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The 3,7-diazabicyclo[3.3.1]nonane scaffold for subtype selective nicotinic acetylcholine receptor (nAChR) ligands: Part 1. The influence of different hydrogen bond acceptor systems on alkyl and (hetero)aryl substituents

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Abstract

3,7-Diazabicyclo[3.3.1]nonane is a naturally occurring scaffold interacting with nicotinic acetylcholine receptors (nAChRs). When one nitrogen of the 3,7-diazabicyclo[3.3.1]nonane scaffold was implemented in a carboxamide motif displaying a hydrogen bond acceptor (HBA) functionality, compounds with higher affinities and subtype selectivity for $\alpha 4\beta 2^*$ were obtained. The nature of the HBA system (carboxamide, sulfonamide, urea) had a strong impact on nAChR interaction. High affinity ligands for $\alpha 4\beta 2^*$ possessed small alkyl chains, small un-substituted hetero-aryl groups or para-substituted phenyl ring systems along with a carboxamide group. Electrophysiological responses of selected 3,7-diazabicyclo[3.3.1]nonane derivatives to *Xenopus oocytes* expressing various nAChR subtypes showed diverse activation profiles. Compounds with strongest agonistic profiles were obtained with small alkyl groups whereas a shift to partial agonism/antagonism was observed for aryl substituents.

Graphical Abstract

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Supplementary data

Supplementary data associated with this article can be found in the online version at

Keywords

3,7-Diazabicyclo[3.3.1]nonane; Bispidine; Nicotinic acetylcholine receptor; nAChR; Structure-activity relationship

1. Introduction

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated excitatory cation channels and can form homomeric or heteromeric subtypes.^{1–4} Each nAChR complex is composed of a combination of five identical or different subunits ($\alpha 1$ – $\alpha 10$, $\beta 1$ – $\beta 4$, γ , δ and ϵ) capable of forming a water-filled pore in the cell membrane.^{1–4} Stimulation of these receptors have an impact on membrane potential and the release of diverse neurotransmitters, which is often subtype specific and can vary across areas of a specific organ, e.g. different brain areas.^{1–4} NACHRs have been proposed as potential drug targets for the treatment of various central nervous system (CNS) diseases.^{5–7} For example, $\beta 2$ -containing nAChRs have a wide-spread expression in the brain and subunit combination with $\alpha 4$, $\alpha 5$, $\alpha 6$, and/or $\beta 3$ are implemented in depression and addiction.^{8–11}

The majority of nAChR ligands have been derived from very potent natural products displaying the important pharmacophoric features found in the neurotransmitter acetylcholine (ACh) **1**.^{6,7,12} Cation- π /HB forces along with HBA interactions corresponding to the charged/protonable nitrogen and e.g. carbonyl or heteroaryl moieties, respectively, are involved in the interaction with the receptors.^{13–18}

(Di)azabicyclic octane and diazabicyclic nonane scaffold bearing compounds are the majority representing the nAChR pharmacopeia in the recent past.^{6,7} Among these bicyclic N-containing structural templates is 3,7-diazabicyclo[3.3.1]nonane.^{6,7} It is a naturally occurring scaffold also known as bispidine found e.g. in the nAChR ligand cytosine and sparteine, a sodium ion channel blocker.¹⁹ 3,7-diazabicyclo[3.3.1]nonane derivatives have been the subject of considerable interest in the field of novel nAChR compounds, but also as e. g., antiarrhythmic drugs, opioid receptor ligands, and as multidentate ligands for organometallic compounds.^{20–37} The most prominent 3,7-diazabicyclo[3.3.1]nonane compound interacting with nAChRs is the natural product cytosine **3** with high affinity for $\alpha 4\beta 2^*$ nAChR (Fig. 1; Table 1).^{38,39} Cytosine **3**, its derivative 3-(pyridine-3-yl)-cytosine (3PC) **4**, recently developed by us, and varenicline **5** (Chantix®, used for smoking cessation) (Fig. 1), derived from cytosine, have antidepressant-like effects in mice (Fig. 1; Table 1).^{40–43} All three compounds possess high affinity and partial agonist functionality for the $\alpha 4\beta 2^*$ subtype to a various degree, but the rigid compounds cytosine **3** and varenicline **5** have limited subtype selectivity.^{41–43}

Since the intact cytosine template is limited in its synthetic access, chemical space, ADMET properties, affinity and functional selectivity profiles, we revisited the 3,7-diazabicyclo[3.3.1]nonane ring system (bispidine) as a nAChR ligand itself. This scaffold is synthetically easily accessible via double Mannich reaction and displays one pharmacophoric element. To explore the chemical space around this scaffold further, 3,7-diazabicyclo[3.3.1]nonane was attached to a variety of aromatic and non-aromatic substituents via different HBA motifs. In contrast to cytosine **3** where the HBA system (pyridone) is fused to the 3,7-diazabicyclo[3.3.1]nonane scaffold, the HBA motifs of the synthesized derivatives are acyclic, thus compounds display higher flexibility. A similar approach, but limited to a carboxamide HBA motif and limited substitution pattern have been done by Targacept, Inc. which resulted in the development of the 03B14 β 2 agonist TC-6683/AZD1446 bearing the diazabicyclic system 3,7-diazabicyclo[3.3.0]octane.^{27–29} This compound showed positive effects on a rodent model for working memory. Our extensive study around the bispidine scaffold started with bispidine (3,7-diazabicyclo[3.3.1]nonane) itself which was tested for affinities at different nAChRs and functional properties. Simple 3,7-diazabicyclo[3.3.1]nonane compounds with different HBA systems, like carboxamides, sulfonamides and urea groups attached to simple alkyl or (heter)aryl substituents were synthesized (Fig. 2) to get more insight into structure activity relationships for nAChRs. Compounds were tested for their affinities, and selected candidates displaying nAChR affinity in the nanomolar range were additionally evaluated for their functionality in *Xenopus oocyte* experiments.

2. Results and discussion

2.1. Chemistry

The 3,7-diazabicyclo[3.3.1]nonane (bispidine) scaffold was synthesized according to a previously published method.^{24,25,46–48} N-benzyl-N'-*t*-boc-bispidinone **10** was obtained by a double Mannich reaction from commercially available *tert*-butyl 4-oxopiperidine carboxylate **9**, benzylamine, and paraformaldehyde. It was purified by flash chromatography.

The reduction of the carbonyl functionality of N-benzyl-N'-*t*-boc-bispidinone **10** was attempted by several published methods but in our hands none of them produced more than 33 % yield of the desired N-benzyl-N'-*t*-boc-bispidine **11**. We found the Huang-Minlon variation of the Wolff-Kishner reduction suitable to produce **11** in yields as high as 73 %, if the reaction temperature would not exceed 140 °C.^{24,25,49} The desired intermediate Nbenzyl-N'-*t*-boc-bispidine **11** was obtained after purification by flash chromatography.

N-benzylbispidine **12** could be obtained by cleaving the N-*t*-boc protection group under acidic conditions, e.g. with hydrochloric acid in 1,4-dioxane. Exceeding 140 °C in the above mentioned Wolff-Kishner reaction (Huang-Minlon variation) also lead to N-benzylbispidine **12** but side product formation hampered the purification process. N-benzylbispidine **12** could also be used as an intermediate to further substitute the secondary amine of **12**, but the purification of the N-benzyl protected intermediates was often more difficult and cumbersome than the purification of the N-*t*-boc protected intermediates. Furthermore, the

final N-benzyl deprotection often produced low yields depending on the nature of the substituent. Therefore, the N-benzyl protection group was cleaved first leading to N-*t*-boc protected intermediates, which could easily be purified and cleaved from the N-*t*-boc group in a final step (Scheme 1).

The N-benzyl protecting group was cleaved from N-benzyl-N'-*t*-boc-bispidine **11** using palladium on activated charcoal (Pd/C) 5 % as a catalysts under a hydrogen atmosphere. The resulting N-*t*-boc-bispidine **13** was obtained in quantitative yields and no further purification was necessary besides filtering off the catalyst.

N-*t*-boc-bispidine **13** was used as a starting material to introduce a wide variety of moieties to the bispidine backbone (Scheme 1). Different synthetic approaches were used to synthesize N-*t*-boc protected 3,7-diazabicyclo[3.3.1]nonane carboxamides, sulfonamides or urea compounds (Scheme 1).^{50–54} The N-*t*-boc protected intermediates **Boc-8**, **Boc-15–63**, and **Boc-67–69** were isolated and purified, but not analyzed and described in detail.

Boc-8 and **Boc-15–33** intermediates were synthesized by aminolysis of N-*t*-boc-bispidine and various carboxylic acid chlorides. Due to the simplicity of this reaction and the fact that many carboxylic acids are commercially available in form of their acid chlorides, we preferred this method. Purification was accomplished by flash chromatography. Aminolysis was also used to synthesize N-*t*-boc protected sulfonamides **Boc-34–40** and the urea compounds **Boc-41–42**. 1,1'-Carbonyldiimidazole (CDI) as coupling reagents was used when certain carboxylic acid chlorides were not available. For the CDI method, N-*t*-bocbispidine **13** was allowed to react with CDI, and N-carbonylimidazolyl-N'-*t*-boc-bispidine **14** was isolated after chromatographic purification. Then, **14** was activated with an excess of MeI, and Et₃N and the carboxylic acid were added subsequently. Flash chromatography provided the N-*t*-boc protected bispidinecarboxamides **Boc-44–55**. DCC was used as an alternative method, when CDI did not produce satisfying yields. Using the DCC method, N-*t*-boc-bispidine **13**, the carboxylic acid, DCC and N,N-dimethylaminopyridine (DMAP) were dissolved in CH₂Cl₂ at 0 °C and allowed to react at rt for 12 h. After filtering off the dicyclohexyl urea by-product, the N-*t*-boc protected 3,7-diazabicyclo[3.3.1]nonane carboxamides were purified by flash chromatography. Occasionally, a second filtration or a second chromatographic step was required to eliminate residual dicyclohexyl urea by-product.

For the synthesis of **Boc-67–69**, the three aliphatic, cyclic amines (pyrrolidine, morpholine and 4-benzylpiperidine) were allowed to react with CDI. The carbonylimidazole adducts **64–66** were obtained after extraction, and activated with methyl iodide, subsequently. The activated adducts were coupled with N-*t*-bocbispidine **13**, and the N-*t*-boc protected bispidine urea derivatives **Boc-67–69** were purified by flash chromatography.

A small homologous series **69–71** (methyl, ethyl, propyl) of acetylbispidine **8** was prepared to investigate the influence of the secondary versus a tertiary amine group at the 3,7-diazabicyclo[3.3.1]nonane scaffold on the interaction with $\alpha 4\beta 2^*$ nAChRs. The compounds were obtained by alkylating acetylbispidine **8** with alkyl iodides in the presence of K₂CO₃ in DMF. The final products could be obtained after flash chromatography. N-methyl-

acetylbspidine **70** has been synthesized before but was neither tested for nAChR affinity nor have analytical data been published.⁵⁵

The cleavage of the N-*t*boc protecting group from **Boc-8**, **Boc-15–63**, and **Boc-69–71** was accomplished by using acidic conditions at room temperature, either hydrogen chloride in 1,4-dioxane or anhydrous ZnBr₂ in CH₂Cl₂.⁵⁶ Both methods resulted in the desired bispidine derivatives **8**, **15–63**, and **67–69** after alkaline workup.

Most compounds were transferred into their corresponding salt forms, either fumaric or hydrochloric acid salts for in vitro testing. This is indicated as “F” or “H” for the compounds in the *Experimental Section* and the compounds are also analyzed in their salt forms. The salt formation step was advantageous for further purifying our final compounds from residual N-*t*boc-protected 3,7-diazabicyclo[3.3.1]nonane derivatives or other byproducts. Compounds **35–38**, **40**, **48**, **62**, **63**, and **70–72** were used as free bases.

2.2. Biological activity and structure-activity relationship (SAR)

The affinities of the 3,7-diazabicyclo[3.3.1]nonane derivatives **8**, **12–13**, **15–63**, and **67–72** were determined in radioligand binding studies as previously described.^{38,39,57} Membrane fractions of native tissue from Sprague-Dawley rat forebrains ($\alpha 4\beta 2^*$, $\alpha 7^*$), calf adrenals ($\alpha 3\beta 4^*$) or Torpedo californica electroplax ($(\alpha 1)_2\beta 1\gamma\delta$) were prepared and [³H]epibatidine ($\alpha 4\beta 2^*$, $\alpha 3\beta 4^*$, $(\alpha 1)_2\beta 1\gamma\delta$) and [³H]MLA ($\alpha 7^*$) were used as radioligands.

The K_i values of 3,7-diazabicyclo[3.3.1]nonane (bispidine), the two intermediates **12** and **13**, and of the final compounds **8**, **15–63**, and **67–72** are summarized in tables 2 and 3. The scaffold 3,7-diazabicyclo[3.3.1]nonane (bispidine) itself is interacting with nAChRs and has a K_i value of 600 nM for $\alpha 4\beta 2^*$. N-benzylbispidine **12** showed affinity for the $\alpha 3\beta 4^*$ subtype in the high nanomolar range (K_i = 569.6 nM) but no affinity for the other subtypes tested. In contrast, N-*t*boc-bispidine **13** has high affinity for the $\alpha 4\beta 2^*$ subtype in the low nanomolar range (K_i = 45 nM) whereas affinity for the $\alpha 3\beta 4^*$ subtype was in the low micromolar range (K_i = 1.3 μ M). In general, all active compounds except for the intermediate N-benzyl-bispidine **12** showed higher affinity for the $\alpha 4\beta 2^*$ nAChR subtype than for the other subtypes tested.

As we reported before, acetylbspidine **8** can be considered as a simplified cytosine **3** analog missing the pyridone moiety, but still displaying the same pharmacophoric components as **3** (Fig. 1), the protonable secondary nitrogen and the carbonyl functionality which serves as a HBA system.^{24–26} Compound **8** can also be considered as a more rigid and stable analog of ACh **1**. In contrast to the rigid cytosine **3** (table 1), acetylbspidine **8** showed reduced affinity for all subtypes measured (table 2), but still preference for the $\alpha 4\beta 2^*$ subtype (K_i = 5.6 nM) and higher affinity than tetrahydrocytosine **6** (K_i = 17 nM), an analog with intermediate rigidity.

