**), the synthesis of the test compounds **41** and **43** was accomplished via the intermediates **40** and **42**, respectively, by benzoylation, epoxidation, selective ring-opening, reduction with $Pd(OH)_2/C/H_2$, and reductive alkylation. The synthesis of the two isomers differed only in the epoxidation step. Whereas the epoxide with *endo* oxygen was synthesized under Corey−Chaykovsky conditions,[19,20] a Prileschajew reaction[31] with the appropriate olefin yielded the epoxide with *exo* oxygen selectively.

In the case of azabicyclo[3.2.1]octane derivatives, *endo* methylene groups are axial and *exo* methylene groups are equatorial because of the chair conformation of the central

Scheme 1[a]

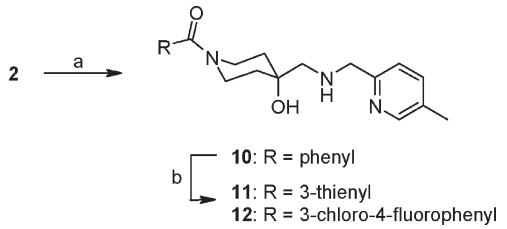


[a] Reagents and conditions: (a) trimethylsulfoxonium iodide, NaH, DMSO, RT, 1.5 h; (b) HF·Pyr, CH_2Cl_2, −10 °C, 3 h; (c) trifluoromethanesulfonic acid anhydride, pyridine, RT, 2 h; (d) NaN_3, DMF, 80 °C, 15 h; (e) (i) PPh_3, 5-methylpyridine-2-carbaldehyde, MeOH, reflux, 3 h; (ii) $NaCNBH_3$, RT, 15 h; (f) 6 N HCl, reflux, 15 h; (g) carboxylic acid, TBTU, DIPEA, DMF, CH_2Cl_2, RT, 2 h; (h) (i) 3-chloro-4-fluorobenzoic acid, TBTU, DIPEA, DMF, CH_2Cl_2, RT, 2 h; (ii) paraformaldehyde, $NaCNBH_3$, RT, 16 h.

six-membered ring.[32−34] Because of a boat type conformation of the piperidine ring, thus avoiding 1,4-interactions with the propylene bridge, azabizyclo[3.3.1]nonane derivatives usually have equatorially oriented *endo* methylene group. To establish the configuration of our azabizyclo[3.3.1]nonanes, we recorded an X-ray structure of the intermediate **42**, which is depicted in Figure 2. In fact, a boat conformation of the 4-substituted piperidine substructure could be observed.

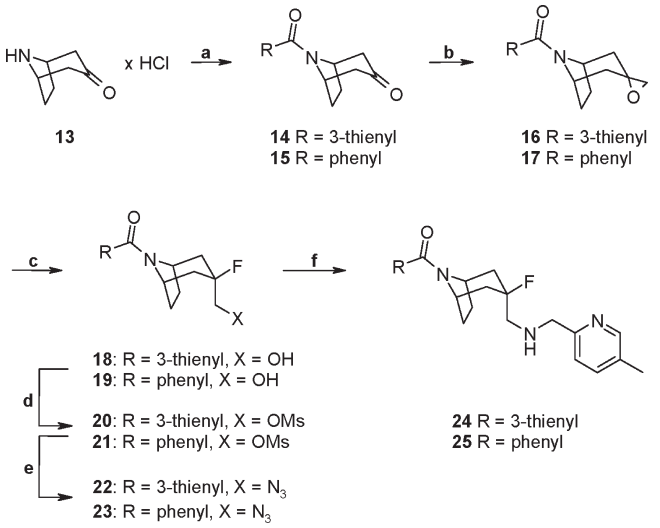
Receptor Binding. Radioligand binding assays were employed to analyze affinity and selectivity profiles of the target compounds. The binding data were generated by measuring their ability to compete with [^{3}H]WAY-100635, [^{3}H]-ketanserin, [^{3}H]prazosin, and [^{3}H]RX821002 when employing porcine 5-HT_{1A}, 5-HT_2, α_1, and α_2 receptors, respectively.[35] The ligands were also investigated for their potency to displace [^{3}H]spiperone for the cloned human dopamine receptor subtypes D_{2long}, D_{2short},[36] D_3,[37] and $D_{4.4}$[38] stably expressed in Chinese hamster ovary cells (CHO).[39] D_1 receptor affinities were determined utilizing porcine striatal membranes and the D_1 selective radioligand [^{3}H]SCH23390.

Scheme 2[a]



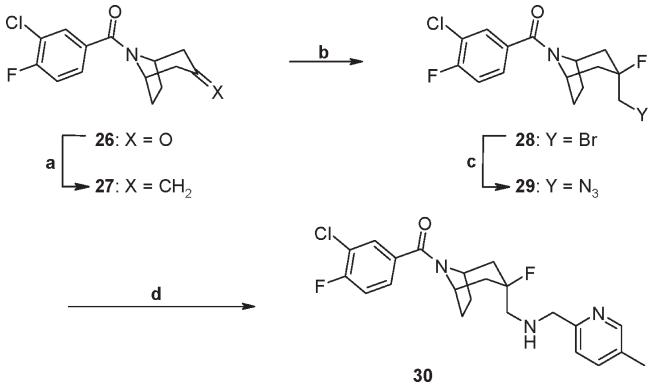
[a] Reagents and conditions: (a) (i) saturated solution of NH_3 in MeOH, RT, 1 d; (ii) 5-methylpyridine-2-carbaldehyde, $NaCNBH_3$, MeOH, RT, 16 h; (b) (i) 6 N HCl, reflux, 16 h; (ii) carboxylic acid, TBTU, DIPEA, CH_2Cl_2, DMF, RT, 16 h.

Scheme 3[a]



[a] Reagents and conditions. (a) Method 1: benzoyl chloride, Et_3N, CH_2Cl_2, 0 °C to RT, 5 h. Method 2: carboxylic acid, TBTU, CH_2Cl_2, DMF, 0 °C to RT, 2 h. (b) Trimethylsulfoxonium iodide, NaH, DMSO, 60 °C, 3.5 h; (c) HF·Pyr, CH_2Cl_2, −10 °C to RT; 16 h; (d) MsCl, CH_2Cl_2, THF, 0 °C to RT, 3 h; (e) NaN_3, DMF, 120 °C; 2 d; (f) (i) PPh_3, 5-methylpyridine-2-carbaldehyde, MeOH, reflux, 3 h; (ii) $NaCNBH_3$, RT, 18 h.

Scheme 4[a]

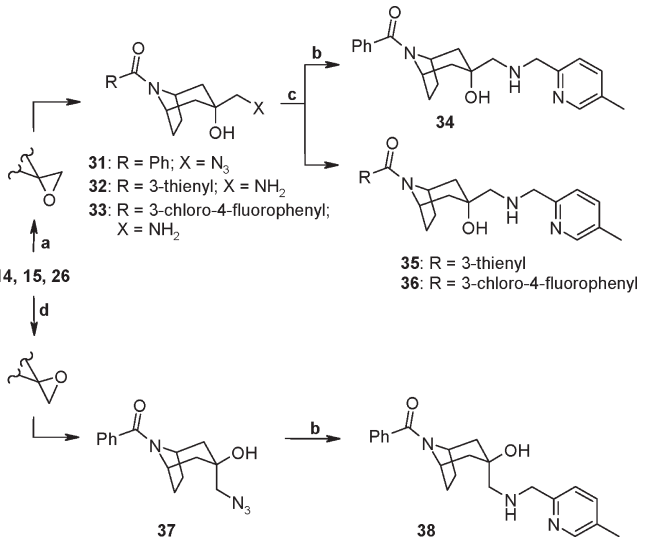


[a] Reagents and conditions: (a) *t*-BuOK, $MePPh_3Br$, THF, 80 °C for 2 h, then addition of **26**, RT for 16 h; (b) HF·Pyr, NBS, CH_2Cl_2, 0 °C, 1 h; (c) NaN_3, DMF, 80 °C, 2 d; (d) (i) PPh_3, 5-methylpyridine-2-carbaldehyde, MeOH, reflux, 3 h; (ii) $NaCNBH_3$, 4 h, RT.

Compared to the lead compound befiradol, the resulting K_i values are listed in Tables 1−4. Representative serotonergic ligands were tested for their ability to stimulate [^{35}S]-GTPγS binding when CHO cells stably transfected with the human 5-HT_{1A} were employed.[35] Ligand efficacy was compared to the full agonist serotonin (Table 1).

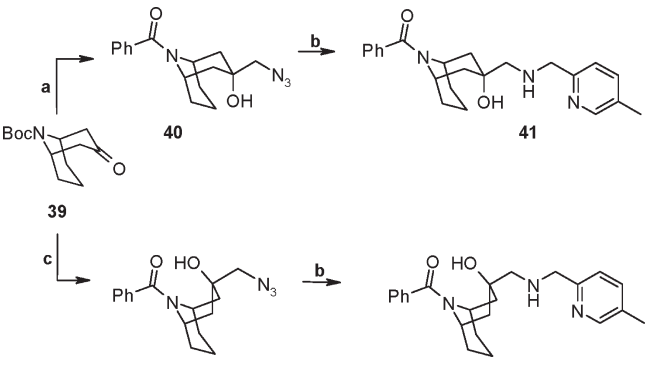
Our initial investigations were directed to the ligand binding properties of the test compounds **8aa**−**ag** incorporating unsaturated carbocyclic substituents. When these molecular probes were compared with the unsubstituted phenylcarboxamide **6** (K_i = 15 nM), a significant reduction of the affinity was observed. As an exception, the naphthylcarboxamide **8ad** showed comparable affinity. Interestingly, the

Scheme 5[a]



[a] Reagents and conditions. (a) Method 1 (in the cases of **14** and **26**): (i) trimethylsulfoxonium iodide, NaH, DMSO, 60 °C, 3.5 h; (ii) saturated solution of NH_3 in MeOH, 60 °C, 5 d. Method 2 (in the case of **15**): (i) *t*-BuOK, $MePPh_3Br$, THF, 80 °C, 2 h, then addition of **15**, RT, 16 h; (ii) *m*-CPBA, CH_2Cl_2, RT, 16 h, separation; (iii) NaN_3, DMF, 120 °C, 2 d; (b) (i) $Pd(OH)_2$/C, H_2, MeOH, RT, 2 h; (ii) 5-methylpyridine-2-carbaldehyde, $NaCNBH_3$, MeOH, RT, 16 h; (c) 5-methylpyridine-2-carbaldehyde, $NaCNBH_3$, MeOH, RT, 18 h; (d) (i) *t*-BuOK, $MePPh_3Br$, THF, 80 °C for 2 h, then addition of **15**, RT for 16 h; (ii) *m*-CPBA, CH_2Cl_2, RT, 16 h, separation; (iii) NaN_3, DMF, 120 °C, 2 d.