Acyclic and small cyclic alkyl substituents—Methylene homologs **15** and **16** of acetylbspidine **8** provided compounds with similar high affinity for the $\alpha 4\beta 2^*$ receptor (K_i for **8**: 5.6 nM; **15**: 4.5 nM; **16**: 3.6 nM). The butan-1-one homolog **16** exhibited higher affinity for the $\alpha 3\beta 4^*$ subtype compared to **8**, but still displayed an about 74-fold higher

affinity for the $\alpha 4\beta 2^*$ receptor. In contrast, acetylbispidine **8** showed similar affinity for $\alpha 3\beta 4^*$ and $\alpha 7^*$ receptors. Compound **17**, bearing an isopropyl chain, had lower affinities for the $\alpha 4\beta 2^*$ ($K_i = 50.3$ nM) and the $\alpha 3\beta 4^*$ subtypes ($K_i = 828$ nM) than its unbranched isomer **16**. A cyclopentyl moiety (compound **43**) and its homolog bearing a cyclopentylmethyl moiety (compound **55**) showed affinities for the $\alpha 4\beta 2^*$ subtype in the low nanomolar range (K_i for **43**: 10.8 nM; **55**: 43.5 nM) whereas its cyclohexyl homolog **18** was inactive at all nAChR subtypes tested. These data indicate that small hydrocarbon moieties in close proximity to the carbonyl functionality contribute to high affinity for the $\alpha 4\beta 2^*$ nAChR subtype. Compounds **8**, **15–17**, and **43** have also been synthesized and evaluated by Targacept, Inc. (**8**: $\alpha 4\beta 2^*$: $K_i = 18.7$ nM; $\alpha 4\beta 2^*$: $K_i = 20.2$ nM; $\alpha 7^*$: 3277.9 nM; **15**: $\alpha 4\beta 2^*$: $K_i = 12.2$ nM; $\alpha 4\beta 2^*$: $K_i = 10.4$ nM; $\alpha 7^*$: 795.1 nM; **16**: $\alpha 4\beta 2^*$: $K_i = 8.1$ nM; $\alpha 4\beta 2^*$: $K_i = 2.9$ nM; $\alpha 7^*$: 230.3 nM; **17**: $\alpha 4\beta 2^*$: $K_i = 101.6$ nM; $\alpha 4\beta 2^*$: $K_i = 44.4$ nM; $\alpha 7^*$: 644.7 nM; **43**: $\alpha 4\beta 2^*$: $K_i = 26.6$ nM; $\alpha 4\beta 2^*$: $K_i = 20.2$ nM; $\alpha 7^*$: 211.2 nM).^{22,23,28} Compound **18** has only been claimed in this patent but no biological data have been published. The use of a different radioligand and different tissues for the membrane preparation may account for some, but minor differences in K_i values compared to our results.

It is known that a tertiary amine motif in cytosine, displayed in the naturally occurring compound caulophylline, reduces the $\alpha 4\beta 2^*$ nAChR affinity.³⁷ Similar observations have also been made for tetrahydrocytosine **6** and its N-methyl analog **7**. To study the more flexible compounds bearing the same diazabicyclic scaffold attached to the same HBA linker, we evaluated three N-alkyl analogs of acetylbispidine (cpds **70–72**). There is a dramatic decrease of $\alpha 4\beta 2^*$ affinity from N-methyl ($K_i = 200$ nM) to N-propyl ($K_i > 5,000$ nM; table 3). Only the methyl group was tolerated but produced a compound with a 35-fold lower affinity for the $\alpha 4\beta 2^*$ subtype.

Simple aryl substituents—With the introduction of an aromatic moiety at the 3,7-diazabicyclo[3.3.1]nonane carboxamide template (**19**), a reduction of affinity was observed compared to acetylbispidine **8**, but **19** displayed higher affinity comparing with its saturated cyclohexyl derivative **18**. Benzoylbispidine **19** exhibited affinity for the $\alpha 4\beta 2^*$ nAChR subtype in the nanomolar range ($K_i = 453.6$ nM) and did not show any affinity for the other receptor subtypes tested.

Additional substitution at the aromatic part provided important insight into structural requirements for $\alpha 4\beta 2^*$ nAChR ligands. The steric input caused by substituents at the ortho position resulted in a complete loss of activity. Substitution at the ortho position (compounds **44**, **20**, and **21**) is likely to force the aromatic ring to an out-of-plane arrangement which seems to be not tolerated by the nAChRs evaluated. Compounds with a substitution at the meta position of the phenyl ring **45** (3-fluoro) and **46** (3-trifluoromethyl) showed affinity in the nanomolar range for the $\alpha 4\beta 2^*$ subtype ($K_i = 386.4$ nM and $K_i = 147.1$ nM, respectively), but compounds **22** (3-chloro) and **23** (3-nitro) were inactive at this receptor subtype. This seems to indicate that small electron withdrawing groups (fluoro **45**, trifluoromethyl **46**) are still tolerated in the meta position, whereas bulkier electron withdrawing groups (chloro **22**, nitro **23**) are not.

Compounds with substitution at the para position of the phenyl ring **24–28**, **47–49**, and **56** exhibited higher affinities for $\alpha 4\beta 2^*$ nAChR in most cases compared with the meta-substituted ligands except for the bulky 4-*tert*-butyl group (**25**, K_i values > 10,000 nM), or if an additional ortho substituent was present (2,4-dimethoxy compound **29**). Halogen substituents (compound **26**, **27**, and **28**) increased the affinity for $\alpha 4\beta 2^*$ receptors compared to benzoylbispidine **19** (K_i = 453.6 nM). The 4-chloro **27** and 4-bromo **28** analogs showed very similar K_i values (**27**: K_i = 130.2 nM; **28**: K_i = 138 nM) and slightly higher affinities comparing with the 4-fluoro derivative **26**. (K_i = 197.3 nM). A methyl group (**24**, K_i = 221 nM) also enhances affinity for $\alpha 4\beta 2^*$ receptors while keeping high subtype selectivity. Interestingly, the nitrile group (compound **48**) was capable to increase $\alpha 4\beta 2^*$ affinity by a factor of ten compared to **24** (methyl group) along with high subtype selectivity. This group, displaying a polarized triple bond, has a tiny steric demand and is about eight times smaller than a methyl group. Because of its strong dipole character, polar interactions or hydrogen bonds are possible. Compared to the 4-cyanobenzoylbispidine **48**, the 4-nitro group (compound **49**) showed a similar K_i value for the $\alpha 4\beta 2^*$ subtype (K_i = 15.9 nM), but lower subtype selectivity displaying K_i values for $\alpha 3\beta 4^*$ and $\alpha 7^*$ subtypes in the micromolar range. Compound **56** bearing a hydroxy group in the para position, which can serve as a hydrogen bond donor, showed also high affinity (K_i = 104.6 nM) for the $\alpha 4\beta 2^*$ nAChR subtype. In general, electron withdrawing groups exhibited increased affinity for the $\alpha 4\beta 2^*$ nAChR subtype. Also, the introduction of a π -electron rich substituent in position 4 had the same effect on affinity for $\alpha 4\beta 2^*$. In addition, it provides insight about spatial requirements if the aromatic part directly attached to the carbonyl function is considered as an arenologue spacer. Fused ring systems (compound **32** and **33**) showed no activity or reduced affinity, respectively, compared to the biphenyl derivative **47** (K_i = 39.9 nM). The 1-naphthoyl derivative **32** mimicking an ortho/meta substitution was lacking any affinity for the subtypes tested, whereas 2-naphthoyl derivative **33**, which mimicks a meta/para substitution displayed a similar K_i value for $\alpha 4\beta 2^*$ (K_i = 447 nM) as benzoylbispidine **19**. Except for the 4-biphenyl derivative **47** ($\alpha 3\beta 4^*$: K_i = 1.1 μ M) and the 4-nitro derivative **49** ($\alpha 3\beta 4^*$: K_i = 4.2 μ M; $\alpha 7^*$: K_i = 1.7 μ M), no compound showed activity for the other tested receptor subtypes. Taken together, these data show that derivatives with a substitution at the ortho position of the phenyl ring are not tolerated by the receptor, regardless of the nature of the substituent. Derivatives with a substituent at the meta position are only tolerated if the substituents are small electron withdrawing groups. Bulkier electron withdrawing substituents are not tolerated. And derivatives with a substitution at the para position showed the broadest tolerance. Both, small electron donating as well as electron withdrawing groups, resulted in compounds with high affinity for the $\alpha 4\beta 2^*$ nAChR subtype.

Heteroaryl substituents—Diverse heteroaryl containing derivatives (**30–31**, **50–54**, and **57–63**) were tested for their ability to compete with [3 H]epibatidine or [3 H]MLA (table 2). The 3-pyridyl moiety (compound **50**) has an almost identical affinity for the $\alpha 4\beta 2^*$ nAChR subtype compared to **19**, also displaying high subtype selectivity. An additional bromo substituent in the 5 position (compound **51**) increases affinity slightly, and the incorporation of an additional nitrogen (pyrazine derivative **57**) had a strong influence on the affinity for $\alpha 4\beta 2^*$ (K_i = 73.2 nM) together with a high subtype selectivity profile. Other ring equivalents like 2-furanyl (**30**) and 2-thiophenyl (**31**) showed affinity in the low nanomolar

range for the $\alpha 4\beta 2^*$ receptor subtype (**30**: $K_i = 21.4$ nM; **31**: $K_i = 17.6$ nM). Whereas compound **31** displayed high subtype selectivity, the furanyl containing compound **30** showed affinity for the $\alpha 3\beta 4^*$ subtype, but in the micromolar range ($K_i = 2.2$ μ M). Targacept, Inc. also synthesized and evaluated the 2-furanyl analog **30** as a nAChR ligand and the reported affinities (r $\alpha 4\beta 2^*$: $K_i = 31$ nM using [3 H]nicotine on rat brain membrane fractions; h $\alpha 4\beta 2^*$: $K_i = 9.9$ nM using [3 H]nicotine on SH-EP1 clonal cell membrane fractions; r $\alpha 7^*$: 15 μ M using [3 H]MLA on rat brain membrane fractions) correspond well with our data.^{22,23,28} The N-methylpyrrol-2-yl derivative (**59**) showed less affinity for the $\alpha 4\beta 2^*$ subtype compared to **30** and **31**, which could be due to its N-methyl substituent mimicking an ortho-substituent. In contrast to **44** (2-methylphenyl), which is lacking any affinity, **59** displayed a K_i value of 661.6 nM for this subtype. Bispidine amide derivatives substituted with small five-membered aromatic ring systems **30** and **31**, including hetero atoms with hydrogen bond acceptor properties, are likely to enhance the affinity for $\alpha 4\beta 2^*$ nAChR.

Fused heteroaryl substituents—The influence of fused aryl systems (naphthoyl derivatives **32** and **33**) was already mentioned above, but the introduction of an additional nitrogen atom at various positions created some additional important aspects. If the nitrogen is in close proximity to the carbonyl function (e.g. 2-quinolinyl compound **52**, 2-indole compound **60**, or 3-indole compound **61**), the affinity drops enormously or even disappears, and this is regardless of the HB nature of this nitrogen. Interestingly, the naphthoyl derivative **33**, showed affinity in the higher nanomolar range for $\alpha 4\beta 2^*$ ($K_i = 447.2$ nM), whereas the nitrogen in **52** causes a dramatic drop ($K_i > 1,000$ nM). In contrast, the quinolin-6-yl analog **54** displayed an increase in affinity ($K_i = 81.3$ nM) compared to its non nitrogen containing naphthoyl derivative **33**. The affinity of the naphthoyl derivative **32**, which showed a K_i value of $> 10,000$ nM for $\alpha 4\beta 2^*$ could be improved by the introduction of a nitrogen observed in the quinolin-4-yl analog **53** displaying a K_i value of 162.1 nM for $\alpha 4\beta 2^*$. In summary, fused N-heteroaryl systems with nitrogen atoms in close proximity to the HBA/carbonyl group showed a reduced affinity for the $\alpha 4\beta 2^*$ subtype compared to compounds bearing the nitrogen atom in a longer distance to this group.

HBA linkers—To investigate the influence of the carboxamide linker as the HBA group, we replaced it by a sulfonamide or urea group. As shown in table 3 the two sulfonamides **34** and **35** do not exhibit any affinity at the tested receptor subtypes. Compounds **36** (3-cyano), **37** (4-methyl), and **38** (4-cyano) exhibited affinity for the $\alpha 4\beta 2^*$ subtype in the high nanomolar range (**36**: $K_i = 970.4$ nM; **37**: $K_i = 858.3$ nM; **38**: $K_i = 645.1$ nM), while showing no affinity for the other nAChR subtypes tested. Interestingly, the small electron withdrawing 3-cyano group (compound **36**) exhibited a similar low affinity than the small electron donating 4-methyl group (compound **37**). The small electron withdrawing 4-cyano group (compound **38**) displayed a slightly higher affinity for the $\alpha 4\beta 2^*$ nAChR. The introduction of a nitro group at the para position of the phenyl ring (compound **40**) resulted in a K_i value of 135.2 nM for the $\alpha 4\beta 2^*$ subtype. In contrast, the exchange of this nitro group by a bromo atom at the para position (compound **39**), caused a nonactive compound for the $\alpha 4\beta 2^*$ subtype. Within this subset of bispidine sulfonamides, only compound **40** showed a weak affinity for the $\alpha 3\beta 4^*$ subtype ($K_i = 5.7$ μ M). It appears that either small

electron withdrawing groups in the meta or para position or electron donating groups in the para position generate compounds with affinity for the $\alpha 4\beta 2^*$ nAChR. However, it is not explainable, why the 4-bromo compound is inactive at the nAChR, whereas the 4-nitro compound showed affinity in the nanomolar range. So, sulfonamide derivatives **34–35** and **37–40** compared with their corresponding carboxamide analogs **8, 19, 24, 48, 28, and 49** (see table 2) exhibited lower or no affinity for the $\alpha 4\beta 2^*$ subtype. Thus, the replacement of the carboxamide linker by a sulfonamide group erases or decreases the affinity of the compounds for the $\alpha 4\beta 2^*$ subtype. The sulfonamide linker has a weaker HB basicity than the carboxamide, but this difference is too small to explain the strong influence on affinity. The impact of change in linker geometry and therefore the orientation of the HBA system in space seem to be of much higher importance.

Since both an acyclic amide and acyclic urea have about the same HB basicity, compounds with urea linker were investigated for affinity. The N,N-dimethyl urea compound **41** showed an affinity in the nanomolar range ($K_i = 499.3$ nM) for the $\alpha 4\beta 2^*$ subtype, but the homologous N,N-diethyl urea analog **42** lost its affinity. Interestingly, compound **41** displayed a 10-fold lower affinity for the $\alpha 4\beta 2^*$ nAChR than the corresponding carboxamide analog **17**. From the three cyclic urea compounds **67–69** only the morpholino compound **68** had affinity for the $\alpha 4\beta 2^*$ subtype, however, only in the micromolar range ($K_i = 3.8$ micromolar). The carboxamide analog **43** exhibited high affinity in the low nanomolar range ($K_i = 10.8$ nM), whereas its urea analog **67** was not active. Taken together this emphasises that the urea group cannot replace the carboxamide linker at the bispidine backbone and that bulkier alkyl groups are not tolerated by the receptor. Similar observations have been obtained in the affinity evaluation of $\alpha 7^*$ ligands bearing the 1,4-diazabicyclo[3.2.2]-nonane scaffold which was directly linked via a sulfonamide or urea motif to a spectrum of phenyl substituents.⁵⁶ The affinity dropped enormously in this case in contrast to a carbamate functionality used.⁵⁶

Selected compounds showing affinity for $\alpha 4\beta 2^*$ in the lower nanomolar range were evaluated electrophysiologically in an initial characterization for their functionality using human and mouse (for muscle) nAChRs expressed in *Xenopus* oocytes (Fig. 3).^{59–61} The observed responses should help to promote certain compounds for more detailed and complete functional evaluation in the future. Most compounds showed a tendency towards a partial agonistic/antagonistic profile for $\alpha 4\beta 2^*$ except compound **16** bearing a simple alkyl chain. Possible agonistic effects for $\alpha 3\beta 4^*$ were found for compounds **15, 16** and **43**. All of them are displaying small acyclic and cyclic substituents. For compounds **8, 16, and 43**, belonging to the same structural category, agonism at $\alpha 7$ was observed. There were only weak or no effects on the muscle type. The scaffold 3,7-diazabicyclo[3.3.1]nonane (bispidine) showed weak activation of $\alpha 7$, and even lower activity at other nAChR subtypes. When a spacer motif was introduced, e.g. a methylene motif for compound **43**, obtaining compound **55**, the agonistic effect at $\alpha 3\beta 4^*$ and $\alpha 7$ of **43** changed to having essentially no effect at $\alpha 3\beta 4^*$ and apparent antagonistic activity at $\alpha 7$ and muscle types. In general, small alkyl substituents showed the tendency towards agonism at $\alpha 4\beta 2^*$, $\alpha 3\beta 4^*$ (strongest for compound **16**), and $\alpha 7$, whereas aromatic substituents displayed partial agonism/antagonism (e.g. compound **47**). Several research groups have used the bispidine scaffold for the

development of nAChR ligands like mentioned before, but most of them were focused on the development of $\alpha 4\beta 2$ agonists and the chemical space used was limited. Our first part of an extensive SAR investigation around the bispidine scaffold showed that a carboxamide HBA system was preferred over other HBA systems investigated here. Para-substitution in the phenyl group series was best tolerated and could serve as a starting point for further evaluation of the chemical space for $\alpha 4\beta 2^*$ ligands. Compounds #55 and #47 gave first hints that the introduction of a spacer motif has an important impact on functionality leading to ligands with a possible antagonistic profile speculating about an additional binding site accessible through a spacer motif. Therefore, a more detailed SAR examination on spacer motifs will be presented in another study (“part 2”). Both studies were the foundation for the development of *in vivo* active compounds recently published.⁶²

2.3. Physicochemical properties and druglikeness

ACD/ADME Suite 5.0 (ACD/Labs) software has been used to calculate physicochemical properties and druglikeness parameters (e.g. ClogP, TPSA, and logBB; Tables 1, 2 and 3). The compounds do not violate the Ro5.⁶³ Some physicochemical properties associated with drug-likeness parameters for CNS drugs are ideally between 250 and 350 for Mr, ClogP between 1–3, PSA < 75, and more parameters important for CNS compounds have been calculated (Table 4; supplementary data) for compounds showing nanomolar affinity for $\alpha 4\beta 2^*$ (K_i < 1,000 nM).⁶⁴ Most active compounds showed “good” or “acceptable” values for most parameters calculated. There were no correlations between affinity and ClogP or TPSA values. The logBB values can also be used to estimate the likelihood for blood brain barrier (BBB) penetration. Values below –0.5 would reflect very poor or no BBB penetration and > 0.7 very high penetrants. The cyano group is producing a borderline TPSA value, and especially the nitro group shows the least ideal values for TPSA and logBB. In addition, the nitro group is also a toxophoric group and along with bromoaryl substituents which could also produce toxic metabolites, both are here only used to get a fast SAR insight regarding lipophilic input, steric aspects, and additional pharmacophoric points.

3. Conclusions

We prepared a simple series of 3,7-diazabicyclo[3.3.1]nonane based compound series with three different HBA linkers and evaluated their affinities and initial functionality for different nAChR subtypes. The scaffold 3,7-diazabicyclo[3.3.1]nonane displaying the essential pharmacophoric element for cation- π /HB interaction has an affinity for $\alpha 4\beta 2^*$ in the higher nanomolar range (K_i = 600 nM) and weak $\alpha 7$ agonism. Intermediates in the synthetic pathway of this series like N-*tboc*-bispidine **13** and N-benzyl-bispidine **12** are active at nAChRs and display different subtype preferences. Structure-activity relationship studies revealed that the carboxamide linker was preferred over a sulfonamide or urea motif. Active carboxamide derivatives showed selectivity for the $\alpha 4\beta 2^*$ nAChR except for small hydrocarbon substituents which exhibit high affinity for the $\alpha 4\beta 2^*$ nAChR subtype but comparably low selectivity over $\alpha 3\beta 4^*$ and $\alpha 7^*$ subtypes. These compounds displayed also more agonistic profiles for the neuronal subtypes. Para-substituted benzoylbispidines with small electron withdrawing groups were well tolerated by the $\alpha 4\beta 2^*$ nAChR displaying

nanomolar affinities. The impact of heteroaryl substituents (five-membered, six-membered, fused) on $\alpha 4\beta 2^*$ affinity were dependent on size and the position of the heteroatom.

Further SAR studies will focus on the influence of an additional spacer motif between the HBA system and the attached substituent moiety.

In summary, the 3,7-diazabicyclo[3.3.1]nonane scaffold can serve as an important starting point for the development of nAChR compounds with diverse and desired affinity and functionality pattern.

4. Experimental section

All reagents and solvents were obtained from various suppliers (ABCR, Acros, Aldrich, Alfa Aesar, Fluka, Merck or Sigma) and used without further purification unless otherwise noted. Dichloromethane was freshly distilled from calcium hydride. Methanol was treated with sodium, distilled afterwards and stored under nitrogen. Sodium wires were used to dry diethyl ether, petroleum ether, tetrahydrofuran, and toluene. Water was taken from a water purification system PureLab Plus UV (ELGA Labwater) or Direct-Q™ 5 (Millipore). Amines were purified prior to use with a Kugelrohr distillation apparatus (Büchi). Reactions were monitored by thin-layer chromatography (TLC) using aluminum sheets coated with silica gel 60 F₂₅₄ (Merck). Compounds were visualized using UV light (254 or 365 nm) and using a KMnO₄ (1 %). Column chromatography was carried out on silica gel (0.035–0.060 nm) using different mixtures of CH₂Cl₂ with MeOH (40:1, 20:1 or 9:1) or of PE with EtOAc (4:1 or 3:1) as mobile phases. ¹H NMR spectra (400 or 500 MHz) and ¹³C NMR spectra (100 or 125 MHz) were recorded on an Avance 400 or on an Avance 500 NMR spectrometer (Bruker). All NMR spectra were recorded at rt. Chemical shifts (δ) are given in parts per million (ppm) relative to the remaining protons of the deuterated solvents used as internal standard. Coupling constants *J* are given in Hertz (Hz) and spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet) and br (broad). Mass spectra were recorded on an API 2000 mass spectrometer with an electron spray ionization source (Applied Biosystems) coupled to an Agilent 1100 HPLC system (LC/ESI-MS) or on a Varian 500-MS mass spectrometer (ESI-MS). The purity of the compounds was determined by LC/ESI-MS or a Shimadzu Prominence HPLC system at an appropriate wavelength. HRMS runs were performed on Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS. All compounds proved to possess 95 % purity. Melting points were determined in open capillary tubes with a melting point apparatus (Weiss-Gallenkamp) or with a Melting Point B-540 (Büchi) and are uncorrected. Infrared spectroscopy was performed with a Tensor-27 FTIR infrared spectrometer (Bruker Optic) using KBr pellet or with a Nicolet iS10 (Thermo Scientific). Elemental microanalyses (C, H, N) were performed with a VarioEL (Elementar Analysensysteme) or a Costech elemental combustion apparatus and the determined values are generally within ± 0.4 % of the theoretical values. Hydrogen for hydrogenations was produced by a Hogen GC hydrogen generator (Proton Energy Systems) or by a 60H hydrogen generator (Parker, domnick hunter). Lyophilizations were performed with an Alpha 1–4 LSC freeze dryer (Martin Christ).

Compounds in their salt form are named with “F” or “H” along with their number, and they are also analyzed in their salt forms.

4.1. General procedure A: Synthesis of N-tboc protected bispidinecarboxamides, bispidinesulfonamides, or bispidine urea derivatives

The appropriate carboxyl chloride, sulfonyl chloride, or carbamoyl chloride (1 mmol), either neat or dissolved in dry toluene (1–2 mL), was added dropwise to a stirred solution of N-tboc-bispidine **13** (230 mg, 1 mmol) and Et₃N (101 mg, 1 mmol) in dry toluene (5 mL) at rt. The volatiles were removed under reduced pressure after 2 h and the residue was purified by flash chromatography (silica gel, mixtures of CH₂Cl₂ and MeOH - 40:1, 20:1 or 9:1).

4.2. General procedure B: Synthesis of N-tboc protected bispidinecarboxamides

Methyl iodide (570 mg, 4 mmol) was added to a stirred solution of **14** (320 mg, 1 mmol) dissolved in dry MeCN (2 mL) and dry THF (2 mL) at rt. The volatiles were removed under reduced pressure after 24 h, the residue was dissolved in dry MeCN (4 mL), and Et₃N (101 mg, 1 mmol) and the appropriate carboxylic acid (1 mmol) were added. The solution was allowed to stir at rt for 12–120 h before the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (silica gel, mixtures of CH₂Cl₂ and MeOH - 40:1, 20:1 or 9:1).

4.3. General procedure C: Synthesis of N-tboc protected bispidinecarboxamides

The appropriate carboxylic acid (1 mmol) and N-tboc-bispidine **13** (248 mg, 1.1 mmol) were dissolved in dry CH₂Cl₂ (5 mL) and cooled to 0 °C. DMAP (6.1 mg, 0.05 mmol) and DCC (206 mg, 1 mmol) were added and the mixture was allowed to warm up and stir at rt. The precipitate was filtered off after 12 h and washed with cold CH₂Cl₂ (2 mL). The solvent of the filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography (silica gel, mixtures of CH₂Cl₂ and MeOH - 40:1, 20:1 or 9:1).

4.4. General procedure D: Cleavage of the N-tboc protecting group from N-tboc protected bispidine derivatives

HCl in 1,4-dioxane (4 M, 4–5 mL) was added to a stirred solution of the N-tboc protected bispidine derivative (0.2 – 1.0 mmol), dissolved in 4–5 mL of 1,4-dioxane, and the mixture was allowed to stir at rt for 2–12 h. The volatiles were removed under reduced pressure and before the residue was dissolved in KOH solution (0.25 M, 20 mL) and extracted with CH₂Cl₂ (3–5 × 20 mL). The combined organic layers were washed with saturated NaHCO₃ solution (10 mL), water (10 mL), dried with MgSO₄ and filtered. The product was obtained after evaporating the solvent under reduced pressure.

4.5. General procedure E: Cleavage of the N-tboc protecting group from N-tboc protected bispidine derivatives

The N-tboc protected bispidine derivative (0.2 – 1.0 mmol) was dissolved in dry CH₂Cl₂ (5 mL), anhydrous ZnBr₂ (2–3 equiv.) was added, and the mixture was allowed to stir at rt for 12–120 h. After the removal of the volatiles under reduced pressure the residue was dissolved in KOH solution (0.25 M, 20 mL) and extracted with CH₂Cl₂ (5 × 20 mL). The

combined organic layers were washed with saturated NaHCO_3 solution (10 mL), water (10 mL), dried over MgSO_4 , and filtered. The product was obtained after evaporating the solvent under reduced pressure.

4.6. General procedure F. Formation of fumaric acid salts of bispidine derivatives

The amine (0.2 – 1.0 mmol) was dissolved in a mixture of Et_2O and MeOH (9:1, 2–5 mL). A saturated solution of fumaric acid in the same mixture of solvents was added dropwise to a stirred solution of the amine until no further precipitation was observed. The solution was kept at 4–8 °C overnight before the precipitate was filtered off and washed with the same mixture of solvents (2×5 mL) and dry Et_2O (5 mL). The solid was dissolved in water (20–30 mL), and freeze-dried.

4.7. General procedure G. Formation of fumaric acid salts of bispidine derivatives

The amine (0.2 – 1.0 mmol) was dissolved in isopropanol (3–5 mL), filtered, and heated to 70–80 °C. The same molar amount of fumaric acid was dissolved in isopropanol (3 mL) and also heated to 70–80 °C. The two solutions were combined and allowed to cool to rt. Dry Et_2O (10 mL) were added and the mixture was kept at 4–8 °C overnight. The solid was filtered off, washed with dry Et_2O (3×5 mL), dissolved in water (20–30 mL), and freeze-dried.

4.8. General procedure H: Synthesis of alkyl substituted acetylbispidine derivatives

Acetylbispidine **8** (110 mg, 0.65 mmol) was dissolved in 4 mL of dry DMF and K_2CO_3 (90.4 mg, 0.65 mmol) and the appropriate alkyl iodide (0.65 mmol) were added. The reaction was allowed to stir at rt for 12 h before the volatiles were removed under reduced pressure. The residue was dissolved in aqueous KOH solution (1M, 5 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried with MgSO_4 , filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using a mixture of CH_2Cl_2 and MeOH (20:1 or 9:1) as eluents. After evaporating the solvents the final products were obtained as clear oils.

4.9. 3,7-diazabicyclo[3.3.1]nonane dihydrochloric acid salt (bispidine dihydrochloric acid salt)

N-*t*-boc-bispidine **13** (150 mg, 0.66 mmol) was dissolved in 1,4-dioxane (3 mL) and a HCl/1,4-dioxane mixture (4M) was added. The volatiles were removed under reduced pressure after 6 h (stirring at rt). The residue was dissolved in 5 mL Et_2O and filtered. The precipitate was washed at least three times with Et_2O . The final compound was obtained as a white solid in 94 % yield; mp 272–279 °C (dec). ^1H NMR (400 MHz, D_2O) δ 2.01 (br s, 2H), 2.53 (br s, 2H); 3.43–3.57 (br m, 8H). ^{13}C NMR (100 MHz, D_2O) δ 24.0, 25.2, 46.0. HRMS for $\text{C}_7\text{H}_{14}\text{N}_2$: calc m/z = 127.123, found m/z = 127.1126. Anal. ($\text{C}_7\text{H}_{14}\text{N}_2 \cdot 2.0\text{HCl} \cdot 0.5\text{H}_2\text{O}$) C, H, N.