Scheme 6[a]



[a] Reagents and conditions: (a) (i) 50% TFA in CH_2Cl_2, RT, 16 h; (ii) BzCl, TEA, CH_2Cl_2, RT, 2 h; (iii) trimethylsulfoxonium iodide, NaH, 60 °C, 3 h; (iv) NaN_3, DMF, 120 °C, 2 d; (b) (i) $Pd(OH)_2$/C, H_2, MeOH, RT, 20 h; (ii) 5-methylpyridine-2-carbaldehyde, $Na(AcO)_3BH$ (in the case of **41**) or $NaCNBH_3$ (in the case of **43**), MeOH, RT, 16 h; (c) (i) 50% TFA in CH_2Cl_2, RT, 16 h; (ii) BzCl, TEA, CH_2Cl_2, RT, 2 h; (iii) *t*-BuOK, $MePPh_3Br$, THF, 80 °C, 2 h, then addition of 9-benzoyl-9-azabicyclo-[3.3.1]nonan-3-one, RT, 16 h; (iv) *m*-CPBA, CH_2Cl_2, RT, 2 h; (v) NaN_3, DMF, 120 °C, 2 d.

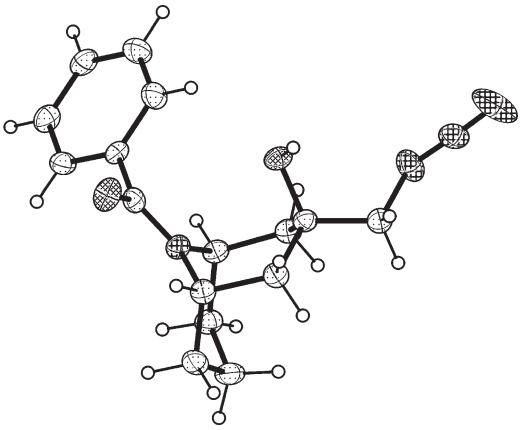
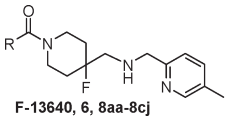


Figure 2. X-ray structure of the synthetic intermediate **42** displaying a boat-type conformation of the hydroxypiperidine partial structure and an *endo* configuration for the azidomethyl substituent.

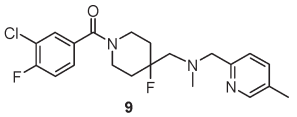
nonaromatic, adamantane derived carboxamides **8ah**−**aq** showed also significant 5-HT_{1A} binding with K_i values in the submicromolar and nanomolar ranges for most representatives. For this group of test compounds, the noradamantane derivative **8aj** displayed the highest affinity (K_i = 11 nM). Surprisingly, both the naphthalene and the noradamantane derived test compounds **8ad** and **8aj** gave superior intrinsic activities when compared to our lead befiradol (E_{max} = 84%), resulting in E_{max} values of 110% and 96%, respectively. Within the groups of unsubstituted monoheteroarenes, the thiophenes **8ar** and **8as** indicated the most advantageous binding properties (K_i = 27 nM). On the other hand, the aza-analogues **8av** and **8aw** and the hydroxyadamantane derivative **8an**, incorporating an H-bond donating group, showed only poor receptor recognition.

Starting from the thiophene and furan core structures, the introduction of substituents, especially halogen atoms, proved to be a suitable means to further increase 5-HT_{1A} binding

Table 1. Receptor Binding Data[a] and Intrinsic Activities[b] for Compounds of the Library **8aa**−**cj**[c] in Comparison to Befiradol, **6**, and **9** Employing 5-HT_{1A} Receptors



F-13640, 6, 8aa-8cj



9

	[^{3}H]WAY100635	[^{35}S]GTPγS			[^{3}H]WAY100635	[^{35}S]GTPγS	
compd	K_i ± SD/SEM [nM]	EC_{50} [nM]	E_{max} [%]	compd	K_i ± SD/SEM [nM]	EC_{50} [nM]	E_{max} [%]
befiradol	1.1 ± 0.45[e]	3.3	84	**8bf**	21 ± 1.4[d]	46	101
6	15 ± 1.3[e]	13	96	**8bg**	25 ± 5.7[d]	30	99
8aa	300 ± 120[e]	nd	nd	**8bh**	35 ± 2.1[d]	nd	nd
8ab	330 ± 92[e]	nd	nd	**8bi**	18 ± 0.71[d]	54	91
8ac	69 ± 24[e]	nd	nd	**8bj**	56 ± 2.8[d]	99	93
8ad	15 ± 1.7[e]	52	110	**8bk**	4.8 ± 0.64[d]	nd	nd
8ae	160 ± 21[d]	nd	nd	**8bl**	8.9 ± 0.64[d]	nd	nd
8af	320 ± 78[d]	nd	nd	**8bm**	17 ± 3.5[d]	62	95
8ag	46 ± 8.9[e]	37	99	**8bn**	18 ± 3.5[d]	50	102
8ah	17 ± 1.9[e]	11	98	**8bo**	500 ± 170[e]	nd	nd
8ai	19 ± 1.4[d]	26	96	**8bp**	420 ± 120[e]	nd	nd
8aj	11 ± 0.71[d]	47	96	**8bq**	470 ± 180[e]	nd	nd
8ak	92 ± 28[e]	48	91	**8br**	450 ± 21[d]	nd	nd
8al	120 ± 35[e]	nd	nd	**8bs**	360 ± 28[d]	nd	nd
8am	29 ± 5.7[d]	nd	nd	**8bt**	2.7 ± 0.39[e]	10	124
8an	1 300 ± 190[e]	600	90	**8bu**	190 ± 33[e]	240	116
8ao	1 300 ± 350[e]	nd	nd	**8bv**	220 ± 35[d]	nd	nd
8ap	470 ± 42[d]	nd	nd	**8bw**	4.2 ± 0.92[e]	16	101
8aq	460 ± 0[d]	nd	nd	**8bx**	64 ± 15[d]	34	87
8ar	27 ± 6.8[e]	18	91	**8by**	93 ± 24[d]	310	96
8as	27 ± 6.4[d]	12	95	**8bz**	180 ± 21[d]	93	80
8at	62 ± 3.5[d]	15	81	**8ca**	51 ± 2.8[d]	36	46
8au	182 ± 50[e]	240	99	**8cb**	94 ± 0[d]	nd	nd
8av	660 ± 12[e]	nd	nd	**8cc**	380 ± 78[d]	100	94
8aw	910 ± 97[e]	nd	nd	**8 cd**	910 ± 130[d]	nd	nd
8ax	6.2 ± 1.3[d]	17	116	**8ce**	3 500 ± 140[d]	nd	nd
8ay	19 ± 0[d]	30	95	**8cf**	20 ± 1.4[d]	86	104
8az	32 ± 8.5[d]	20	104	**8cg**	32 ± 9.9[d]	63	102
8ba	16 ± 1.4[d]	nd	nd	**8ch**	37 ± 1.4[d]	130	100
8bb	26 ± 0.71[d]	nd	nd	**8ci**	46 ± 9.9[d]	39	103
8bc	8.3 ± 0.66[e]	20	101	**8cj**	25 ± 0.71[d]	59	97
8bd	14 ± 3.5[d]	42	104	**9**	74 ± 7.1[d]	8.6	77
8be	26 ± 2.1[d]	35	96				

[a] Binding data are the mean values of two to nine individual experiments with 5-HT_{1A} receptors from porcine cortex membranes each done in triplicate. nd = not determined. [b] Agonist stimulated [^{35}S]GTPγS binding derived from a mean curve out of four experiments with human 5-HT_{1A} receptors stably expressed in CHO cells; E_{max} is displayed relative to the maximum effect of serotonin. [c] R according to Scheme 1. [d] K_i ± SD. [e] K_i ± SEM.

Table 2. Selectivity Pattern for Selected Compounds from the Library **8bt**, **8ax**, and **8bw** in Comparison to the Lead Befiradol Employing Porcine 5-HT_{1A}, 5-HT_2, D_1, α_1, α_2, and Human D_{2long}, D_{2short}, D_3, and $D_{4.4}$ Receptors

	K_i[a] ± SD/SEM [nM]									
compd	5-HT_{1A}[b]	5-HT_{1A}[c]	5-HT_2[d]	D_1[e]	D_{2long}[f]	D_{2short}[f]	D_3[f]	$D_{4.4}$[f]	α_1[g]	α_2[h]
befiradol	1.1[j]	0.33[j]	23 000[j]	26 000[j]	15 000[j]	46 000[j]	10 000[j]	2 000[i]	4 500[j]	3 700[i]
8ax	6.2[i]	1.8[j]	18 000[i]	34 000[i]	73 000[i]	100 000[i]	19 000[i]	2 000[i]	2 300[i]	3 500[i]
8bt	2.7[j]	0.86[j]	22 000[j]	45 000[i]	20 000[i]	54 000[i]	8 700[i]	460[i]	2 000[i]	1 700[i]
8bw	4.2[j]	1.1[j]	53 000[j]	48 000[i]	27 000[i]	28 000[i]	12 000[i]	590[i]	2 800[i]	2 800[i]

[a] Binding data are the mean values of two to nine experiments each done in triplicate. [b] [^{3}H]WAY-100635. [c] [^{3}H]8-OH-DPAT. [d] [^{3}H]Ketanserin. [e] [^{3}H]SCH23390. [f] [^{3}H]Spiperone. [g] [^{3}H]Prazosin. [h] [^{3}H]RX821002. [i] SD < 30%. [j] SEM < 30%.