4.10. (1R, 5S)-1-(3,7-diazabicyclo[3.3.1]nonan-3-yl)ethanone fumaric acid salt (8F)

The N-*t*-boc protected compound was obtained by using general procedure A with acetyl chloride (79 mg, 1 mmol). A mixture of CH_2Cl_2 and MeOH (9:1) was used for the

chromatographic purification. After removal of the solvents a white solid (268 mg, 98 %) was obtained. The *N*-*t*boc protection group of this solid (250 mg, 0.93 mmol) was cleaved using general procedure E with anhydrous ZnBr₂ (420 mg, 1.86 mmol) for 48 h and an off white solid **8** (146 mg, 93 %) was obtained after extraction. This solid **8** (48 mg, 0.29 mmol) was transferred to its fumaric acid salt **8F** by using the general procedure G with fumaric acid (33 mg, 0.29 mmol). Compound **8F** (66 mg, 69 %) was obtained as a white solid in 63 % yield over three steps; mp 152–156 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.93 (br m, 1H), 1.99 (br m, 1H), 2.16 (s, ³H), 2.32 (br m, 2H), 3.06 (br d, *J* = 14.1 Hz, 1H), 3.32 (br m, 2H), 3.44 (br d, *J* = 13.1 Hz, 1H), 3.50 (br d, *J* = 13.4 Hz, 1H), 3.54 (br d, *J* = 13.4 Hz, 1H), 4.05 (br d, *J* = 13.2 Hz, 1H), 4.35 (br d, *J* = 14.0 Hz, 1H), 6.68 (s, 2.5H). ¹³C NMR (125 MHz, D₂O) δ 24.3, 28.0, 28.4, 30.1, 48.7, 50.3, 50.6, 52.8, 137.4, 173.6, 178.9. LC/ESI-MS: positive mode *m/z* = 169.1 ([M + H]⁺). Purity (> 99.9 %). IR (KBr, cm⁻¹) 3455, 1696, 1624, 984, 975. Anal. (C₉H₁₆N₂O*1.25C₄H₄O₄*1.15H₂O) C, H, N.

4.11. (1R,5S)-tert-butyl 7-benzyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (10)

Compound **10** was obtained following the synthetic procedures published by Stead et al.⁴⁶ A solution of *tert*-butyl 4-oxopiperidine-1-carboxylate **9** (10.0 g, 50.2 mmol), acetic acid (2.9 mL, 50.9 mmol), and benzylamine (5.5 mL, 50.4 mmol) in methanol (40 mL) was added dropwise to a stirred suspension of paraformaldehyde (3.32 g, 110.6 mmol). The resulting mixture was heated under reflux for 1 h before another portion of paraformaldehyde (3.32 g, 110.6 mmol) was added. This mixture was heated at reflux for additional 5 h before the reaction was allowed to cool to rt and the solvent was evaporated under reduced pressure. The residue was dissolved in Et₂O (150 mL) and washed with aqueous KOH solution (1 M, 2 × 80 mL). The combined aqueous layers were extracted with Et₂O (3 × 50 mL). The combined organic layers were dried with MgSO₄, filtered, and the solvent was evaporated under reduced pressure. Flash column chromatography (silica gel, PE:EtOAc 3:1) of the residue afforded a white solid **10** (13.0 g, 78 %) after extensive evaporation of the solvents; mp 83 °C. ¹H NMR (500 MHz, CDCl₃) δ 1.53 (s, 9H), 2.42 (br m, 2H), 2.70 (br m, 2H), 3.17 (br m, 2H), 3.27 (br d, *J* = 12.5 Hz, 1H), 3.35 (br d, *J* = 12.5 Hz, 1H), 3.52 (br m, 2H), 4.41 (br d, *J* = 12.9 Hz, 1H), 4.57 (br d, *J* = 12.9 Hz, 1H), 7.24–7.38 (m, 5H). ¹³C NMR (125 MHz, CDCl₃) δ 28.7, 47.7, 50.0, 50.6, 58.8, 59.1, 62.0, 80.2, 127.4, 128.5, 128.9, 137.5, 154.9, 213.6. LC/ESI-MS: positive mode *m/z* = 331.3 ([M + H]⁺). Purity (> 98.5 %). IR (KBr, cm⁻¹) 1731, 1695. Anal. (C₁₉H₂₆N₂O₃) C, H, N.

4.12. (1R,5S)-tert-butyl 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (11)

A solution of **10** (18.9 g, 57.2 mmol), NaOH (10.0 g, 250 mmol), and hydrazine hydrate (80 %, 10.0 mL, 160 mmol) in 150 mL of diethylene glycol was heated at 125 °C under reflux conditions. After 2 h the reflux condenser was exchanged for a Dean-Stark apparatus and the mixture was heated at 140 °C for additional 8 h. After cooling to rt 250 mL of water were added and the resulting mixture was extracted with toluene (4 × 150 mL). The combined organic layers were washed with saturated NaHCO₃ solution (1 × 30 mL), water (2 × 30 mL), dried with MgSO₄ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (silica gel, PE:EtOAc 4:1) to afford **11** as a white solid (13.2 g, 73 %); mp 66 °C. ¹H NMR (500 MHz, CDCl₃) δ 1.52 (s, 9H),

1.61 (m, 1H), 1.66 (m, 1H), 1.79 (br s, 1H), 1.87 (br s, 1H), 2.16 (br d, $J = 10.9$ Hz, 1H), 2.22 (br d, $J = 10.9$ Hz, 1H), 2.89 (br d, $J = 10.8$ Hz, 1H), 2.99 (br d, $J = 10.9$ Hz, 1H), 3.05 (ddd, $J = 13.1, 3.9, 1.7$ Hz, 1H), 3.10 (ddd, $J = 13.1, 3.9, 1.7$ Hz, 1H), 3.30 (d, $J = 13.5$ Hz, 1H), 3.44 (d, $J = 13.5$ Hz, 1H), 3.99 (br d, $J = 13.1$ Hz, 1H), 4.16 (br d, $J = 13.1$ Hz, 1H), 7.19–7.34 (m, 5H). ^{13}C NMR (125 MHz, CDCl_3) δ 28.9, 29.2, 31.3, 47.7, 48.6, 58.9, 59.2, 63.7, 78.9, 126.8, 128.2, 128.7, 139.1, 155.2. LC/ESI-MS: positive mode $m/z = 317.1$ ($[\text{M} + \text{H}]^+$). Purity ($> 99.5\%$). IR (KBr, cm^{-1}) 1681. Anal. ($\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_2$) C, H, N.

4.13. (1R,5S)-3-benzyl-3,7-diazabicyclo[3.3.1]nonane fumaric acid salt (12F)

HCl dissolved in 1,4-dioxane (4 M, 6 mL) was added to a solution of **11** (192 mg, 0.61 mmol) in 1,4-dioxane (6 mL). The mixture was stirred at rt for 12 h before the volatiles were evaporated under reduced pressure. The residue was dissolved in aqueous KOH solution (1 M, 20 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were dried with MgSO_4 , filtered, and the solvent was evaporated under reduced pressure. General procedure F afforded **12F** as an off-white solid (139 mg, 0.42 mmol, 68 % over two steps); mp 167–170 °C (dec). ^1H NMR (500 MHz, MeOD) δ 1.77 (br m, 1H), 1.93 (br m, 1H), 2.10 (br s, 2H), 2.46 (dt, $J = 11.9, 2.4$ Hz, 2H), 3.13 (br m, 2H), 3.25 (dt, $J = 12.8, 2.8$ Hz, 2H), 3.43 (br m, 2H), 3.53 (s, 2H), 6.69 (s, 2.0H), 7.26–7.38 (m, 5H). ^{13}C NMR (125 MHz, MeOD) δ 28.6, 31.1, 50.5, 59.0, 64.0, 128.6, 129.6, 130.5, 136.2, 138.2, 171.5. LC/ESI-MS: positive mode $m/z = 217.4$ ($[\text{M} + \text{H}]^+$). Purity ($> 99.8\%$). IR (KBr, cm^{-1}) 3433, 1708, 1636, 986, 970. Anal. ($\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_2 \cdot 1.0\text{C}_4\text{H}_4\text{O}_4$) C, H, N.

4.14. (1R,5S)-tert-butyl 3,7-diazabicyclo[3.3.1]nonane-3-carboxylate fumaric acid salt (13F)

200 mg of Pd/C (5 %) was added to a solution of **11** (1.5 g, 4.74 mmol) in MeOH (7 mL) and the mixture was allowed to react under an atmosphere of hydrogen (10 psi) at rt for 4 h. After the mixture was filtered and washed thoroughly with MeOH the solvent was evaporated under reduced pressure. The product was obtained as a clear oil (1.05 g, 4.64 mmol) in 98 % yield. The free amine **13** was used for further syntheses. General procedure F was used to transfer this clear oil **13** (161 mg, 0.71 mmol) into a white solid, its fumaric acid salt **13F** (200 mg, 82 %); mp 170 °C (dec). ^1H NMR (500 MHz, D_2O) δ 1.47 (s, 9H), 1.86 (br d, $J = 13.5$ Hz, 1H), 1.96 (br d, $J = 13.5$ Hz, 1H), 2.25 (br s, 2H), 3.17 (br d, $J = 13.2$ Hz, 2H), 3.31 (br d, $J = 13.2$ Hz, 2H), 3.48 (br d, $J = 13.2$ Hz, 2H), 4.05 (br d, $J = 13.2$ Hz, 2H), 6.80 (s, 2.0H). ^{13}C NMR (125 MHz, MeOD) δ 28.2, 30.3, 30.5, 50.7, 50.9, 85.3, 137.6, 161.0, 174.4. LC/ESI-MS: positive mode $m/z = 226.9$ ($[\text{M} + \text{H}]^+$). Purity ($> 99.9\%$). IR (KBr, cm^{-1}) 3438, 1691, 1657, 985. Anal. ($\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_2 \cdot 1.0\text{C}_4\text{H}_4\text{O}_4 \cdot 0.1\text{H}_2\text{O}$) C, H, N.

4.15. (1R,5S)-tert-butyl 7-(1H-imidazole-1-carbonyl)-3,7-diazabicyclo[3.3.1]nonan-3-carboxylate (14)

N-*t*Boc-bispidine **13** (1.5 g, 6.63 mmol) was dissolved in dry THF (20 mL) and CDI (1.18 g, 7.29 mmol) was added. The solution was refluxed for 2 h before the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, mixture of CH_2Cl_2 and MeOH - 20:1). Evaporation of the solvents afforded a white solid **14** (1.98 g, 6.2 mmol, 93 %); mp 143 °C (dec). ^1H NMR (500 MHz, CDCl_3) δ 1.43 (s, 9H), 1.87 (s, 2H), 1.96 (br s, 2H), 3.01 (br m, 1H), 3.09 (br m, 1H), 3.26 (br s, 2H), 3.97 (br s,

1H), 4.25 (br m, ³H), 7.07 (s, 1H), 7.33 (s, 1H), 7.89 (s, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 27.8, 28.5, 31.2, 47.4, 48.8, 50.2, 51.8, 80.3, 118.0, 129.4, 137.0, 151.8, 155.0. LC/ESI-MS: positive mode *m/z* = 321.1 ([M + H]⁺), negative mode *m/z* = 319.9 ([M – H][–]). Purity (> 99.8 %). IR (KBr, cm^{–1}) 1675. Anal. (C₁₆H₂₄N₄O₃) C, H, N.

4.16. (1R,5S)-1-(3,7-diazabicyclo[3.3.1]nonan-3-yl)propan-1-one fumaric acid salt (15F)

The N-*t*-boc protected compound was obtained by using general procedure A with propionyl chloride (93 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (285 mg, 99 %) was obtained. The N-*t*-boc protection group of this solid (210 mg, 0.74 mmol) was cleaved using the general procedure D for 12 h and an off white solid **15** (132 mg, 97 %) was obtained after extraction. This solid **15** (35 mg, 0.19 mmol) was transferred to its fumaric acid salt **15F** by using the general procedure G with fumaric acid (22 mg, 0.19 mmol). Compound **15F** (32 mg, 54 %) was obtained as a white solid in 52 % yield over three steps; mp 158–161 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.07 (t, *J* = 7.5 Hz, ³H), 1.95 (br m, 1H), 2.00 (br m, 1H), 2.32 (br s, 2H), 2.50 (dt, *J* = 17.5, 7.5 Hz, 1H), 3.06 (br d, *J* = 13.1 Hz, 1H), 3.33 (br m, 2H), 3.46 (br m, 2H), 3.53 (br d, *J* = 13.2 Hz, 1H), 4.11 (br d, *J* = 13.2 Hz, 1H), 4.39 (br d, *J* = 13.8 Hz, 1H), 6.70 (s, 2.0H). ¹³C NMR (125 MHz, D₂O) δ 11.1, 28.1, 28.4, 29.9, 30.2, 48.9, 50.3, 50.6, 52.0, 137.5, 174.3, 182.0. LC/ESI-MS: positive mode *m/z* = 183.4 ([M + H]⁺). Purity (> 99.6 %). IR (KBr, cm^{–1}) 3440, 1679, 1638, 984, 972. Anal. (C₁₀H₁₈N₂O*1.0C₄H₄O₄*0.6H₂O) C, H, N.

4.17. (1R,5S)-1-(3,7-diazabicyclo[3.3.1]nonan-3-yl)butan-1-one fumaric acid salt (16F)

The N-*t*-boc protected compound was obtained by using the general procedure A with butyryl chloride (107 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (292 mg, 97 %) was obtained. The N-*t*-boc protection group of this solid (200 mg, 0.67 mmol) was cleaved using the general procedure D for 12 h and a yellowish oil **16** (128 mg, 97 %) was obtained after extraction. This oil **16** (45 mg, 0.23 mmol) was transferred to its fumaric acid salt **16F** by using the general procedure G with fumaric acid (27 mg, 0.23 mmol). Compound **16F** (46 mg, 73 %) was obtained as a white solid in 59 % yield over three steps; mp 159–161 °C (dec). ¹H NMR (500 MHz, D₂O) δ 0.94 (t, *J* = 7.4 Hz, ³H), 1.58 (br m, 2H), 1.95 (br m, 1H), 2.00 (br m, 1H), 2.32 (br s, 2H), 2.42 (br m, 1H), 2.53 (br m, 1H), 3.07 (br d, *J* = 13.9 Hz, 1H), 3.33 (br m, 2H), 3.42–3.55 (br m, ³H), 4.14 (br d, *J* = 13.4 Hz, 1H), 4.39 (br d, *J* = 14.1 Hz, 1H), 6.69 (s, 2.0H). ¹³C NMR (125 MHz, D₂O) δ 15.9, 20.7, 28.1, 28.4, 30.2, 38.5, 48.7, 50.2, 50.6, 52.2, 137.6, 174.5, 181.3. LC/ESI-MS: positive mode *m/z* = 197.4 ([M + H]⁺). Purity (> 99.8 %). IR (KBr, cm^{–1}) 3466, 1700, 1650, 1619, 994, 980. Anal. (C₁₁H₂₀N₂O*1.0C₄H₄O₄*0.3H₂O) C, H, N.

4.18. (1R,5S)-1-(3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-methylpropan-1-one fumaric acid salt (17F)

The N-*t*-boc protected compound was obtained by using the general procedure A with isobutyryl chloride (107 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a clear oil (281 mg, 95 %)

was obtained. The N-*t*-boc protection group of this oil (210 mg, 0.71 mmol) was cleaved using the general procedure D for 18 h and a clear oil **17** (130 mg, 93 %) was obtained after extraction. This oil **17** (64 mg, 0.33 mmol) was transferred to its fumaric acid salt **17F** by using the general procedure G with fumaric acid (38 mg, 0.33 mmol). Compound **17F** (60 mg, 57 %) was obtained as a white solid in 51 % yield over three steps; mp 165–168 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.04 (br m, ³H), 1.12 (br m, ³H), 1.95 (br m, 1H), 2.00 (br m, 1H), 2.33 (br s, 2H), 3.06 (br m, 2H), 3.28–3.39 (br m, 2H), 3.44 (br m, 1H), 3.52 (br m, 2H), 4.24 (br d, *J* = 12.7 Hz, 1H), 4.40 (br d, *J* = 13.3 Hz, 1H), 6.69 (s, 2.0H). ¹³C NMR (125 MHz, D₂O) δ 20.4, 21.1, 28.1, 28.5, 30.3, 33.5, 49.1, 50.1, 50.7, 52.1, 137.6, 174.4, 184.9. LC/ESI-MS: positive mode *m/z* = 197.3 ([M + H]⁺). Purity (> 99.7 %). IR (KBr, cm⁻¹) 3448, 1700, 1650, 1638, 984, 975. Anal. (C₁₁H₂₀N₂O*1.0C₄H₄O₄*0.45H₂O) C, H, N.

4.19. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(cyclohexyl)methanone fumaric acid salt (18F)

The N-*t*-boc protected compound was obtained by using the general procedure A with cyclohexanecarbonyl chloride (147 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (332 mg, 97 %) was obtained. The N-*t*-boc protection group of this solid (220 mg, 0.65 mmol) was cleaved using the general procedure D for 18 h and a white solid **18** (153 mg, 99 %) was obtained after extraction. This solid **18** (93 mg, 0.39 mmol) was transferred to its fumaric acid salt **18F** by using the general procedure G with fumaric acid (46 mg, 0.39 mmol). Compound **18F** (107 mg, 73 %) was obtained as a white solid in 70 % yield over three steps; mp 166–167 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.21 (br m, 2H), 1.31 (br m, 2H), 1.47 (br m, 1H), 1.65–1.82 (br m, 5H), 1.95 (br m, 1H), 2.00 (br m, 1H), 2.32 (br s, 2H), 2.75 (tt, *J* = 11.6, 2.9 Hz, 1H), 3.05 (br d, *J* = 13.3 Hz, 1H), 3.28–3.39 (br m, 2H), 3.43 (br d, *J* = 12.7 Hz, 1H), 3.51 (br m, 2H), 4.24 (br d, *J* = 12.9 Hz, 1H), 4.39 (br d, *J* = 13.6 Hz, 1H), 6.69 (s, 2.0H). ¹³C NMR (125 MHz, D₂O) δ 27.9, 28.07, 28.11, 28.3, 28.5, 30.3, 30.9, 31.7, 43.8, 50.0, 50.1, 50.7, 52.1, 137.6, 174.4, 183.9. LC/ESI-MS: positive mode *m/z* = 237.4 ([M + H]⁺). Purity (> 99.7 %). IR (KBr, cm⁻¹) 3443, 1709, 1633, 985, 975. Anal. (C₁₄H₂₄N₂O*1.0C₄H₄O₄*1.05H₂O) C, H, N.

4.20. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(phenyl)methanone fumaric acid salt (19F)

The N-*t*-boc protected compound was obtained by using the general procedure A with benzoyl chloride (141 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (325 mg, 97 %) was obtained. The N-*t*-boc protection group of this solid (200 mg, 0.61 mmol) was cleaved using the general procedure D for 12 h and an off white solid **19** (138 mg, 99 %) was obtained after extraction. This solid **19** (67 mg, 0.29 mmol) was transferred to its fumaric acid salt **19F** by using the general procedure G with fumaric acid (34 mg, 0.29 mmol). Compound **19F** (46 mg, 44 %) was obtained as a white solid in 42 % yield over three steps; mp 162–165 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.99 (br m, 1H), 2.07 (br m, 1H), 2.27 (br s, 2H), 3.35–3.37 (br m, 2H), 3.37–3.40 (br m, 2H), 3.46 (br d, *J* = 13.1 Hz, 1H), 3.98 (br m, 1H), 4.56 (br s, 1H), 6.73 (s, 1.8H), 7.53 (m, 5H). ¹³C NMR (125 MHz,

D₂O) δ 27.3, 29.1, 48.3, 48.5, 128.3, 129.7, 131.2, 136.2, 136.8, 171.3, 175.4. LC/ESI-MS: positive mode m/z = 231.4 ($[M + H]^+$). Purity (> 99.9 %). IR (KBr, cm⁻¹) 3420, 1701, 1613, 987, 969. Anal. (C₁₄H₁₈N₂O*0.9C₄H₄O₄*1.5H₂O) C, H, N.

4.21. (1R, 5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(2-chlorophenyl)methanone fumaric acid salt (20F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 2-chlorobenzoyl chloride (175 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (323 mg, 87 %) was obtained. The N-*t*-boc protection group of this solid (250 mg, 0.69 mmol) was cleaved using the general procedure D for 12 h and a clear oil **20** (180 mg, 99 %) was obtained after extraction. This solid **20** (96 mg, 0.36 mmol) was transferred to its fumaric acid salt **20F** by using the general procedure G with fumaric acid (42 mg, 0.36 mmol). Compound **20F** (109 mg, 79 %) was obtained as a white solid in 68 % yield over three steps; mp 183–184 °C (dec). ¹H NMR (500 MHz, D₂O, rotamers present) δ 1.95–2.07 (br m, 2H), 2.17–2.24 (br m, 1H), 2.43–2.50 (br m, 1H), 3.31–3.45 (br m, 4H), 3.49–3.65 (br m, ³H), 4.51–4.62 (br m, 1H), 6.68 (s, 1.8H), 7.35–7.61 (m, 4H). ¹³C NMR (125 MHz, D₂O, rotamers present) δ 27.8, 28.2, 29.9, 48.8, 49.5, 50.5, 53.0, 129.8, 130.7, 131.0, 132.6, 132.7, 134.2, 137.0, 137.6, 174.4, 175.5. LC/ESI-MS: positive mode m/z = 265.4 ($[M + H]^+$). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3433, 1705, 1648, 984, 977. Anal. (C₁₄H₁₇ClN₂O*0.9C₄H₄O₄*0.5H₂O) C, H, N.

4.22. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(2-nitrophenyl)methanone fumaric acid salt (21F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 2-nitrobenzoyl chloride (186 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a yellowish solid (371 mg, 97 %) was obtained. The N-*t*-boc protection group of this oil (290 mg, 0.77 mmol) was cleaved using the general procedure D for 18 h and a yellowish oil **21** (205 mg, 96 %) was obtained after extraction. This oil **21** (103 mg, 0.37 mmol) was transferred to its fumaric acid salt **21F** by using the general procedure G with fumaric acid (43 mg, 0.37 mmol). Compound **21F** (95 mg, 65 %) was obtained as a yellow solid in 61 % yield over three steps; mp 184–185 °C (dec). ¹H NMR (500 MHz, D₂O, rotamers present) δ 1.97–2.04 (br m, 2H), 2.16–2.24 (br m, 1H), 2.48 (br s, 1H), 2.34–3.73 (br m, 7H), 4.49–4.57 (br m, 0.5H), 4.68–4.76 (br m, 0.5H), 6.68 (s, 1.8H), 7.54 (br s, 0.5H), 7.70–7.76 (br m, 0.5H), 7.78 (m, 1H), 7.93 (t, J = 7.5 Hz, 1H), 8.35 (d, J = 8.3 Hz, 1H). ¹³C NMR (125 MHz, D₂O, rotamers present) δ 27.8, 28.1, 30.2, 48.7, 49.6, 50.8, 53.3, 128.3, 130.3, 133.6, 134.0, 137.6, 138.9, 147.2, 174.4, 175.4. LC/ESIMS: positive mode m/z = 276.4 ($[M + H]^+$). Purity (> 99.9 %). IR (KBr, cm⁻¹) 3442, 1706, 1647, 1531, 1348, 970. Anal. (C₁₄H₁₇N₃O₃*0.9C₄H₄O₄*0.6H₂O) C, H, N.

4.23. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(3-chlorophenyl)methanone fumaric acid salt (22F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 3-chlorobenzoyl chloride (175 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a clear oil (362 mg, 98 %) was obtained. The N-*t*-boc protection group of this oil (280 mg, 0.77 mmol) was cleaved using the general procedure D for 12 h and a white solid **22** (200 mg, 98 %) was obtained after extraction. This solid **22** (132 mg, 0.50 mmol) was transferred to its fumaric acid salt **22F** by using the general procedure G with fumaric acid (58 mg, 0.50 mmol). Compound **22F** (126 mg, 58 %) was obtained as a yellow solid in 56 % yield over three steps; mp 163–165 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.00 (br m, 2H), 2.22 (br s, 1H), 2.43 (br s, 1H), 3.30–3.40 (br m, ³H), 3.42–3.54 (br m, ³H), 3.84 (br d, *J* = 13.2 Hz, 1H), 4.50 (br d, *J* = 13.6 Hz, 1H), 6.73 (s, 2.65H), 7.39 (m, 1H), 7.50 (m, 2H), 7.57 (m 1H). ¹³C NMR (125 MHz, D₂O) δ 28.0, 28.4, 30.1, 49.3, 49.6, 50.6, 54.6, 127.9, 129.5, 133.26, 133.29, 137.0, 137.4, 139.0, 173.6, 176.4. LC/ESI-MS: positive mode *m/z* = 265.5 ([M + H]⁺). Purity (> 99.9 %). IR (KBr, cm⁻¹) 3445, 1699, 1616, 983, 969. Anal. (C₁₄H₁₇ClN₂O*1.32C₄H₄O₄*0.85H₂O) C, H, N.

4.24. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(3-nitrophenyl)methanone fumaric acid salt (23F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 3-nitrobenzoyl chloride (186 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a yellowish oil (369 mg, 97 %) was obtained. The N-*t*-boc protection group of this oil (290 mg, 0.77 mmol) was cleaved using the general procedure D for 18 h and a yellowish oil **23** (206 mg, 97 %) was obtained after extraction. This oil **23** (87 mg, 0.32 mmol) was transferred to its fumaric acid salt **23F** by using the general procedure G with fumaric acid (37 mg, 0.32 mmol). Compound **23F** (101 mg, 79 %) was obtained as a yellow solid in 74 % yield over three steps; mp 166–169 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.02 (br m, 2H), 2.23 (br s, 1H), 2.46 (br s, 1H), 3.34–3.46 (br m, 4H), 3.52–3.61 (br m, 2H), 3.82 (br d, *J* = 12.9 Hz, 1H), 4.55 (br d, *J* = 13.6 Hz, 1H), 6.68 (s, 2.0H), 7.77 (m, 1H), 7.90 (m, 1H), 8.38 (m, 1H), 8.40 (m 1H). ¹³C NMR (125 MHz, D₂O) δ 27.9, 28.4, 30.1, 49.4, 49.6, 50.5, 54.6, 125.0, 128.0, 133.2, 136.1, 137.6, 138.8, 150.7, 174.5, 175.4. LC/ESIMS: positive mode *m/z* = 276.4 ([M + H]⁺). Purity (> 99.7 %). IR (KBr, cm⁻¹) 3443, 1707, 1643, 1535, 1355, 978, 970. Anal. (C₁₄H₁₇N₃O₃*1.0C₄H₄O₄*0.75H₂O) C, H, N.

4.25. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(4-methylphenyl)methanone fumaric acid salt (24F)

The N-*t*-boc protected compound was obtained by using the general procedure A with p-toluoyl chloride (155 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a clear oil (322 mg, 92 %) was obtained. The N-*t*-boc protection group of this oil (200 mg, 0.58 mmol) was cleaved using the general procedure D for 12 h and an off white solid **24** (130 mg, 92 %) was obtained after extraction. This solid **24** (49 mg, 0.20 mmol) was transferred to its fumaric acid salt **24F** by using the general procedure G with fumaric acid (23 mg, 0.20 mmol). Compound

24F (49 mg, 56 %) was obtained as a white solid in 47 % yield over three steps; mp 166–167 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.99 (br m, 2H), 2.22 (br s, 1H), 2.40 (s, ³H), 2.4 (br s, 1H), 3.30–3.40 (br m, ³H), 3.43–3.53 (br m, ³H), 3.93 (br s, 1H), 4.50 (br s, 1H), 6.74 (s, 3.0H), 7.38 (m, 4H). ¹³C NMR (125 MHz, D₂O) δ 23.4, 28.1, 28.4, 30.3, 49.4, 49.7, 50.6, 54.8, 129.8, 132.1, 134.2, 137.3, 144.2, 173.4, 178.3. LC/ESI-MS: positive mode *m/z* = 245.4 ([M + H]⁺). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3429, 1702, 1610, 982. Anal. (C₁₅H₂₀N₂O*1.5C₄H₄O₄*1.0H₂O) C, H, N.