Table 3. Receptor Binding Data[a] and Intrinsic Activities[b] for the 4-Hydroxylated Analogues **10**−**12** Employing 5-HT_{1A} Receptors

	[^{3}H]WAY100635	[^{35}S]GTPγS	
compd	K_i ± SEM [nM]	EC_{50} [nM]	E_{max} [%]
10	79 ± 9.0	nd	nd
11	120 ± 11	nd	nd
12	11 ± 2.4	6.6	109

[a] Derived from four to six individual experiments with porcine 5-HT_{1A} receptors each done in triplicate. [b] Average of data from four experiments with human 5-HT_{1A} receptors. E_{max} relative to the maximum effect of serotonin.

when K_i values of 6.2 and 4.8 nM could be observed for the monobromo- and the dibromothiophene carboxamide **8ax** and **8bk**, respectively. On the other hand, unsaturated cyclic substituents at the thiophene unit (**8bo**−**bs**) resulted in a significant reduction of affinity.

Finally, 17 fused heteroarenes were investigated (**8bt**−**cj**). The evaluation of this family of compounds led to the identification of two further serotonergic ligands with K_i values in the single digit nanomolar range. Thus, the benzothiophene-3-carboxamide **8bt** and its oxa-analogue **8bw** displayed K_i values of 2.7 and 4.2 nM, respectively. Whereas the benzofuran **8bw** gave a ligand efficacy that was comparable to that of serotonin, the benzothiophene **8bt** revealed superpotent properties with a maximal efficacy of 124%. Compared to 84% that we measured for the lead compound befiradol, this means an improvement of about 50%. Table 1 also displays a K_i value of the tertiary amine **9**, indicating an NH group of the aminomethylpiperidine moiety is important for high 5-HT_{1A} binding.

For the most promising test compounds **8ax**, **8bt**, and **8bw** and the reference agent befiradol, the ability to displace the agonist radioligand [^{3}H]8-OH-DPAT was investigated revealing K_i values that were similar to those determined for the displacement of [^{3}H]WAY100635. Binding selectivities over 5-HT_2, the dopaminergic subtypes D1, $D2_{long}$, $D2_{short}$, D3, and D4, and the α-adrenergic receptors α_1 and α_2 were also studied. Besides the D4 affinities of **8bt** and **8bw** (K_i = 500 and 590 nm, respectively), all K_i values were in the single digit and double digit micromolar range, indicating excellent selectivity ratios (Table 2).

To investigate a bioisosteric replacement of the fluoro substituent in the 4-position of the piperidine ring by a more hydrophilic hydroxy substituent, 5-HT_{1A} binding of the piperidinols **10**, **11**, and **12** was compared to the properties of the fluoro analogues **6**, **8as**, and befiradol, respectively. Interestingly, only a weak reduction of affinity (4- to 11-fold) was observed (Table 3).

In comparison to the 4,4-disubstituted benzoylpiperidine **10** (K_i = 79 nm), the consequence of conformational rigidization by an ethylene or propylene bridge was investigated.

Table 4. Receptor Binding Data[a] and Intrinsic Activities[b] for Azabicyclo[3.2.1]octane and Azabicyclo[3.3.1]nonane Derivatives Employing 5-HT_{1A} Receptors

	[^{3}H]WAY100635	[^{35}S]GTPγS	
compd	K_i ± SD/SEM [nM]	EC_{50} [nM]	E_{max} [%]
24	260 ± 55[d]	nd	nd
25	340 ± 160[d]	nd	nd
30	110 ± 17[c]	nd	nd
34	100 ± 44[d]	270	113
35	43 ± 5.3[d]	32	101
36	17 ± 7.3[d]	18	121
38	63 ± 33[d]		< 10
41	150 ± 47[d]	nd	nd
43	1 600 ± 350[c]	nd	nd

[a] K_i values are the mean of two to eight experiments with porcine 5-HT_{1A} receptors each done in triplicate. [b] Average of functional data from four experiments with human 5-HT_{1A} receptors. E_{max} relative to the maximum effect of serotonin. [c] K_i ± SD. [d] K_i ± SEM.

Thus, the corresponding azabicyclo[3.2.1]octanes **34** and **38** simulating the chair conformation of the piperidine with the aminomethyl substituent in the equatorial and axial positions, respectively, showed K_i values of 100 and 63 nM (Table 4). The structural analogues **35** and **36** displayed K_i values of 43 and 17 nM, respectively, indicating superior binding when compared to their surrogate **34**. Interestingly, the intrinsic activity strongly depended on the stereochemistry of the bicyclic scaffold. Whereas the diastereomer **34** displayed 113% ligand efficacy, the *endo*-aminomethyl substituted isomer **38** proved to be a neutral antagonist (E_{max} < 10%). Thus, the bioactive conformation of the family of aminomethylpiperidines, which is responsible for their 5-HT_{1A} agonist properties, adopts obviously an equatorial orientation of the crucial basic element. The azabicyclo[3.3.1]nonanes **41** and **43** gave K_i values of 150 and 1600 nM, respectively. The similarity between the K_i values of **34** and its homologue **41** reflects that both compounds adopt a chair type structure for the hydroxypiperidine unit with an equatorially positioned aminomethyl group. In the $5HT_{1A}$ binding pocket, however, the entropy advantage of conformational rigidization is obviously compensated by repulsive interactions with the bridging moieties. The boatlike conformation of the *endo*-aminomethyl substituted bicyclononane **43** leads to a significantly lower binding affinity in the micromolar range.

Whereas the conformational restriction of the hydroxypiperidines in the chair conformation led to maintenance of binding affinity, conformational restriction of the fluoropiperidines leading to the azabicyclooctanes **24**, **25**, and **30** even led to a reduction of binding affinity (Table 4).

This work concentrates on the characterization of in vitro pharmacodynamic properties. Pharmacokinetic studies are not involved. The critical metabolic elements are identical to our lead compound befiradol. Although minor structural

modifications can influence the metabolic fate, we expect preferred biotransformation to the respective pyridine-3-carboxylates as the major metabolites.[18] However, different appendages that have been introduced are expected to influence lipophilicity and, thus, distribution and elimination. As an example, the 3-benzothiophenyl and the benzofuranyl derived bioisosteres **8bt** and **8bw** display clogP values that significantly differ from befiradol (for befiradol clogP = 2.61, for **8bt** clogP = 3.64, and for **8bw** clogP = 1.93).[40] To optimize skin penetration, fine-tuning of lipophilicity will be necessary for the development of transdermal therapeutic systems (TDS), which become more and more important for the treatment of pain. Preliminary results measuring the reduction of licking time in a formalin induced paw pain assay (second phase at 1 mg/kg test compound administrated intraperitoneally) for representative test compounds indicated substantial antinociceptive activity (70% for **8ag**, 45% for **8ar**, 35% for **8at**) and bioavailability.[41]

Conclusion

A focused library of 5-HT_{1A} agonists was synthesized. Among the 63 test compounds, several derivatives with excellent 5-HT_{1A} affinities and superior potency could be found. Our SAR studies showed that the 3-chloro-4-fluorophenyl group of befiradol can be successfully replaced by both unsaturated and saturated lipophilic moieties. The benzothiophene-3-carboxamide **8bt** revealed almost exclusive 5-HT_{1A} recognition with a K_i value of 2.7 nM and a maximal efficacy of 124%. To get insights into the bioactive conformation of our compound collection, we synthesized bicyclic scaffolds in which the geometry of the central piperidine moiety was conformationally restrained. The substantial reduction of binding of the boatlike azabicyclo[3.3.1]nonanes **43** indicated a chair-type conformation for the 4,4-disubstituted piperidine scaffold. 5-HT_{1A} binding experiments showed that both equatorial and axial disposition of the aminomethyl substitution of the central piperidine chair leads to comparable receptor binding. However the stereochemical outcome of the synthesis is crucial for ligand efficacy. Thus, comparison of the azabicyclo-[3.2.1]octanes **34**−**36** and **38** proved that only the equatorially substituted diastereomers **34**−**36** act as agonists (E_{max} = 101−121%). On the other hand, ligand efficacy below 10% was observed for **38**, the axially substituted diastereomer of **34**.

Experimental Section

Chemistry. All reactions were carried out under nitrogen atmosphere. Dry solvents and reagents were of commercial quality and were used as purchased. Melting points have been measured on a Büchi 510. MS experiments were run on a Finnigan MAT TSQ 700 spectrometer by EI (70 eV) with solid inlet. HR-EIMS experiments were run on a JEOL GCmateII with a resolution of $M/\Delta M > 5000$. NMR spectra were obtained on a Bruker Avance 360 or a Bruker Avance 600 spectrometer relative to TMS in the solvents indicated (J value in Hz). IR spectra were performed on a Jasco FT/IR 410 spectrometer. Purification by flash chromatography was performed using silica gel 60 if not stated otherwise. TLC analyses were performed using Merck 60 F254 aluminum sheets and analyzed by UV light (254 nm) or by spraying with ninhydrin reagent. Preparative and analytical HPLC was performed on Agilent 1100 HPLC systems employing a VWL detector. As column, a Zorbax Eclipse XDB-C8 (4.6 mm × 150 mm, 5 μm) was used. HPLC was run with MeOH (eluent I) and 0.1% aqueous formic acid (eluent II) and the following gradients: System A was MeOH 10% for 3 min, ascending to 100% in 15 min, 100% for 6 min: flow rate, 0.5 mL/min; λ = 254 nm. System B started with MeOH 30% for 1 min, ascending to 100% in 11 min, 100% for 4 min: flow rate, 0.5 mL/min; λ = 254 nm. The purity of all test compounds and key intermediates was determined to be >95%.