4.26. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(4-tertbutylphenyl) methanone fumaric acid salt (25F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 4-*tert*-butylbenzoyl chloride (197 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (384 mg, 98 %) was obtained. The N-*t*-boc protection group of this solid (340 mg, 0.88 mmol) was cleaved using the general procedure D for 12 h and a white solid **25** (242 mg, 96 %) was obtained after extraction. This solid **25** (113 mg, 0.39 mmol) was transferred to its fumaric acid salt **25F** by using the general procedure G with fumaric acid (46 mg, 0.39 mmol). Compound **25F** (100 mg, 60 %) was obtained as a white solid in 56 % yield over three steps; mp 151–153 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.34 (s, 9H), 2.00 (br m, 2H), 2.22 (br s, 1H), 2.43 (br s, 1H), 3.30–3.40 (br m, ³H), 3.43–3.54 (br m, ³H), 3.91 (br m, 1H), 4.51 (br m, 1H), 6.70 (s, 1.9H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H). ¹³C NMR (125 MHz, D₂O) δ 28.0, 28.5, 30.3, 33.2, 37.2, 49.4, 49.6, 50.6, 54.8, 128.6, 129.8, 134.4, 137.6, 157.3, 174.2, 178.1. LC/ESI-MS: positive mode *m/z* = 287.0 ([M + H]⁺). Purity (> 99.9 %). IR (KBr, cm⁻¹) 3491, 1705, 1611, 975. Anal. (C₁₈H₂₆N₂O*0.95C₄H₄O₄*1.6H₂O) C, H, N.

4.27. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(4-fluorophenyl)methanone fumaric acid salt (26F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 4-fluorobenzoyl chloride (159 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a clear oil (347 mg, 98 %) was obtained. The N-*t*-boc protection group of this oil (260 mg, 0.75 mmol) was cleaved using the general procedure D for 12 h and a clear oil **26** (178 mg, 96 %) was obtained after extraction. This oil **26** (87 mg, 0.35 mmol) was transferred to its fumaric acid salt **26F** by using the general procedure G with fumaric acid (41 mg, 0.35 mmol). Compound **26F** (126 mg, 95 %) was obtained as a white solid in 89 % yield over three steps; mp 157–158 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.00 (br m, 2H), 2.22 (br s, 1H), 2.43 (br s, 1H), 3.31–3.39 (br m, ³H), 3.44–3.54 (br m, ³H), 3.91 (br m, 1H), 4.51 (br m, 1H), 6.69 (s, 1.8H), 7.62 (m, 2H), 7.52 (m, 2H). ¹³C NMR (125 MHz, D₂O) δ 28.0, 28.4, 30.2, 49.4, 49.6, 50.6, 54.8, 118.6 (d, *J*_{C,F} = 22.1 Hz), 132.2 (d, *J*_{C,F} = 8.9 Hz), 133.4 (d, *J*_{C,F} = 3.3 Hz), 137.5, 166.4 (d, *J*_{C,F} = 248.2 Hz), 174.2, 177.2. LC/ESI-MS: positive mode *m/z* = 249.6 ([M + H]⁺). Purity (> 99.5 %). IR (KBr, cm⁻¹) 3427, 1701, 1616, 984, 969. Anal. (C₁₄H₁₇FN₂O*0.9C₄H₄O₄*1.5H₂O) C, H, N.

4.28. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(4-chlorophenyl)methanone fumaric acid salt (27F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 4-chlorobenzoyl chloride (175 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a clear oil (355 mg, 96 %) was obtained. The N-*t*-boc protection group of this oil (300 mg, 0.82 mmol) was cleaved using the general procedure D for 12 h and a clear oil **27** (211 mg, 97 %) was obtained after extraction. This oil **27** (83 mg, 0.31 mmol) was transferred to its fumaric acid salt **27F** by using the general procedure G with fumaric acid (36 mg, 0.31 mmol). Compound **27F** (78 mg, 63 %) was obtained as a yellow solid in 59 % yield over three steps; mp 150–154 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.00 (br m, 2H), 2.22 (br s, 1H), 2.43 (br s, 1H), 3.30–3.40 (br m, ³H), 3.42–3.54 (br m, ³H), 3.87 (br m, 1H), 4.50 (br m, 1H), 6.70 (s, 2.0H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H). ¹³C NMR (125 MHz, D₂O) δ 28.0, 28.5, 30.2, 49.4, 49.6, 50.6, 54.7, 131.4, 131.8, 135.8, 137.5, 138.8, 174.1, 177.0. LC/ESIMS: positive mode *m/z* = 265.5 ([M + H]⁺). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3433, 1706, 1637, 981, 970. Anal. (C₁₄H₁₇ClN₂O*1.0C₄H₄O₄*0.75H₂O) C, H, N.

4.29. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(4-bromophenyl)methanone fumaric acid salt (28F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 4-bromobenzoyl chloride (219 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (406 mg, 99 %) was obtained. The N-*t*-boc protection group of this solid (320 mg, 0.78 mmol) was cleaved using the general procedure D for 18 h and a clear oil **28** (237 mg, 98 %) was obtained after extraction. This oil **28** (134 mg, 0.43 mmol) was transferred to its fumaric acid salt **28F** by using the general procedure G with fumaric acid (50 mg, 0.43 mmol). Compound **28F** (143 mg, 78 %) was obtained as a yellow solid in 76 % yield over three steps; mp 147–149 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.00 (br m, 2H), 2.22 (br s, 1H), 2.42 (br s, 1H), 3.29–3.39 (br m, ³H), 3.42–3.54 (br m, ³H), 3.86 (br m, 1H), 4.50 (br m, 1H), 6.68 (s, 1.7H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H). ¹³C NMR (125 MHz, D₂O) δ 28.0, 28.4, 30.2, 49.4, 49.6, 50.6, 54.7, 127.1, 131.5, 134.7, 136.2, 137.6, 174.4, 177.0. LC/ESIMS: positive mode *m/z* = 309.4 and 311.4 ([M + H]⁺). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3433, 1705, 1636, 970. Anal. (C₁₄H₁₇BrN₂O*0.85C₄H₄O₄*0.7H₂O) C, H, N.

4.30. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(2,4-dimethoxyphenyl)methanone fumaric acid salt (29F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 2,4-dimethoxybenzoyl chloride (201 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (325 mg, 82 %) was obtained. The N-*t*-boc protection group of this solid (320 mg, 0.82 mmol) was cleaved using the general procedure E with anhydrous ZnBr₂ (369 mg, 1.6 mmol) for 12 h and a yellowish oil **29** (231 mg, 97 %) was obtained after extraction. This oil **29** (96 mg, 0.33 mmol) was transferred to its fumaric acid salt **29F** by using the general procedure G with fumaric acid (38 mg, 0.33 mmol). Compound **29F** (106 mg, 78 %) was obtained as an

off white solid in 62 % yield over three steps; mp 175 °C (dec). ^1H NMR (500 MHz, D_2O) δ 1.98 (br d, J = 13.4 Hz, 1H), 2.04 (br d, J = 13.7 Hz, 1H), 2.16 (br s, 1H), 2.40 (br s, 1H), 3.25 (br d, J = 13.6 Hz, 1H), 3.33–3.42 (br m, ^3H), 3.48 (br d, J = 12.8 Hz, 1H), 3.61 (br d, J = 12.6 Hz, 1H), 3.72 (br d, J = 14.4 Hz, 1H), 3.88 (s, ^3H), 3.90 (s, ^3H), 4.55 (br d, J = 13.8 Hz, 1H), 6.68 (s, 1.8H), 6.74 (m, 2H), 7.23 (d, J = 8.8 Hz, 1H). ^{13}C NMR (125 MHz, D_2O) δ 28.4, 31.1, 49.2, 50.8, 51.0, 54.2, 58.3, 58.5, 101.5, 109.5, 119.4, 132.2, 137.5, 158.0, 165.0, 174.3, 175.2. LC/ESI-MS: positive mode m/z = 291.4 ($[\text{M} + \text{H}]^+$). Purity (> 99.7 %). IR (KBr, cm^{-1}) 3442, 1704, 1628, 985, 970. Anal. ($\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_3 \cdot 0.9\text{C}_4\text{H}_4\text{O}_4 \cdot 1.0\text{H}_2\text{O}$) C, H, N.

4.31. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(furan-2-yl)methanone fumaric acid salt (30F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 2-furoyl chloride (131 mg, 1 mmol). A mixture of CH_2Cl_2 and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a yellowish solid (267 mg, 82 %) was obtained. The N-*t*-boc protection group of this solid (240 mg, 0.75 mmol) was cleaved using the general procedure D for 12 h and a yellowish oil **30** (164 mg, 99 %) was obtained after extraction. This oil **30** (79 mg, 0.36 mmol) was transferred to its fumaric acid salt **30F** by using the general procedure G with fumaric acid (42 mg, 0.36 mmol).

Compound **30F** (48 mg, 38 %) was obtained as an off white solid in 31 % yield over three steps; mp 157–162 °C (dec). ^1H NMR (500 MHz, D_2O) δ 2.05 (br m, 2H), 2.37 (br s, 2H), 3.35–3.45 (br m, 4H), 3.57 (br d, J = 13.0 Hz, 2H), 4.51 (br d, J = 13.2 Hz, 2H), 6.65 (dd, J = 3.6, 1.8 Hz, 1H), 6.69 (s, 2.0H), 7.13 (dd, J = 3.6, 0.6 Hz, 1H), 7.73 (dd, J = 1.8, 0.6 Hz, 1H). ^{13}C NMR (125 MHz, D_2O) δ 28.4, 30.7, 50.2, 114.6, 120.8, 137.6, 148.6, 148.7, 166.7, 174.5. LC/ESI-MS: positive mode m/z = 221.1 ($[\text{M} + \text{H}]^+$). Purity (> 99.4 %). IR (KBr, cm^{-1}) 3426, 1701, 1613, 983, 968. Anal. ($\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2 \cdot 1.0\text{C}_4\text{H}_4\text{O}_4 \cdot 1.0\text{H}_2\text{O}$) C, H, N.

4.32. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(thiophen-2-yl)methanone fumaric acid salt (31F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 2-thiophenecarbonyl chloride (147 mg, 1 mmol). A mixture of CH_2Cl_2 and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (275 mg, 80 %) was obtained. The N-*t*-boc protection group of this solid (240 mg, 0.71 mmol) was cleaved using the general procedure D for 12 h and a yellowish solid **31** (150 mg, 89 %) was obtained after extraction. This solid **31** (67 mg, 0.28 mmol) was transferred to its fumaric acid salt **31F** by using the general procedure G with fumaric acid (33 mg, 0.28 mmol). Compound **31F** (73 mg, 70 %) was obtained as a white solid in 50 % yield over three steps; mp 158–162 °C (dec). ^1H NMR (500 MHz, D_2O) δ 2.03 (br m, 2H), 2.36 (br s, 2H), 3.35–3.40 (br m, 2H), 3.44–3.56 (br m, 4H), 4.46 (br d, J = 13.8 Hz, 2H), 6.69 (s, 1.9H), 7.19 (dd, J = 5.0, 3.7 Hz, 1H), 7.50 (dd, J = 3.7, 1.0 Hz, 1H), 7.72 (dd, J = 5.0, 0.8 Hz, 1H). ^{13}C NMR (125 MHz, D_2O) δ 28.4, 30.4, 50.2, 130.2, 133.3, 133.8, 137.6, 138.1, 171.2, 174.4. LC/ESI-MS: positive mode m/z = 237.1 ($[\text{M} + \text{H}]^+$). Purity (> 99.8 %). IR (KBr, cm^{-1}) 3379, 1702, 1610, 989, 969. Anal. ($\text{C}_{12}\text{H}_{16}\text{N}_2\text{OS} \cdot 0.95\text{C}_4\text{H}_4\text{O}_4 \cdot 1.25\text{H}_2\text{O}$) C, H, N.

4.33. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(naphthalene-1-yl)methanone fumaric acid salt (32F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 1-naphthoyl chloride (191 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (353 mg, 91 %) was obtained. The N-*t*-boc protection group of this solid (240 mg, 0.63 mmol) was cleaved using the general procedure D for 12 h and a white solid **32** (172 mg, 97 %) was obtained after extraction. This solid **32** (62 mg, 0.22 mmol) was transferred to the fumaric acid salt **32F** by using the general procedure G with fumaric acid (26 mg, 0.22 mmol). Compound **32F** (73 mg, 80 %) was obtained as a white solid in 70 % yield over three steps; mp 152–154 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.96 (br m, 2H), 2.00 (br s, 1H), 2.47 (br s, 1H), 3.27–3.33 (br m, ³H), 3.35–3.40 (br m, 1H), 3.48–3.53 (br m, ³H), 3.55 (br d, *J* = 13.0 Hz, 1H), 4.66 (br d, *J* = 13.9 Hz, 1H), 6.66 (s, 2.0H), 7.56–7.66 (m, 5H), 8.00–8.06 (m, 2H). ¹³C NMR (125 MHz, D₂O) δ 27.9, 28.2, 29.9, 48.8, 49.3, 50.6, 53.6, 126.6, 126.8, 128.4, 129.8, 130.6, 131.5, 131.6, 132.7, 135.4, 136.0, 137.5, 174.3, 177.8. LC/ESI-MS: positive mode *m/z* = 281.5 ([M + H]⁺). Purity (> 98 %). IR (KBr, cm⁻¹) 3433, 1707, 1635, 983, 970. Anal. (C₁₈H₂₀N₂O*1.0C₄H₄O₄*1.5H₂O) C, H, N.

4.34. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(naphthalene-2-yl)methanone fumaric acid salt (33F)

The N-*t*-boc protected compound was obtained by using the general procedure A with 2-naphthoyl chloride (191 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (342 mg, 88 %) was obtained. The N-*t*-boc protection group of this solid (250 mg, 0.66 mmol) was cleaved using the general procedure D for 12 h and a white solid **33** (181 mg, 98 %) was obtained after extraction. This solid **33** (103 mg, 0.37 mmol) was transferred to the fumaric acid salt **33F** by using the general procedure G with fumaric acid (43 mg, 0.37 mmol). Compound **33F** (101 mg, 68 %) was obtained as a white solid in 58 % yield over three steps; mp 152–154 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.97 (br m, 2H), 2.11 (br s, 1H), 2.42 (br s, 1H), 3.30–3.55 (br m, 6H), 3.82 (br d, *J* = 11.9 Hz, 1H), 4.54 (br d, *J* = 12.6 Hz, 1H), 6.64 (s, 2.0H), 7.51 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.64 (m, 2H), 7.94–7.99 (m, ³H), 8.01 (d, *J* = 8.5 Hz, 1H). ¹³C NMR (125 MHz, D₂O) δ 28.0, 28.4, 30.2, 49.4, 49.6, 50.6, 54.7, 126.5, 129.7, 130.1, 130.69, 130.70, 131.3, 131.5, 134.7, 135.1, 136.4, 137.5, 174.2, 177.8. LC/ESI-MS: positive mode *m/z* = 281.3 ([M + H]⁺). Purity (> 99.9 %). IR (KBr, cm⁻¹) 3432, 1704, 1635, 983, 970. Anal. (C₁₈H₂₀N₂O*1.0C₄H₄O₄*0.6H₂O) C, H, N.