6-Benzoyl-1-oxa-6-azaspiro[2.5]octane (2). A suspension of NaH (19.6 g, 490 mmol, 60% in oil) in DMSO (600 mL) was stirred at 65 °C for 2 h. After the mixture was cooled to RT, trimethylsulfoxonium iodide (108 g, 490 mmol) was added and stirring at RT was continued for 15 min. Then 1-benzoylpiperidin-4-one (95 g, 470 mmol) dissolved in DMSO (300 mL) was added to the mixture within 30 min and the solution was stirred for 45 min. The reaction mixture was poured into water and extracted with ethyl acetate three times. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated and the residue was purified by flash chromatography ($CHCl_3$−ethyl acetate 9:1) to give pure **2** (84 g, 83%) as a yellow solid (mp 55−60 °C). IR 3492, 3253, 3053, 3001, 2954, 2922, 2868, 1633, 1433, 1277 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 1.35−1.60 (m, 2H), 1.76−2.68 (m, 2H), 2.74 (bs, 2H), 3.43−3.72 (m, 3H), 4.18−4.36 (m, 1H), 7.37−7.46 (m, 5H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 33.0, 33.7, 40.9, 46.2, 53.8, 57.0, 126.9 (2C), 128.6 (2C), 129.7, 136.0, 170.9. APCI-MS m/z 218 $[M + 1]^+$.

(1-Benzoyl-4-fluoropiperidin-4-yl)methanol (3). To a cooled (−10 °C) solution of **2** (84 g, 385 mmol) in 200 mL of CH_2Cl_2, poly(hydrogene fluoride)pyridine 70% (100 mL, 1160 mmol) was added dropwise in 3 h at −10 °C. The solution was warmed to RT, poured into water, which was neutralized with 50% K_2CO_3 to pH 7, and extracted with CH_2Cl_2 three times. The combined organic layers were washed with water, 1 N HCl, and brine, dried (Na_2SO_4), and concentrated in vacuo to get crude brown oil which was purified by flash chromatography (CH_2Cl_2−MeOH 98:2) to give pure **3** (53 g, 60%) as a white solid. ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm) 1.46−2.13 (m, 4H), 2.96−3.53 (m, 3H), 3.64 (dd, J = 19.6 Hz, J = 4.2 Hz, 2H), 4.42−4.76 (m, 1H), 7.37−7.51 (m, 5H). APCI-MS m/z 238 $[M + 1]^+$.

(1-Benzoyl-4-fluoropiperidin-4-yl)methyltrifluoromethanesulfonic Acid (4). A solution of **3** (71 g, 300 mmol) in pyridine (1400 mL) was cooled to 0 °C. Trifluoromethanesulfonic acid anhydride (75 mL, 450 mmol) was added dropwise within 70 min. The mixture was stirred for 1 h at RT and then poured into water. The aqueous layer was extracted with CH_2Cl_2 three times, and the combined organic layers were washed with 5 N HCl, dried (Na_2SO_4), and concentrated under reduced pressure to yield **4** (78 g, 60%) as a white solid, which was used without further purification in the next step. ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm) 1.63−2.13 (m, 4H), 3.10−4.02 (m, 3H), 4.48 (d, J = 18.9 Hz, 2H), 4.58−4.87 (m, 1H), 7.39−7.48 (m, 5H). APCI-MS m/z 370 $[M + 1]^+$. HPLC/MS system A purity 93% (t_R = 0.1 min).

4-(Azidomethyl)-1-benzoyl-4-fluoropiperidine (5). To a solution of **4** (78 g, 212 mmol) in DMF (1000 mL) was added NaN_3 (110 g, 1700 mmol), and the mixture was heated at 80 °C for 15 h. The solvent was reduced by evaporation in vacuo, and 1000 mL of dichloromethane was added. Then the organic layer was washed with brine three times, dried (Na_2SO_4), and concentrated in vacuo to yield dark brown oil, which was purified by flash chromatography (CH_2Cl_2−MeOH 98:2) to give **5** (28 g, 36%) as a white solid (mp 75−77 °C). IR 3411, 2962, 2925, 2870, 2103, 1633, 1435, 1284 cm^{-1}. ^1H NMR ($CDCl_3$, 360 MHz) δ (ppm) 1.48−2.14 (m, 4H), 3.05−3.48 (m, 4H), 3.58−3.83 (m, 1H), 4.48−4.79 (m, 1H), 7.38−7.47 (m, 5H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 32.4, 32.9, 37.7, 43.2, 58.2 (d, J = 23.8 Hz), 93.7 (d, J = 175.7 Hz), 126.9 (2C), 128.6 (2C), 129.9, 135.7, 170.5. APCI-MS m/z 263 $[M + 1]^+$. HPLC/MS system A purity >99% (t_R = 13.4 min).

***N*-(1-Benzoyl-4-fluoropiperidin-4-yl)methyl-*N*-(5-methylpyridin-2-yl)methylamine (6).** A solution of **5** (41 g, 156 mmol), 5-methylpyridine-2-carbaldehyde (19 g, 160 mmol), and triphenylphosphine (41 g, 160 mmol) in MeOH (2800 mL) was heated

to reflux for 3 h. After the mixture was cooled to RT, $NaCNBH_3$ (31 g, 50 mmol) was added and the solution was stirred at RT for 15 h. The solvent was evaporated in vacuo, and the remaining residue was poured into water. The aqueous layer was extracted with CH_2Cl_2 three times, and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated in vacuo to obtain 101 g of a brown oil. The product was purified by flash chromatography (CH_2Cl_2 supplemented with MeOH from 0% to 4%) to give **6** (44 g, 82%) as a brown oil. ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 1.45−2.15 (m, 4H), 2.32 (s, 3H), 2.79 (d, J = 20.2 Hz, 2H), 3.08−3.75 (m, 2H), 3.90 (s, 2H), 4.41−4.67 (m, 2H), 7.20 (d, J = 8.0 Hz, 1H), 7.35−7.43 (m, 5H), 7.45 (dd, J = 7.8 Hz, 1.7 Hz, 1H), 8.34−8.40 (m, 1H). APCI-MS m/z 342 $[M + 1]^+$. HPLC/MS system A purity 97% (t_R = 13.7 min).

***N*-(4-Fluoropiperidin-4-yl)methyl-*N*-(5-methylpyridin-2-yl)-methylamine Trihydrochloride (7).** A solution of **6** (43 g, 125 mmol) in 6 N HCl (4800 mL) was heated to reflux for 15 h. The reaction mixture was washed with diethyl ether three times. The aqueous layer was evaporated under reduced pressure to obtain a viscid oil, which was washed with acetonitrile for several times to obtain a solid. The solid was washed with diethyl ether, suspended in a small amount of MeOH, and concentrated in vacuo to give **7** (31 g, 89%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm) 1.96−2.23 (m, 4H), 2.35 (s, 3H), 2.91−3.02 (m, 2H), 3.18−3.28 (m, 2H), 3.35 (d, J = 21.5 Hz, 2H), 4.37 (s, 2H), 7.70 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 8.56 (s, 1H), 9.43 (bs, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 18.1, 29.4 (d, J = 22.0 Hz), 39.1, 50.1, 52.8 (d, J = 22.0 Hz), 90.9 (d, J = 176.7 Hz), 125.1, 134.9, 140.4, 147.7. APCI-MS m/z 238 $[M + 1]^+$ (free base).

General Procedure 1 for the Synthesis of 8aa−cj. The appropriate aromatic or aliphatic carboxylic acid (0.064 mmol) and DIPEA (0.07 mL) were dissolved in dry CH_2Cl_2 (2 mL) and cooled to 0 °C. TBTU (20.2 mg, 0.062 mmol) was dissolved in DMF (0.2 mL) and added dropwise to the reaction mixture. The mixture was warmed to RT. Compound **7** (20.0 mg, 0.057 mmol) and DIPEA (0.4 mL) were dissolved in CH_2Cl_2 and added to the reaction mixture. Stirring was continued until TLC showed complete conversion (generally 2 h). The mixture was washed with brine, dried (Na_2SO_4), and the solvent was removed in vacuo. The product was purified by flash chromatography (CH_2Cl_2−MeOH 98:2).

If other amounts of carboxylic acid were used, all the other reactants were adjusted stoichiometrical equally.

***N*-[1-[(4-Bromo-2-thienyl)carbonyl]-4-fluoropiperidin-4-yl]-methyl-*N*-(5-methylpyridin-2-yl)methylamine 8ax.** Synthesis was performed according to general procedure 1 employing 4-bromothiophene-2-carboxylic acid (13.3 mg, 0.064 mmol), yielding **8ax** (14.8 mg, 61%) as a pale yellow oil. IR 3324, 2923, 1619, 1434, 1373, 1272, 968, 812, 759 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.82−1.95 (m, 2H), 2.00−2.14 (m, 2H), 2.32 (s, 3H), 2.79 (d, J = 20.2 Hz, 2H), 3.23−3.47 (m, 2H), 3.90 (s, 2H), 4.12−4.43 (m, 2H), 7.21 (d, J = 1.2 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 1.4 Hz, 1H), 7.45 (dd, J = 7.9 Hz, J = 1.8 Hz, 1H), 8.35−8.40 (m, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 18.1, 33.3 (2C), 40.1, 43.5, 55.1, 56.9 (d, J = 22.0 Hz), 94.4 (d, J = 172.3 Hz), 109.3, 121.7, 125.9, 130.6, 131.4, 137.0, 138.5, 149.7, 156.5, 162.0. APCI-MS m/z 427 $[M + 1]^+$. HR-EIMS m/z 425.0573. HPLC/MS system A purity 98% (t_R = 15.0 min).

***N*-[1-[(1-Benzothien-3-yl)carbonyl]-4-fluoropiperidin-4-yl]-methyl-*N*-(5-methylpyridin-2-yl)methylamine (8bt).** Synthesis was performed according to general procedure 1 employing 1-benzothiophene-3-carboxylic acid (11.4 mg, 0.064 mmol), yielding **8bt** (19.4 mg, 86%) as a pale yellow oil. IR 3332, 2923, 1631, 1515, 1434, 1272, 1238, 1126, 763, 748 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.47−1.78 (m, 2H), 1.92−2.17 (m, 2H), 2.32 (s, 3H), 2.80 (d, J = 20.2 Hz, 2H), 3.23−3.42 (m, 2H), 3.53−3.80 (m, 1H), 3.90 (s, 2H), 4.18−5.03 (m, 1H), 7.20 (d, J = 7.7 Hz, 1H), 7.36−7.44 (m, 2H), 7.45 (dd, J = 7.8 Hz, J = 1.7 Hz, 1H), 7.55 (s, 1H), 7.76−7.83 (m, 1H), 7.84−7.90 (m, 1H), 8.36−8.40 (m, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 18.1, 33.1, 33.9, 38.0, 43.3, 55.1, 56.9 (d, J = 23.1 Hz), 94.5 (d, J = 171.2 Hz), 121.6, 122.6, 122.9, 124.9, 125.0, 126.4, 131.4, 131.8, 136.9, 137.1, 139.8, 149.6, 156.5, 164.4. APCI-MS m/z 398 $[M + 1]^+$. HR-EIMS m/z 397.1624. HPLC/MS system A purity 96% (t_R = 15.6 min).

***N*-[1-[(1-Benzofuran-3-yl)carbonyl]-4-fluoropiperidin-4-yl]-methyl-*N*-(5-methylpyridin-2-yl)methyl]amine (8bw).** Synthesis was performed according to general procedure 1 employing 1-benzofuran-3-carboxylic acid (10.4 mg, 0.064 mmol), yielding **8bw** (15.5 mg, 71%) as a pale yellow oil. IR 3332, 2923, 1631, 1565, 1446, 1103, 752 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.50−1.87 (m, 2H), 1.95−2.15 (m, 2H), 2.32 (s, 3H), 2.79 (d, J = 20.6 Hz, 2H), 3.21−3.55 (m, 2H), 3.90 (s, 2H), 4.06−4.91 (m, 2H), 7.19 (d, J = 7.9 Hz, 1H), 7.31 (ddd, J = 7.4 Hz, J = 7.6 Hz, J = 1.0 Hz, 1H), 7.35 (ddd, J = 8.1 Hz, J = 7.2 Hz, J = 1.0 Hz, 1H), 7.45 (dd, J = 7.9 Hz, J = 1.5 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.86 (s, 1H), 8.36−8.39 (m, 1H). APCI-MS m/z 382 $[M + 1]^+$. HR-EIMS m/z 381.1853. HPLC/MS system A purity 98% (t_R = 15.1 min).

***N*-[1-(3-Chloro-4-fluorobenzoyl)-4-fluoropiperidin-4-yl]methyl-*N*-methyl-*N*-(5-methylpyridin-2-yl)methylamine (9).** 3-Chloro-4-fluorobenzoic acid (56.0 mg, 0.321 mmol) and DIPEA (0.35 mL) were dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. TBTU (98.3 mg, 0.306 mmol) was dissolved in DMF (3 mL) and was added to the reaction mixture which was then warmed to RT. Compound **7** (100.0 mg, 0.288 mmol) was dissolved in CH_2Cl_2 supplemented with DIPEA and was added to the solution. Stirring was continued for 2 h. Paraformaldehyde (10.2 mg) and $NaCNBH_3$ (54.3 mg, 0.864 mmol) were added, and stirring was continued for another 16 h at RT. The solvent was removed in vacuo, and the residue was poured into ice−water. The aqueous phase was then extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2−MeOH 95:5) to give pure **9** (55.3 mg, 47%) as a greenish oil. IR 3002, 2952, 2925, 2875, 2845, 2806, 1673, 1437, 1285, 1258 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.37−1.68 (m, 2H), 1.86−2.16 (m, 2H), 2.33 (s, 3H), 2.38 (s, 3H), 2.62 (d, J = 23.0 Hz, 2H), 3.09−3.24 (m, 1H), 3.30−3.44 (m, 1H), 3.46−3.60 (m, 1H), 3.71 (s, 2H), 3.35−4.54 (m, 1H), 7.17 (dd, J = 8.5 Hz, J = 8.5 Hz, 1H), 7.27 (ddd, J = 8.4 Hz, J = 4.5 Hz, J = 1.9 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.44−7.49 (m, 2H), 8.34−8.38 (m, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 18.2, 32.9, 33.8, 38.2, 43.7, 44.8, 64.1 (d, J = 20.9 Hz), 65.1, 95.2 (d, J = 174.5 Hz), 116.8 (d, J = 20.9 Hz), 121.5 (d, J = 17.6 Hz), 122.7, 127.1 (d, J = 7.7 Hz), 129.7, 131.5, 133.0 (d, J = 4.4 Hz), 137.1, 149.4, 156.3, 158.8 (d, J = 252.5 Hz), 168.0. APCI-MS m/z 408 $[M + 1]^+$. HR-EIMS m/z 407.1576. HPLC/MS system A purity 96% (t_R = 16.3 min).

1-Benzoyl-4-[[[(5-methylpyridin-2-yl)methyl]amino]methyl]-piperidin-4-ol (10). 4-(Aminomethyl)-1-benzoylpiperidin-4-ol [42] (108 mg, 0.462 mmol), 5-methylpyridine-2-carbaldehyde (53.3 mg, 0.440 mmol), and $NaCNBH_3$ (77.9 mg, 1.240 mmol) were dissolved in MeOH (10 mL) and stirred for 16 h at RT. The solvent was subsequently removed in vacuo, and the crude product was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried (Na_2SO_4), and the solvent was removed in vacuo. The product was purified by flash chromatography (hexane−ethyl acetate 6:4, then CH_2Cl_2−MeOH 98:2) to give pure **10** (81.7 mg, 52%) as a pale yellow oil. IR 3358, 2921, 1625, 1574, 1489, 1444, 1280 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.36−1.74 (m, 4H), 2.33 (s, 3H), 2.60 (s, 2H), 3.20−3.60 (m, 3H), 3.92 (s, 2H), 4.39−4.58 (m, 1H), 7.13 (d, J = 7.7 Hz, 1H), 7.35−7.41 (m, 5H), 7.46 (dd, J = 7.9 Hz, J = 1.8 Hz, 1H), 8.36−8.40 (m, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 18.2, 35.3, 36.2, 38.4, 43.9, 55.3, 59.1, 68.5, 121.8, 126.9 (2C), 128.4 (2C), 129.4, 131.7, 136.3, 137.2, 149.6, 156.4, 170.4. APCI-MS m/z 394 $[M + 1]^+$. HR-EIMS m/z 339.1946. HPLC/MS system A purity 97% (t_R = 13.6 min).

8-Benzoyl-8-azabicyclo[3.2.1]octan-3-one (15). Nortropinone hydrochloride (**13**) (560.0 mg, 3.465 mmol) was dissolved in CH_2Cl_2 (25 mL) supplemented with Et_3N (5 mL) and was cooled to 0 °C. Benzoyl chloride (487.0 mg, 3.465 mmol) was added dropwise. The reaction mixture was warmed to RT and stirred for 5 h. The solvent was removed in vacuo, and purification by flash chromatography (hexane−ethyl acetate 6:4) gave pure **15** (730.1 mg, 92%) as a colorless oil. IR 3059, 2958, 2923, 2885, 1717, 1635, 1577, 1409 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.72−1.87 (m, 2H), 2.07−2.26 (m, 2H), 2.27−2.70 (m, 3H), 2.79−3.12 (m, 1H), 4.26−4.62 (m, 1H), 4.88−5.22 (m, 1H), 7.40−7.60 (m, 5H). ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 28.2, 29.7, 48.9, 49.7, 51.5, 56.1, 127.1 (2C), 128.6 (2C), 130.7, 135.6, 169.0, 207.4. APCI-MS m/z 230 $[M + 1]^+$. HR-EIMS m/z 229.1103. HPLC/MS system B purity >99% (t_R = 10.1 min).

8-Benzoylspiro[8-azabicyclo[3.2.1]octane-3,2′-oxirane] (*endo*-O) (17). Synthesis was done according to **16** when using pretreated trimethylsulfoxonium iodide (1432.7 mg, 6.510 mmol) and **15** (710.2 mg, 3.098 mmol) to give pure **17** (660.3 mg, 88%) as a pale yellow oil. IR 3564, 3485, 3032, 2983, 2949, 2916, 1631, 1419 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.18−1.28 (m, 1H), 1.32−1.42 (m, 1H), 1.98−2.24 (m, 4H), 2.26−2.35 (m, 1H), 2.48 (d, J = 26.8 Hz, 2H), 2.56−2.67 (m, 1H), 4.11−4.28 (m, 1H), 4.83−5.01 (m, 1H), 7.37−7.52 (m, 5H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 26.9, 28.2, 38.8, 40.8, 48.3, 51.7, 51.7, 54.5, 56.5, 127.0 (2C), 128.5 (2C), 130.1, 136.3, 168.2. APCI-MS m/z 244 $[M + 1]^+$. HR-EIMS m/z 243.1259. HPLC/MS system B purity 99% (t_R = 12.2 min).

(8-Benzoyl-3-fluoro-8-azabicyclo[3.2.1]oct-3-yl)methanol (*endo*-CH_2) (19). Synthesis was done according to **18** using **17** (400.0 mg, 1.644 mmol). Purification was performed with preparative HPLC (MeOH/0.1% aqueous formic acid, gradient (MeOH) 30−59% in 10 min, 59% for 2.5 min, 59−95% in 0.5 min, 95% for 2 min, t_R = 10.5 min) to give pure **19** (200.0 mg, 46%) as a pale colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.59−1.72 (m, 2H), 1.95−2.22 (m, 5H), 2.32−2.47 (m, 1H), 3.62−3.78 (m, 2H), 4.08−4.22 (m, 1H), 4.82−4.97 (m, 1H), 7.38−7.54 (m, 5H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 27.5, 29.0, 37.8 (d, J = 22.0 Hz), 39.0 (d, J = 22.0 Hz), 50.1 (d, J = 7.7 Hz)., 54.9 (d, J = 7.7 Hz), 69.2 (d, J = 25.0 Hz), 95.0 (d, J = 170.2 Hz), 127.0 (2C), 128.6 (2C), 130.5, 135.3, 168.6. APCI-MS m/z 265 $[M + 1]^+$. HR-EIMS m/z 263.1322. HPLC/MS system B purity 100% (t_R = 10.5 min).

(8-Benzoyl-3-fluoro-8-azabicyclo[3.2.1]oct-3-yl)methylmethanesulfonic Acid (*endo*-CH_2) (21). Synthesis was done according to **20** using the alcohol **19** (178.6 mg, 0.678 mmol) to give crude **21** (231.5 mg, 100%) as a yellowish oil. No further purification was performed. APCI-MS m/z 342 $[M + 1]^+$. HPLC/MS system B purity 92% (t_R = 11.2 min).