4.35. (1R,5S)-3-(methylsulfonyl)-3,7-diazabicyclo[3.3.1]nonane fumaric acid salt (34F)

The N-*t*-boc protected compound was obtained by using the general procedure A with methylsulfonyl chloride (115 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (280 mg, 91 %) was obtained. The N-*t*-boc protection group of this solid (230 mg, 0.76 mmol) was cleaved using the general procedure D for 12 h and an white solid **34** (146 mg, 95 %) was obtained after extraction. This solid **34** (110 mg, 0.54 mmol) was transferred to its fumaric acid salt **34F** by using the general procedure G with fumaric acid (63 mg, 0.54

mmol). Compound **34F** (163 mg, 94 %) was obtained as a white solid in 81 % yield over three steps; mp 179 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.90 (br m, 1H), 2.00 (br m, 1H), 2.38 (br s, 2H), 2.99 (s, 3H), 3.18 (br m, 2H), 3.36 (br d, *J* = 13.3 Hz, 2H), 3.59 (br d, *J* = 13.3 Hz, 2H), 3.84 (br m, 2H), 6.69 (s, 1.8H). ¹³C NMR (125 MHz, D₂O) δ 28.4, 30.4, 34.3, 50.2, 53.2, 137.6, 174.5. LC/ESI-MS: positive mode *m/z* = 205.1 ([*M* + *H*]⁺). Purity (99 %). IR (KBr, cm⁻¹) 3457, 1705, 1654, 1337, 1164, 986, 962. Anal. (C₈H₁₆N₂O₂S*0.9C₄H₄O₄*0.7H₂O) C, H, N.

4.36. (1R,5S)-3-(phenylsulfonyl)-3,7-diazabicyclo[3.3.1]nonane (35)

The N-*t*-boc protected compound was obtained by using the general procedure A with benzenesulfonyl chloride (177 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (324 mg, 87 %) was obtained. The N-*t*-boc protection group of this solid (90 mg, 0.25 mmol) was cleaved using the general procedure D for 4 h and compound **35** was obtained as an off white solid (63 mg, 96 %) after extraction, in 84 % yield over two steps; mp 101 °C. ¹H NMR (500 MHz, CDCl₃) δ 1.51 (br m, 1H), 1.86 (br m, 1H), 2.57–2.61 (br m, 4H), 3.05 (br m, 2H), 3.23 (br d, *J* = 14.0 Hz, 2H), 3.92 (br d, *J* = 11.5 Hz, 2H), 7.55 (m, 2H), 7.62 (m, 1H), 7.75 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 28.1, 31.2, 50.7, 51.3, 128.1, 129.2, 133.1, 134.4. LC/ESI-MS: positive mode *m/z* = 267.0 ([*M* + *H*]⁺). Purity (> 99 %). IR (KBr, cm⁻¹) 3417, 1345, 1172. Anal. (C₁₃H₁₈N₂O₂S*0.7H₂O) C, H, N.

4.37. 3-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-ylsulfonyl)benzonitrile (36)

The N-*t*-boc protected compound was obtained by using the general procedure A with m-cyanophenylsulfonyl chloride (202 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (9:1) was used for the chromatographic purification. After removal of the solvents a white solid (385 mg, 98 %) was obtained. The N-*t*-boc protection group of this solid (200 mg, 0.51 mmol) was cleaved using the general procedure E with anhydrous ZnBr₂ (230 mg, 1.0 mmol) for 48 h and compound **36** was obtained as an off white solid (138 mg, 93 %) after extraction, in 91 % yield over two steps; mp 146 °C. ¹H NMR (500 MHz, CDCl₃) δ 1.53 (br m, 1H), 1.75 (br s, 2H), 1.89 (br m, 1H), 2.52 (br s, 1H), 2.62 (br m, 2H), 3.04 (br m, 2H), 3.21 (br d, *J* = 14.1 Hz, 2H), 3.93 (br d, *J* = 11.4 Hz, 2H), 7.70 (ddd, *J* = 7.9, 7.9, 0.5 Hz, 1H), 7.89 (ddd, *J* = 7.8, 1.6, 1.2 Hz, 1H), 7.97 (ddd, *J* = 8.0, 1.8, 1.2, 1H), 8.04 (ddd, *J* = 1.7, 1.7, 0.5 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 28.1, 31.1, 50.8, 51.3, 113.9, 117.3, 130.2, 131.4, 131.9, 136.0, 136.6. LC/ESIMS: positive mode *m/z* = 292.3 ([*M* + *H*]⁺). Purity (95 %). IR (KBr, cm⁻¹) 3364, 2232, 1343, 1159. Anal. (C₁₄H₁₇N₃O₂S*0.75H₂O) C, H, N.

4.38. (1R,5S)-3-tosyl-3,7-diazabicyclo[3.3.1]nonane (37)

The N-*t*-boc protected compound was obtained by using the general procedure A with p-toluenesulfonyl chloride (190 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (9:1) was used for the chromatographic purification. After removal of the solvents a white solid (377 mg, 97 %) was obtained. The N-*t*-boc protection group of this solid (200 mg, 0.53 mmol) was cleaved using the general procedure E with anhydrous ZnBr₂ (237 mg, 1.1 mmol) for 48 h and compound **37** was obtained as an off white solid (145 mg, 98 %) after extraction, in 95 % yield over two steps; mp 111 °C. ¹H NMR (500 MHz, CDCl₃) δ 1.50 (br m, 1H), 1.71 (br

m, 1H), 1.85 (br s, 2H), 2.44 (s, ^3H), 2.58 (br m, 2H), 2.73 (br s, 1H), 3.02 (br m, 2H), 3.21 (br d, $J = 14.1$ Hz, 2H), 3.89 (br d, $J = 10.8$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.62 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 21.7, 28.3, 31.3, 50.9, 51.3, 128.1, 129.7, 131.4, 143.8. LC/ESI-MS: positive mode $m/z = 281.4$ ($[\text{M} + \text{H}]^+$). Purity (99.5 %). IR (KBr, cm^{-1}) 3343, 1341, 1166. Anal. ($\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2\text{S} \cdot 0.5\text{H}_2\text{O}$) C, H, N.

4.39. 4-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-ylsulfonyl)benzonitrile (38)

The N-*t*-boc protected compound was obtained by using the general procedure A with p-cyanophenylsulfonyl chloride (202 mg, 1 mmol). A mixture of CH_2Cl_2 and MeOH (9:1) was used for the chromatographic purification. After removal of the solvents a white solid (295 mg, 75 %) was obtained. The N-*t*-boc protection group of this solid (200 mg, 0.51 mmol) was cleaved using the general procedure E with anhydrous ZnBr_2 (230 mg, 1.0 mmol) for 48 h and compound **38** was obtained as an off white solid (105 mg, 71 %) after extraction, in 53 % yield over two steps; mp 169 °C. ^1H NMR (500 MHz, CDCl_3) δ 1.53 (br m, 1H), 1.75 (br s, 2H), 1.89 (br m, 1H), 2.44 (br s, 1H), 2.62 (br m, 2H), 3.05 (br m, 2H), 3.22 (br d, $J = 14.0$ Hz, 2H), 3.94 (br d, $J = 11.4$ Hz, 2H), 7.86 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3) δ 28.2, 31.2, 51.0, 51.3, 116.8, 117.4, 128.6, 133.0, 139.1. LC/ESI-MS: positive mode $m/z = 292.1$ ($[\text{M} + \text{H}]^+$). Purity (> 99.8 %). IR (KBr, cm^{-1}) 3405, 2237, 1344, 1164. Anal. ($\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_2\text{S} \cdot 0.75\text{H}_2\text{O}$) C, H, N.

4.40. (1R,5S)-3-(4-bromophenylsulfonyl)-3,7-diazabicyclo[3.3.1]nonane hydrochloric acid salt (39H)

The N-*t*-boc protected compound was obtained by using the general procedure A with p-bromophenylsulfonyl chloride (255.5 mg, 1 mmol). A mixture of CH_2Cl_2 and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (407 mg, 91 %) was obtained. This solid (264 mg, 0.59 mmol) was dissolved in a mixture of CH_2Cl_2 (2 mL) and 1,4-dioxane (2 mL), HCl in 1,4-dioxane (4 M, 2 mL) was added for the cleavage of the N-*t*-boc protection group, and the reaction mixture was allowed to stir at rt for 2 h. Then dry Et_2O (2 mL) was added, the precipitate was filtered off, and washed with dry Et_2O (3×2 mL). Compound **39H** (224 mg, 99 %) was obtained as a white solid in 90 % yield over two steps; mp 266–269 °C (dec). ^1H NMR (400 MHz, D_2O) δ 1.57 (br d, $J = 13.5$ Hz, 1H), 1.89 (br d, $J = 13.6$ Hz, 1H), 2.29 (br s, 2H), 2.63 (br d, $J = 11.6$ Hz, 2H), 3.34 (br d, $J = 13.3$ Hz, 2H), 3.61 (br d, $J = 13.2$ Hz, 2H), 3.89 (br d, $J = 11.4$ Hz, 2H), 7.70 (d, $J = 8.6$ Hz, 2H), 7.78 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR (100 MHz, D_2O) δ 26.1, 28.0, 47.8, 51.2, 129.6, 130.4, 131.1, 133.4. ESI-MS: positive mode $m/z = 345.3$ and 347.2 ($[\text{M} + \text{H}]^+$). Purity (> 99 %). IR (cm^{-1}) 2848, 2556, 1570, 1352, 908, 747. Anal. ($\text{C}_{13}\text{H}_{17}\text{BrN}_2\text{O}_2\text{S} \cdot 1.0\text{HCl}$) C, H, N.

4.41. (1R,5S)-3-(4-nitrophenylsulfonyl)-3,7-diazabicyclo[3.3.1]nonane (40)

The N-*t*-boc protected compound was obtained by using the general procedure A with p-nitrophenylsulfonyl chloride (222 mg, 1 mmol). A mixture of CH_2Cl_2 and MeOH (40:1) was used for the chromatographic purification. After removal of the solvents a yellowish solid (272 mg, 65 %) was obtained. The N-*t*-boc protection group of this solid (253 mg, 0.61 mmol) was cleaved using the general procedure E with anhydrous ZnBr_2 (277 mg, 1.23

mmol) for 12 h and compound **40** was obtained as a yellowish solid (177 mg, 92 %) after extraction, in 60 % yield over two steps; mp 185 °C (dec). ¹H NMR (500 MHz, CDCl₃) δ 1.52 (br m, 1H), 1.74 (br s, 2H), 1.89 (br m, 1H), 2.16 (br s, 1H), 2.64 (br m, 2H), 3.03 (br m, 2H), 3.21 (br d, *J* = 14.1 Hz, 2H), 3.96 (br d, *J* = 10.9 Hz, 2H), 7.94 (ddd, *J* = 8.9, 2.2, 2.0 Hz, 2H), 8.40 (ddd, *J* = 8.9, 2.2, 2.0 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 28.2, 31.2, 50.9, 51.3, 124.4, 129.1, 140.7, 150.4. LC/ESI-MS: positive mode *m/z* = 312.0 ([M + H]⁺). Purity (> 99 %). IR (KBr, cm⁻¹) 3424, 1530, 1349, 1168. Anal. (C₁₃H₁₇N₃O₄S*0.5H₂O) C, H, N.

4.42. (1R,5S)-N,N-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide fumaric acid salt (41F)

The N-*t*-boc protected compound was obtained by using the general procedure A with dimethylcarbamoyl chloride (108 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (280 mg, 94 %) was obtained. The N-*t*-boc protection group of this solid (240 mg, 0.81 mmol) was cleaved using the general procedure D for 4 h and a white solid **41** (152 mg, 95 %) was obtained after extraction. This solid **41** (140 mg, 0.71 mmol) was transferred to the fumaric acid salt **41F** by using the general procedure G with fumaric acid (82 mg, 0.71 mmol). Compound **41F** (180 mg, 81 %) was obtained as a white solid in 72 % yield over three steps; mp 144–148 °C (dec). ¹H NMR (400 MHz, D₂O) δ 1.94 (br m, 2H), 2.23 (br s, 2H), 2.90 (s, 6H), 3.18 (br d, *J* = 13.1 Hz, 2H), 3.35 (br d, *J* = 13.0 Hz, 2H), 3.56 (d, *J* = 13.2 Hz, 2H), 3.72 (d, *J* = 13.0 Hz, 2H), 6.69 (s, 1.9H). ¹³C NMR (100 MHz, D₂O) δ 25.7, 28.5, 37.5, 47.4, 50.8, 134.4, 165.8, 171.1. ESI-MS: positive mode *m/z* = 198.3 ([M + H]⁺). Purity (> 99 %). IR (cm⁻¹) 2951, 1713, 1604, 1409, 984, 756, 637. Anal. (C₁₀H₁₉N₃O*1.0C₄H₄O₄*0.7H₂O) C, H, N.

4.43. (1R,5S)-N,N-diethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide fumaric acid salt (42F)

The N-*t*-boc protected compound was obtained by using the general procedure A with diethylcarbamoyl chloride (135.6 mg, 1 mmol). A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (353 mg, 91 %) was obtained. The N-*t*-boc protection group of this solid (240 mg, 0.63 mmol) was cleaved using the general procedure D for 12 h and a white solid **42** (172 mg, 97 %) was obtained after extraction. This solid **42** (62 mg, 0.22 mmol) was transferred to the fumaric acid salt **42F** by using the general procedure G with fumaric acid (26 mg, 0.22 mmol). Compound **42F** (73 mg, 80 %) was obtained as a white solid in 70 % yield over three steps; mp 111–115 °C (dec). ¹H NMR (400 MHz, D₂O) δ 1.14 (t, *J* = 7.1 Hz, 6H); 1.93 (br m, 2H); 2.22 (br s, 2H); 3.20 (br d, *J* = 13.2 Hz, 2H); 3.27 (q, *J* = 7.2 Hz, 4H); 3.34 (br d, *J* = 13.1 Hz, 2H); 3.53 (br d, *J* = 13.1 Hz, 2H); 3.64 (br d, *J* = 13.3 Hz, 2H); 6.68 (s, 2.0H). ¹³C NMR (100 MHz, D₂O) δ 13.0, 26.7, 29.4, 42.5, 48.4, 52.1, 135.3, 166.5, 172.1. ESI-MS: positive mode *m/z* = 226.3 ([M + H]⁺). HRMS for C₁₂H₂₃N₃O: calc *m/z* = 226.1914, found *m/z* = 226.1899. Purity (> 99 %). IR (cm⁻¹) 2969, 2850, 1703, 1634, 1251, 1121, 968, 641. Anal. (C₁₂H₂₃N₃O*1.0C₄H₄O₄*1.3H₂O) C, H, N.