3-(Azidomethyl)-8-benzoyl-3-fluoro-8-azabicyclo[3.2.1]octane (*endo*-CH_2) (23). Synthesis was done according to **22** using **21** (52.2 mg, 0.160 mmol). Purification was performed using flash chromatography (hexane−ethyl acetate 1:1) to yield pure **23** (37.7 mg, 82%) as a pale oil. ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.54−1.64 (m, 2H), 1.96−2.22 (m, 5H), 2.37−2.61 (m, 1H), 3.44 (d, J = 23.4 Hz, 2H), 4.06−4.24 (m, 1H), 4.78−4.99 (m, 1H), 7.39−7.47 (m, 3H), 7.47−7.53 (m, 2H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 27.4, 29.2, 39.0, 40.1, 49.8, 54.7, 59.7 (d, J = 25.8 Hz), 94.4 (d, J = 175.0 Hz), 127.1 (2C), 128.6 (2C), 130.3, 135.9, 168.3. APCI-MS m/z 289 $[M + 1]^+$. HPLC/MS system B purity 96% (t_R = 13.5 min).

***N*-(8-Benzoyl-3-fluoro-8-azabicyclo[3.2.1]oct-3-yl)methyl-*N*-(5-methylpyridin-2-yl)methylamine (*endo*-CH_2) (25).** The synthesis was done according to **24** using **23** (65.7 mg, 0.228 mmol). The product was purified by flash chromatography (CH_2Cl_2−MeOH 98:2) to give pure **25** (53.4 mg, 64%) as a brown oil. IR 3329, 3057, 2962, 2925, 2883, 2852, 1631, 1489, 1425, 1107 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.51−2.48 (m, 8H), 2.32 (s, 3H), 2.89 (d, J = 27.3 Hz, 2H), 3.92 (s, 2H), 4.02−4.16 (m, 1H), 4.79−4.92 (m, 1H), 7.22 (d, J = 7.9 Hz, 1H), 7.36−7.53 (m, 6H), 8.35−8.41 (m, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 18.1, 27.3, 29.0, 39.4, 40.5, 50.1, 55.0, 58.8 (d, J = 24.4 Hz), 95.2 (d, J = 170.4 Hz), 121.8, 127.1 (2C), 128.4 (2C), 130.1, 131.4, 136.2, 137.1, 149.6, 156.8, 168.1. APCI-MS m/z 368 $[M + 1]^+$. HPLC/MS system A purity 98% (t_R = 13.7 min).

3-(Azidomethyl)-8-benzoyl-8-azabicyclo[3.2.1]octan-3-ol (*exo*-CH_2) (31). The three step synthesis started with the preparation of the first intermediate 8-benzoyl-3-methylen-8-azabicyclo[3.2.1]octane, which was done by stirring a solution of *t*-BuOK (221.3 mg, 1.972 mmol) and methyltriphenylphosphonium bromide (715.6 mg, 2.003 mmol) in THF (8 mL) for 2 h at 80 °C. Then a solution of **15** (342.7 mg, 1.495 mmol) in THF was added and stirring was continued for 16 h at RT. After addition of diethyl ether the precipitate was filtered and washed twice with diethyl ether. The filtrate was evaporated under reduced pressure and purified by flash chromatography (hexane−acetone 8:2) to give pure product (205.7 mg (61%) as a pale oil. IR 3467, 3249, 3068, 2978, 2947, 2897, 2831, 1631, 1577, 1421 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.59−1.75 (m, 2H), 1.82−2.02 (m, 2H), 2.02−2.30 (m, 2H), 2.35−2.48 (m, 1H), 2.63−2.77 (m, 1H), 4.05−4.20 (m, 1H), 4.81−4.98 (m, 3H), 7.37−7.45 (m, 3H), 7.46−7.54 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 27.2, 28.7, 40.8, 42.4, 52.5, 57.2, 114.3, 127.1 (2C), 128.4 (2C), 129.9, 136.6, 141.5, 168.2. APCI-MS m/z 228 $[M + 1]^+$. HR-EIMS m/z 227.1310. HPLC/MS system A purity >99% (t_R = 20.0 min).

In a second step a mixture of *endo*-O and *exo*-O 8-benzoylspiro[8-azabicyclo[3.2.1]octane-3,2′-oxirane] was synthesized by stirring a solution of 8-benzoyl-3-methylen-8-azabicyclo-[3.2.1]octane (406.0 mg, 1.786 mmol) and *m*-CPBA (488.8 mg, 2.832 mmol) in CH_2CCl_2 (6 mL) at RT for 16 h. The reaction mixture was washed with a saturated solution of $NaHCO_3$, dried (Na_2SO_4), and evaporated under reduced pressure. Both isomers (*endo*-O and *exo*-O) were separated by flash chromatography (hexane−acetone 85:15).

Analytical Data of the *endo*-O Isomer. Yield 210.8 mg (49%), pale oil. IR 3477, 3249, 3055, 3033, 2983, 2951, 2916, 1630, 1419 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.26−1.41 (m, 2H), 1.99−2.12 (m, 2H), 2.12−2.25 (m, 2H), 2.26−2.34 (m, 1H), 2.45 (d, J = 4.0 Hz, 1H), 2.50 (d, J = 4.0 Hz, 1H), 2.56−2.66 (m, 1H), 4.14−4.25 (m, 1H), 4.82−5.00 (m, 1H), 7.39−7.46 (m, 3H), 7.47−7.51 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 26.9, 28.2, 38.9, 40.8, 48.3, 51.8, 54.5, 56.5, 127.1 (2C), 128.5 (2C), 130.0, 136.3, 168.2. APCI-MS m/z 244 $[M + 1]^+$. HR-EIMS m/z 243.1259. HPLC/MS system A purity >99% (t_R = 17.7 min).

Analytical Data of the *exo*-O Isomer. Yield 144.8 mg (33%), pale oil. IR 3479, 3248, 3055, 2979, 2952, 2921, 2879, 2854, 1633, 1423 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.20−1.50 (m, 2H), 1.75−1.90 (m, 2H), 1.97−2.13 (m, 2H), 2.13−2.26 (m, 1H), 2.34−2.56 (m, 1H), 2.76 (s, 2H), 4.10−4.34 (m, 1H), 4.86−5.09 (m, 1H), 7.37−7.46 (m, 3H), 7.37−7.54 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 27.2, 28.7, 38.8, 40.5, 51.6, 54.4, 56.3, 57.3, 127.1 (2C), 128.5 (2C), 130.2, 136.1, 168.2. APCI-MS m/z 244 $[M + 1]^+$. HR-EIMS m/z 243.1259. HPLC/MS system A purity 99% (t_R = 16.8 min).

Finally, a solution of the *endo*-O isomer of 8-benzoylspiro[8-azabicyclo[3.2.1]octane-3,2′-oxirane] (182.7 mg, 0.751 mmol) and NaN_3 (390.5 mg, 6.007 mmol) in DMF (5 mL) was stirred at 120 °C for 2 days. After the mixture was cooled to RT, ethyl acetate (20 mL) was added to the solution and the organic layer was washed with brine. The aqueous layer was extracted with ethyl acetate, the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane−ethyl acetate 1:1) to give pure **31** (147.5 mg, 69%) as a pale oil. IR 3375, 2980, 2952, 2921, 2864, 2101, 1667, 1608, 1575, 1496 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.67−2.11 (m, 6H), 2.15−2.33 (m, 2H), 2.52 (s, 1H), 3.11−3.24 (m, 2H), 4.03−4.20 (m, 1H), 4.76−4.88 (m, 1H), 7.36−7.51 (m, 5H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 26.8, 28.2, 40.2, 42.0, 50.9, 55.8, 63.9, 71.0, 127.0 (2C), 128.5 (2C), 130.0, 136.2, 168.1.

APCI-MS m/z 287 $[M + 1]^+$. HR-EIMS m/z 286.1430. HPLC/MS system A purity 95% (t_R = 18.0 min).

8-Benzoyl-3-[[[(5-methylpyridin-2-yl)methyl]amino]methyl]-8-azabicyclo[3.2.1]octan-3-ol (*exo*-CH$_2$) (34). A suspension of **31** (31.8 mg, 0.111 mmol) and $Pd(OH)_2/C$ (14.2 mg) in MeOH (4 mL) was stirred for 2 h under hydrogen atmosphere. Subsequent filtration over a short column of Celite and following evaporation of the main part of the MeOH was performed to concentrate the solution to 4 mL. 5-Methylpyridine-2-carbaldehyde (14.1 mg, 0.117 mmol) and $NaCNBH_3$ (22.3 mg, 0.355 mmol) were added, and stirring at RT was continued for 16 h. The solvent was evaporated in vacuo, and the residue was poured into ice−water. The aqueous layer was then extracted with CH_2Cl_2. The combined organic layer was washed with water and brine and was dried (Na_2SO_4). Filtration and evaporation in vacuo gave crude product which was purified by flash chromatography (CH_2Cl_2−MeOH 98:2) to give pure **34** (9.5 mg, 23%) as a pale yellow oil. IR 3349, 2977, 2938, 2868, 2235, 1614, 1574, 1434 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.60−1.73 (m, 2H), 1.75−1.84 (m, 1H), 1.87−2.02 (m, 3H), 2.24−2.38 (m, 5H), 2.46 (s, 2H), 3.88 (s, 2H), 4.00−4.14 (m, 1H), 4.72−4.89 (m, 1H), 7.12 (d, J = 7.7 Hz, 1H), 7.34−7.49 (m, 6H), 8.36−8.42 (m, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 18.2, 26.9, 28.2, 41.4, 43.2, 51.2, 55.0, 56.2, 62.0, 69.4, 121.9, 127.0 (2C), 128.4 (2C), 129.8, 131.7, 136.5, 137.2, 149.8, 156.1, 167.8. APCI-MS m/z 366 $[M + 1]^+$. HR-EIMS m/z 365.2103. HPLC/MS system B purity 97% (t_R = 14.6 min).

3-(Azidomethyl)-8-benzoyl-8-azabicyclo[3.2.1]octan-3-ol (*endo*-CH$_2$) (37). A solution of the *exo*-O isomer of 8-benzoylspiro[8-azabicyclo[3.2.1]octane-3,2′-oxirane] (118.4 mg, 0.487 mmol), which can be synthesized as described for the preparation of **31**, and NaN_3 (253.0 mg, 3.89 mmol) in DMF (5 mL) was stirred at 120 °C for 2 days. After the mixture was cooled to RT, ethyl acetate (20 mL) was added to the solution, the mixture was washed with brine, the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane−ethyl acetate 1:1) to give pure **37** (56.8 mg, 41%) as a pale oil. IR 3376, 3060, 2967, 2929, 2889, 2855, 2101, 1612, 1448 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.63−1.70 (m, 2H), 1.77−2.15 (m, 5H), 2.16−2.32 (m, 1H), 2.43 (s, 1H), 3.42 (s, 2H), 4.00−4.24 (m, 1H), 4.73−4.95 (m, 1H), 7.37−7.47 (m, 3H), 7.48−7.54 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 27.8, 29.4, 41.4, 42.6, 50.1, 55.0, 61.8, 70.5, 127.0, 128.5, 130.3, 136.0, 168.4. APCI-MS m/z 287 $[M + 1]^+$. HR-EIMS m/z 286.1430. HPLC/MS system A purity 93% (t_R = 18.0 min).

8-Benzoyl-3-[[[(5-methylpyridin-2-yl)methyl]amino]methyl]-8-azabicyclo[3.2.1]octan-3-ol (*endo*-CH$_2$) (38). Compound **37** (41.2 mg, 0.144 mmol) was reacted as described for **34**. Purification by flash chromatography (CH_2Cl_2−MeOH 95:5) gave pure **38** (13.9 mg, 26%) as a pale yellow oil. IR 3335, 2968, 2925, 2851, 2235, 1618, 1575, 1446 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.57−1.71 (m, 2H), 1.74−1.86 (m, 1H), 1.86−2.10 (m, 3H), 1.78−2.29 (m, 2H), 2.32 (s, 3H), 2.82 (bs, 2H), 3.95 (s, 2H), 4.00−4.15 (m, 1H), 4.73−4.93 (m, 1H), 7.16 (d, J = 7.9 Hz, 1H), 7.34−7.43 (m, 3H), 7.43−7.56 (m, 3H), 8.34−8.41 (m, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 18.1, 27.6, 29.2, 42.1, 43.4, 50.5, 54.8, 55.4, 62.0, 69.2, 121.9, 127.1 (2C), 128.4 (2C), 129.9, 131.8, 136.3, 137.3, 149.6, 156.0, 167.9. APCI-MS m/z 366$[M + 1]^+$. HR-EIMS m/z 365.2104. HPLC/MS system A purity 96% (t_R = 14.5 min).

3-(Azidomethyl)-9-benzoyl-9-azabicyclo[3.3.1]nonan-3-ol (*exo*-CH$_2$) (40). The synthesis of **40** was achieved in a four-step reaction sequence starting with the deprotection of *N*-butyloxycarbonyl-9-azabicyclo[3.3.1]nonan-3-one (**39**). The boc derivative **39** (4156 mg, 17.2 mmol) was stirred in a mixture of CH_2Cl_2 (15 mL) and TFA (15 mL) for 16 h at RT. The reaction mixture was frozen with liquid nitrogen, and the solvent was removed by sublimation in vacuo. After the residue was dissolved in CH_2Cl_2 (100 mL) and Et_3N (25 mL), the mixture was cooled to 0 °C and benzoyl chloride (2412 mg, 17.2 mmol) was added dropwise. The solution was allowed to warm to RT and was stirred for a further 2 h. The solvent was removed in vacuo and the crude product was purified by flash chromatography (hexane−ethyl acetate 6:4) to give 9-benzoyl-9-azabicyclo[3.3.1]nonan-3-one (3.53 g, 85%) as a white solid. IR 3058, 2947, 2880, 1710, 1630, 1420 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.63−1.99 (m, 6H), 2.28−2.40 (m, 1H), 2.44−2.59 (m, 2H), 2.75−2.89 (m, 1H), 4.23−4.42 (m, 1H), 5.19−5.35 (m, 1H), 7.39−7.51 (m, 5H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 16.5, 30.4, 31.3, 45.3, 45.7, 45.8, 51.8, 126.5 (2C), 128.8 (2C), 130.2, 135.6, 170.1, 208.5. APCI-MS m/z 244 $[M + 1]^+$. HR-EIMS m/z 243.1259. HPLC/MS system A purity >99% (t_R = 16.9 min).

Methenylation reaction to get the *endo*-O isomer of 9-benzoylspiro[9-azabicyclo[3.3.1]nonane-3,2′-oxirane] was done according to the synthesis of **32** employing trimethylsulfoxonium iodide (575 mg, 2.61 mmol) and 9-benzoyl-9-azabicyclo[3.3.1]nonane-3-one (1096 mg, 4.40 mmol). Purification was performed by flash chromatography (hexane−acetone 85:15) to give pure product (456.6 mg, 40%) as a pale resin. IR 3479, 3244, 3053, 3030, 2973, 3941, 2906, 2850, 1627, 1421 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.22−1.31 (m, 1H), 1.37−1.47 (m, 1H), 1.62−1.72 (m, 2H), 1.76−1.89 (m, 2H), 1.92−2.04 (m, 1H), 2.34−2.45 (m, 1H), 2.60−2.70 (m, 2H), 2.70−2.80 (m, 2H), 3.98−4.08 (m, 1H), 5.00−5.09 (m, 1H), 7.40−7.49 (m, 5H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 16.1, 29.2, 30.2, 36.2, 37.5, 43.9, 50.3, 53.7, 53.9, 126.4 (2C), 128.6 (2C), 129.5, 136.4, 169.6. APCI-MS m/z 258 $[M + 1]^+$. HR-EIMS m/z 257.1416. HPLC/MS system A purity 98% (t_R = 18.7 min).

Finally, a solution of 9-benzoylspiro[9-azabicyclo[3.3.1]nonane-3,2′-oxirane] (*endo*-O) (228.5 mg, 0.888 mmol) and NaN_3 (467.0 mg, 7.185 mmol) in DMF (5 mL) was stirred at 120 °C for 2 days. Workup was done as described for **31**. The crude product was purified by flash chromatography (hexane−ethyl acetate 1:1). The product was crystallized from a mixture of CH_2Cl_2 and diisopropyl ether to give pure **40** (84.2 mg, 32%) as colorless crystals (mp 110−112 °C). IR 3377, 3059, 2933, 2854, 2102, 1608, 1446, 1365, 1269 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.47−1.65 (m, 3H), 1.66−1.80 (m, 3H), 1.84−1.98 (m, 2H), 2.04−2.15 (m, 1H), 2.21 (s, 1H), 2.53−2.71 (m, 1H), 3.22−3.36 (m, 2H), 3.88−4.01 (m, 1H), 4.90−5.00 (m, 1H), 7.33−7.46 (m, 5H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 15.4, 29.1, 30.2, 37.9, 38.6, 42.6, 49.0, 64.1, 68.7, 126.3 (2C), 128.7 (2C), 129.6, 136.1, 169.4. APCI-MS m/z 301 $[M + 1]^+$. HR-EIMS m/z 300.1587. HPLC/MS system A purity 97% (t_R = 19.2 min).

9-Benzoyl-3-[[[(5-methylpyridin-2-yl)methyl]amino]methyl]-9-azabicyclo[3.3.1]nonan-3-ol (*exo*-CH$_2$) (41). A suspension of **40** (19.8 mg, 0.07 mmol) and $Pd(OH)_2/C$ (8.5 mg) in MeOH (2 mL) was stirred for 20 h under hydrogen atmosphere. After subsequent filtration over a short column of Celite a small amount of poly(4-vinylpyridine) resin was added and stirring was continued at RT for 1 h. Another filtration step over Celite was needed to remove the resin. 5-Methylpyridine-2-carbaldehyde (7.9 mg, 0.07 mmol) and $Na(AcO)_3BH$ (20.6 mg, 0.10 mmol) were added to the filtrate, and stirring at RT was continued for 16 h. The solvent was evaporated in vacuo, and the residue was poured into ice−water. The aqueous layer was then extracted with CH_2Cl_2, and the combined organic layer was washed with water and brine and was dried (Na_2SO_4). Filtration and evaporation in vacuo gave crude product which was purified by flash chromatography (CH_2Cl_2−MeOH 98:2 to 95:5) to give pure **41** (5.6 mg, 23%) as a pale oil. IR 3419, 2925, 2848, 1621, 1430, 1197 cm^{-1}. ^{1}H NMR(360 MHz, $CDCl_3$) δ (ppm) 1.43−1.53 (m, 1H), 1.56−1.66 (m, 2H), 1.67−1.80 (m, 3H), 1.84−1.95 (m, 1H), 1.95−2.04 (m, 2H), 2.33 (s, 3H), 2.48−2.58 (m, 2H), 2.75−2.92 (m, 1H), 3.86−3.94 (m, 3H), 4.88−4.96 (m, 1H), 7.13 (d, J = 7.7 Hz, 1H), 7.13−7.41 (m, 5H), 7.44−7.49 (m, 1H), 8.36−8.42 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 15.5, 18.2, 29.1, 30.3, 39.1, 40.2, 43.1, 49.6, 55.1, 62.5, 66.7, 121.9, 126.2 (2C), 128.4

(2C), 129.4, 131.7, 136.6, 137.2, 149.8, 156.1, 169.2. APCI-MS m/z 380 $[M + 1]^+$. HR-EIMS m/z 379.2259. HPLC/MS system B purity 96% (t_R = 9.5 min).

3-(Azidomethyl)-9-benzoyl-9-azabicyclo[3.3.1]nonan-3-ol (*endo*-CH_2) (42). Synthesis of **42** was achieved in a multistep reaction starting from 9-benzoyl-9-azabicyclo[3.3.1]nonan-3-one (see synthesis of **40**). A solution of *t*-BuOK (502 mg, 4.55 mmol) and methyltriphenylphosphonium bromide (1652 mg, 4.62 mmol) in THF (15 mL) was stirred for 2 h at 80 °C. A solution of 9-benzoyl-9-azabicyclo[3.3.1]nonan-3-one (840.0 mg, 3.452 mmol) in THF was added and was stirred for 16 h at RT. After addition of diethyl ether, the precipitate was filtered and washed with diethyl ether twice. The filtrate was evaporated under reduced pressure and purified by flash chromatography (hexane−acetone 8:2) to give pure 9-benzoyl-3-methylene-9-azabicyclo[3.3.1]nonane (758.0 mg, 91%) as a pale resin. IR 3246, 3068, 3027, 2963, 2932, 2877, 2848, 2821, 1628, 1419 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.40−1.52 (m, 1H), 1.60−1.70 (m, 1H), 1.70−1.85 (m, 2H), 1.86−2.00 (m, 1H), 2.23−2.56 (m, 4H), 2.65−2.77 (m, 1H), 3.89−3.97 (m, 1H), 3.76−3.87 (m, 2H), 4.92−5.02 (m, 1H), 7.34−7.47 (m, 5H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 18.1, 30.5, 31.5, 38.2, 39.3, 45.0, 51.3, 110.0, 126.4 (2C), 128,6 (2C), 129.4, 136.6, 145.1, 169.7. APCI-MS m/z 242 $[M + 1]^+$. HR-EIMS 241.1466. HPLC/MS system A purity 100% (t_R = 18.8 min).

Stereoselective epoxidation of the methylene derivative was done when a solution of 9-benzoyl-3-methylen-9-azabicyclo-[3.3.1]nonane (440 mg, 1.825 mmol) and *m*-CPBA (500 mg, 2.90 mmol) in CH_2Cl_2 (6 mL) was stirred at RT for 2 h. The mixture was washed with a saturated solution of $NaHCO_3$, dried (Na_2SO_4), and evaporated under reduced pressure. Purification was performed by flash chromatography (hexane−acetone 85:15) to give the pure *exo*-O isomer of 9-benzoylspiro[9-azabicyclo-[3.3.1]nonan-3,2′-oxirane] (388.2 mg, 83%) as a yellowish solid. IR 3481, 3057, 3028, 2939, 2881, 2850, 1628, 1423 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.26−1.34 (m, 1H), 1.41−1.50 (m, 1H), 1.53−1.61 (m, 1H), 1.71−1.88 (m, 3H), 1.91−2.04 (m, 2H), 2.19−2.30 (m, 1H), 2.41−2.52 (m, 1H), 2.77−2.88 (m, 2H), 4.03−4.12 (m, 1H), 5.05−5.15 (m, 1H), 7.39−7.46 (m, 5H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 19.4, 29.3, 30.4, 36.8, 37.9, 45.0, 51.3, 55.7, 59.6, 126.4 (2C), 128.7 (2C), 129.7, 136.2, 169.5. APCI-MS m/z 258 $[M + 1]^+$. HR-EIMS m/z 257.1416. HPLC/MS system A purity 98% (t_R = 17.8 min).

A solution of 9-benzoylspiro[9-azabicyclo[3.3.1]nonan-3,2′-oxirane] (*exo*-O) (193.6 mg, 0.752 mmol) and NaN_3 (396.2 mg, 6.095 mmol) in DMF (5 mL) was stirred at 120 °C for 2 days. After the mixture was cooled to RT, ethyl acetate (20 mL) was added to the solution, which was washed with brine to remove the DMF. The aqueous layer was extracted with ethyl acetate, the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane−ethyl acetate 1:1). The product crystallized from a mixture of CH_2Cl_2 and diisopropyl ether to give pure **42** (171.7 mg, 76%) as colorless crystals (mp 140−142 °C). ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.32−1.49 (m, 2H), 1.49−1.57 (m, 1H), 1.57−1.70 (m, 3H), 1.75−1.90 (m, 2H), 1.91−2.03 (m, 1H), 2.13−2.27 (m, 1H), 2.91 (s, 1H), 3.18−3.30 (m, 2H), 4.02−4.13 (m, 1H), 4.97−5.08 (m, 1H), 7.33−7.43 (m, 3H), 7.45−7.53 (m, 2H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm) 14.2, 31.1, 32.4, 34.3, 35.3, 41.1, 47.9, 61.8, 70.7, 126.7 (2C), 128.4 (2C), 129.5, 136.4, 170.5. APCI-MS m/z 301 $[M + 1]^+$. HPLC/MS system B purity 97% (t_R = 13.8 min).

9-Benzoyl-3-[[[(5-methylpyridin-2-yl)methyl]amino]methyl]-9-azabicyclo[3.3.1]nonan-3-ol (*endo*-CH_2) (43). Synthesis of **43** was achieved according to **41** employing **42** (31.4 mg, 0.11 mmol), 5-methylpyridine-2-carbaldehyde (20.5 mg, 0.17 mmol), and $NaCNBH_3$ (21.1 mg, 0.34 mmol). Purification by flash chromatography (CH_2Cl_2−MeOH 98:2 to 95:5) gave pure **43** (16.0 mg, 40%) as a pale oil. IR 3419, 2931, 2852, 1614, 1446, 1197 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) 1.31−1.43 (m, 2H), 1.47−1.68 (m, 4H), 1.73−1.91 (m, 2H), 1.91−2.02 (m, 1H), 2.18−2.29 (m, 1H), 2.32 (s, 3H), 2.54−2.64 (m, 2H), 3.90 (s, 2H), 4.00−4.09 (m, 1H), 5.04−5.16 (m, 1H), 7.17 (d, J = 7.9 Hz, 1H), 7.33−7.41 (m, 3H), 7.44−7.55 (m, 3H), 8.38−8.40 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 14.3, 18.1, 31.2, 32.3, 35.8, 36.3, 40.9, 47.9, 55.4, 60.2, 69.2, 121.8, 126.6 (2C), 128.3 (2C), 129.0, 131.5, 137.1, 137.2, 149.7, 156.5, 170.0. APCI-MS m/z 380 $[M + 1]^+$. HR-EIMS m/z 379.2261. HPLC/MS system A purity 95% (t_R = 15.2 min).

Receptor Binding Studies. Receptor binding studies were carried out as previously described.[39] In brief, the dopamine D_1 receptor assay was done with porcine striatal membranes at a final protein concentration of 40 μg/assay tube and the radioligand [^{3}H]SCH 23390 at 0.3 nM (K_D = 0.41−0.56 nM). Competition experiments with human D_{2long},[36] D_{2short},[36] D_3,[37] and $D_{4.4}$[38] receptors were run with preparations of membranes from CHO cells stably expressing the corresponding receptor and [^{3}H]spiperone at a final concentration of 0.1−0.4 nM. The assays were carried out at a protein concentration of 5−20 μg/assay tube and K_D values of 0.04−0.14, 0.04−0.24, 0.11−0.28, and 0.17−0.35 nM for the D_{2long}, D_{2short}, D_3, and $D_{4.4}$ receptors, respectively. 5-HT and α_1 receptor binding experiments were performed with homogenates prepared from porcine cerebral cortex as described.[35] Assays were run with membranes at a protein concentration per assay tube of 100, 80, and 60 μg/assay tube for 5-HT_{1A}, 5-HT_2, and α_1 receptor, respectively, and radioligand concentrations of 0.2−0.3 nM ([^{3}H]WAY100635 and [^{3}H]prazosin) and 0.5 nM ([^{3}H]ketanserin) with K_D values of 0.03−0.15 nM for 5-HT_{1A}, 0.67−1.6 nM for 5-HT_2, and 0.07−0.16 nM for the α_1 receptor. Binding affinities to the agonist labeled high affinity binding site of the 5-HT_{1A} receptor were determined similar to the protocol for α_1 in 24-well microplates at a final volume of 800 μL employing membranes from porcine cerebral cortex at 320 μg/assay tube and the selective agonist radioligand [^{3}H]8-OH-DPAT (Biotrend, Cologne, Germany, with a specific activity of 187 Ci/mmol) at a final concentration of 0.5 nM and with K_D values of 0.66−1.1 nM. Binding affinities to α_2 receptors were determined similarly (total volume of 800 μL, homogenates from porcine cerebral cortex at 240 μg/assay tube) using the subtype selective radioligand [^{3}H]RX821002[43] at 0.2−0.5 nM and considering K_D values of 0.21−0.52 nM. Unspecific binding was determined in the presence of 10 μM RX821002.

Protein concentration was established by the method of Lowry using bovine serum albumin as standard.[44]

Determination of [^{35}S]GTPγS Binding. The [^{35}S]GTPγS binding assay for functional activity was done as described in the literature.[45] In brief, ligand induced binding of the radioligand [^{35}S]GTPγS (specific activity of 1250 Ci/mmol, Perkin-Elmer) to membranes of CHO cells stably expressing the human 5-HT_{1A} receptor was determined at a radioligand concentration of 0.1 nM and in the presence of test compounds in eight different concentration (0.01−10000 nM) as hexaduplicates at a final volume of 200 μL. Maximum stimulation (= 100%) of [^{35}S]GTPγS binding was measured using the reference quinpirole (10 μM).

Data Analysis. The resulting competition curves of the receptor binding experiments were analyzed by nonlinear regression using the algorithms in PRISM 3.0 (GraphPad Software, San Diego, CA). The data were fit using a sigmoid model to provide an IC_{50} value, representing the concentration corresponding to 50% of maximal inhibition. IC_{50} values were transformed to K_i values according to the equation of Cheng and Prusoff.[46]

Binding curves resulting from the [^{35}S]GTPγS binding assay were analyzed by nonlinear regression. The data were normalized (basal effect of 0%, maximum effect of the full agonist quinpirole of 100%) and then combined to get a mean curve. Nonlinear regression analysis of this curve provided the EC_{50} values representing the concentration corresponding to 50% of maximal stimulation as a measure of potency.

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Supporting Information Available: Experimental and spetroscopic data of nonkey target compounds **8aa**−**8aw**, **8ay**−**bs**, **8bu**, **8bv**, **8bx**−**cj**, **11**, **12**, **24**, **30**, **35**, and **36** and the respective precursors thereof; receptor binding data employing porcine 5-HT_2, D_1, α_1, and α_2 and the human D_{2long}, D_{2short}, D_3, and $D_{4.4}$ receptors; X-ray crystal structure determination details. This material is available free of charge via the Internet at http://pubs.acs.org.

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