4.44. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(cyclopentyl)methanone fumaric acid salt (43F)

The N-*t*-boc protected compound was obtained by using the general procedure B with cyclopentanecarboxylic acid (114 mg, 1 mmol) for 72 h. A mixture of CH₂Cl₂ and MeOH (40:1) was used for the chromatographic purification. After removal of the solvents a white solid (228 mg, 71 %) was obtained. The N-*t*-boc protection group of this solid (198 mg, 0.61 mmol) was cleaved using the general procedure D for 12 h and a white solid **43** (134 mg, 98 %) was obtained after extraction. This solid **43** (134 mg, 0.60 mmol) was transferred to its fumaric acid salt **43F** by using the general procedure G with fumaric acid (70 mg, 0.60 mmol). Compound **43F** (164 mg, 79 %) was obtained as a white solid in 55 % yield over three steps; mp 164–166 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.40–1.48 (br m, 1H), 1.57–1.72 (br m, 4H), 1.77–1.87 (br m, 2H), 1.93–2.03 (br m, ³H), 2.32 (br s, 2H), 3.06 (br d, *J* = 13.7 Hz, 1H), 3.18 (quint, *J* = 8.0 Hz, 1H), 3.29–3.39 (br m, 2H), 3.45 (br m, 2H), 3.52 (br d, *J* = 13.0 Hz, 1H), 4.27 (br d, *J* = 13.1 Hz, 1H), 4.41 (br d, *J* = 13.8 Hz, 1H), 6.69 (s, 2.0H). ¹³C NMR (125 MHz, D₂O) δ 28.2, 28.4, 28.5, 28.6, 30.4, 31.9, 32.2, 44.5, 49.2, 50.2, 50.7, 52.3, 137.6, 174.4, 184.0. LC/ESI-MS: positive mode *m/z* = 223.4 ([M + H]⁺). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3441, 1707, 1654, 979. Anal. (C₁₃H₂₂N₂O*1.0C₄H₄O₄*0.35H₂O) C, H, N.

4.45. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(otolyl) methanone fumaric acid salt (44F)

The N-*t*-boc protected compound was obtained by using the general procedure B with 2-methylbenzoic acid (136 mg, 1 mmol) 48 h. A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a clear oil (186 mg, 54 %) was obtained. The N-*t*-boc protection group of this oil (165 mg, 0.48 mmol) was cleaved using the general procedure E with anhydrous ZnBr₂ (216 mg, 0.96 mmol) for 12 h and a white solid **44** (92 mg, 79 %) was obtained after extraction. This solid **44** (77 mg, 0.32 mmol) was transferred to its fumaric acid salt **44F** by using the general procedure G with fumaric acid (37 mg, 0.32 mmol). Compound **44F** (61 mg, 52 %) was obtained as a white solid in 22 % yield over three steps; mp 155–157 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.00 (br m, 2H), 2.17 (br s, 1H), 2.20 (s, ³H), 2.45 (br s, 1H), 3.33–3.44 (br m, 5H), 3.52 (br d, *J* = 13.2 Hz, 1H), 3.66 (br d, *J* = 13.4 Hz, 1H), 4.54 (br d, *J* = 14.2 Hz, 1H), 6.68 (s, 2.0H), 7.33–7.39 (m, ³H), 7.41–7.45 (m, 1H). ¹³C NMR (125 MHz, D₂O) δ 20.8, 20.9, 28.3, 30.0, 48.6, 49.5, 50.6, 53.3, 127.9, 129.1, 132.6, 133.6, 137.4, 137.5, 137.6, 174.4, 178.5. LC/ESI-MS: positive mode *m/z* = 245.4 ([M + H]⁺). Purity (> 99.7 %). IR (KBr, cm⁻¹) 3485, 1704, 1615, 984, 967. Anal. (C₁₅H₂₀N₂O*1.0C₄H₄O₄*0.55H₂O) C, H, N.

4.46. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(3-fluorophenyl)methanone fumaric acid salt (45F)

The N-*t*-boc protected compound was obtained by using the general procedure B with 3-fluorobenzoic acid (140 mg, 1 mmol) for 24 h. A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a clear oil (230 mg, 66 %) was obtained. The N-*t*-boc protection group of this oil (210 mg, 0.60 mmol) was cleaved using the general procedure D for 12 h and a clear oil **45** (107 mg, 71 %) was obtained after extraction. This oil **45** (96 mg, 0.39 mmol) was transferred to its fumaric acid

salt **45F** by using the general procedure G with fumaric acid (45 mg, 0.39 mmol). Compound **45F** (84 mg, 58 %) was obtained as a yellow solid in 27 % yield over three steps; mp 157–158 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.00 (br m, 2H), 2.22 (br s, 1H), 2.43 (br s, 1H), 3.30–3.41 (br m, ³H), 3.43–3.56 (br m, ³H), 3.86 (br d, *J* = 12.9 Hz, 1H), 4.50 (br d, *J* = 13.9 Hz, 1H), 6.70 (s, 2.0H), 7.28 (m, ³H), 7.54 (dt, *J*_{H,H} = 8.0 Hz, *J*_{H,F} = 5.8 Hz, 1H). ¹³C NMR (125 MHz, D₂O) δ 27.9, 28.4, 30.1, 49.3, 49.6, 50.6, 54.6, 116.7 (d, *J*_{C,F} = 23.6 Hz), 120.2 (d, *J*_{C,F} = 21.2 Hz), 125.5 (d, *J*_{C,F} = 3.0 Hz), 133.8 (d, *J*_{C,F} = 8.3 Hz), 137.5, 139.2 (d, *J*_{C,F} = 7.4 Hz), 165.1 (d, *J*_{C,F} = 245.5 Hz), 174.0, 176.5. LC/ESI-MS: positive mode *m/z* = 249.4 ([M + H]⁺). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3448, 1701, 1648, 982, 971. Anal. (C₁₄H₁₇FN₂O*1.0C₄H₄O₄*0.7H₂O) C, H, N.

4.47. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(3-(trifluoromethyl)phenyl)methanone fumaric acid salt (**46F**)

The N-*t*-boc protected compound was obtained by using the general procedure B with 3-trifluoromethylbenzoic acid (190 mg, 1 mmol) for 72 h. A mixture of CH₂Cl₂ and MeOH (40:1) was used for the chromatographic purification. After removal of the solvents a clear oil (190 mg, 48 %) was obtained. The N-*t*-boc protection group of this oil (180 mg, 0.45 mmol) was cleaved using the general procedure D for 12 h and a clear oil **46** (126 mg, 93 %) was obtained after extraction. This oil **46** (126 mg, 0.42 mmol) was transferred to its fumaric acid salt **46F** by using the general procedure G with fumaric acid (49 mg, 0.42 mmol). Compound **46F** (70 mg, 39 %) was obtained as a yellow solid in 18 % yield over three steps; mp 154–156 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.01 (br m, 2H), 2.22 (br s, 1H), 2.44 (br s, 1H), 3.32–3.56 (br m, 6H), 3.81 (br d, *J* = 13.3 Hz, 1H), 4.54 (br d, *J* = 13.4 Hz, 1H), 6.65 (s, 1.6H), 7.68–7.90 (m, 4H). ¹³C NMR (125 MHz, D₂O) δ 27.9, 28.4, 30.1, 49.4, 49.6, 50.5, 54.7, 126.61 (q, *J*_{C,F} = 271.8 Hz), 126.63 (q, *J*_{C,F} = 3.8 Hz), 130.0 (q, *J*_{C,F} = 3.6 Hz), 132.5, 133.2, 133.3 (q, *J*_{C,F} = 32.6 Hz), 137.7, 138.1, 175.0, 176.4. LC/ESI-MS: positive mode *m/z* = 299.3 ([M + H]⁺). Purity (> 99.7 %). IR (KBr, cm⁻¹) 3440, 1680, 1637, 985, 975. Anal. (C₁₅H₁₇F₃N₂O*0.8C₄H₄O₄*1.6H₂O) C, H, N.

4.48. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(biphenyl-4-yl)methanone fumaric acid salt (**47F**)

The N-*t*-boc protected compound was obtained by using the general procedure B with 4-biphenylcarboxylic acid (198 mg, 1 mmol) for 12 h. A mixture of CH₂Cl₂ and MeOH (40:1) was used for the chromatographic purification. After removal of the solvents a clear oil (293 mg, 72 %) was obtained. The N-*t*-boc protection group of this oil (250 mg, 0.61 mmol) was cleaved using the general procedure D for 12 h and a clear oil **47** (141 mg, 75 %) was obtained after extraction. This oil **47** (60 mg, 0.20 mmol) was transferred to its fumaric acid salt **47F** by using the general procedure G with fumaric acid (23 mg, 0.20 mmol). Compound **47F** (54 mg, 63 %) was obtained as a white solid in 34 % yield over three steps; mp 148–150 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.99 (br m, 2H), 2.20 (br s, 1H), 2.43 (br s, 1H), 3.30–3.41 (br m, ³H), 3.42–3.54 (br m, ³H), 3.91 (br m, 1H), 4.53 (br m, 1H), 6.67 (s, 2.0H), 7.48 (m, 1H), 7.56 (m, 4H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H). ¹³C NMR (125 MHz, D₂O) δ 28.0, 28.5, 30.3, 49.4, 49.6, 50.6, 54.8, 129.9, 130.0, 130.5, 131.2, 132.1, 136.2, 137.6, 142.4, 145.5, 174.6, 177.8. LC/ESI-MS: positive mode *m/z* = 307.5 ([M

+ H]⁺). Purity (> 99.9 %). IR (KBr, cm⁻¹) 3427, 1705, 1624, 982, 970. Anal. (C₂₀H₂₂N₂O*1.0C₄H₄O₄*0.9H₂O) C, H, N.

4.49. 4-((1R,5S)-3,7-diazabicyclo[3.3.1]nonane-3-carbonyl)benzonitrile (48)

The N-*t*-boc protected compound was obtained by using the general procedure B with 4-cyanobenzoic acid (147 mg, 1 mmol) for 12 h. A mixture of CH₂Cl₂ and MeOH (9:1) was used for the chromatographic purification. After removal of the solvents a white solid (109 mg, 31 %) was obtained. The N-*t*-boc protection group of this solid (100 mg, 0.28 mmol) was cleaved using the general procedure D for 2 h and compound **48** was obtained as a white solid (69 mg, 96 %) after extraction, in 30 % yield over two steps; mp 157 °C (dec). ¹H NMR (500 MHz, CDCl₃) δ 1.68 (br s, 1H), 1.88 (br m, ³H), 2.12 (br m, 1H), 3.00 (br s, 1H), 3.05 (br d, *J* = 12.2 Hz, 2H), 3.14 (br d, *J* = 12.1 Hz, 2H), 3.27 (br d, *J* = 11.3 Hz, 1H), 3.36 (br d, *J* = 10.1 Hz, 1H), 3.66 (br d, *J* = 10.8 Hz, 1H), 4.81 (br d, *J* = 11.7 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 28.4, 28.8, 32.2, 47.1, 51.0, 51.3, 52.7, 113.1, 118.4, 127.6, 132.6, 141.7, 168.9. LC/ESI-MS: positive mode *m/z* = 256.1 ([M + H]⁺). Purity (> 99.5 %). IR (KBr, cm⁻¹) 3365, 2234, 1633. Anal. (C₁₅H₁₇N₃O*0.25H₂O) C, H, N.

4.50. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(4-nitrophenyl)methanone fumaric acid salt (49F)

The N-*t*-boc protected compound was obtained by using the general procedure B with 4-nitrobenzoic acid (167 mg, 1 mmol) for 12 h. A mixture of CH₂Cl₂ and MeOH (40:1) was used for the chromatographic purification. After removal of the solvents a yellowish solid (184 mg, 49 %) was obtained. The N-*t*-boc protection group of this solid (170 mg, 0.45 mmol) was cleaved using the general procedure E with anhydrous ZnBr₂ (204 mg, 0.90 mmol) for 12 h and a yellowish solid **49** (76 mg, 61 %) was obtained after extraction. This solid **49** (42 mg, 0.15 mmol) was transferred to its fumaric acid salt **49F** by using the general procedure G with fumaric acid (18 mg, 0.15 mmol). Compound **49F** (37 mg, 54 %) was obtained as a yellow solid in 20 % yield over three steps; mp 144–146 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.96–2.07 (br m, 2H), 2.23 (br s, 1H), 2.46 (br s, 1H), 3.34–3.49 (br m, 6H), 3.77 (br d, *J* = 13.4 Hz, 1H), 4.50 (br d, *J* = 14.0 Hz, 1H), 6.73 (s, 2.0H), 7.72 (d, *J* = 8.9 Hz, 2H), 8.37 (d, *J* = 8.9 Hz, 2H). ¹³C NMR (125 MHz, D₂O) δ 27.9, 28.4, 30.1, 49.3, 49.5, 50.5, 54.5, 127.0, 130.9, 137.6, 143.7, 151.3, 174.5, 175.8. LC/ESI-MS: positive mode *m/z* = 276.3 ([M + H]⁺). Purity (> 99 %). IR (KBr, cm⁻¹) 3433, 1704, 1634, 1521, 1353, 983, 969. Anal. (C₁₄H₁₇N₃O₃*1.0C₄H₄O₄*3.0H₂O) C, H, N.

4.51. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(pyridine-3-yl)methanone fumaric acid salt (50F)

The N-*t*-boc protected compound was obtained by using the general procedure B with nicotinic acid (185 mg, 1 mmol) for 12 h. A mixture of CH₂Cl₂ and MeOH (9:1) was used for the chromatographic purification. After removal of the solvents a clear oil (197 mg, 59 %) was obtained. The N-*t*-boc protection group of this oil (175 mg, 0.53 mmol) was cleaved using the general procedure E with anhydrous ZnBr₂ (358 mg, 1.6 mmol) for 72 h and a clear oil **50** (105 mg, 86 %) was obtained after extraction. This oil **50** (48 mg, 0.21 mmol)

was transferred to its fumaric acid salt **50F** by using the general procedure G with fumaric acid (24 mg, 0.21 mmol). Compound **50F** (47 mg, 63 %) was obtained as a white solid in 32 % yield over three steps; mp 144–148 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.01 (br m, 2H), 2.25 (br s, 1H), 2.45 (br s, 1H), 3.33–3.40 (br m, ³H), 3.46 (br d, *J* = 13.3 Hz, 1H), 3.52 (br d, *J* = 12.7 Hz, 1H), 3.59 (br d, *J* = 13.0 Hz, 1H), 3.84 (br d, *J* = 12.8 Hz, 1H), 4.54 (br d, *J* = 13.6 Hz, 1H), 6.65 (s, 2.0H), 7.68 (dd, *J* = 8.0, 5.2 Hz, 1H), 8.10 (ddd, *J* = 8.0, 2.1, 1.6 Hz, 1H), 8.71 (m, 2H). ¹³C NMR (125 MHz, D₂O) δ 27.9, 28.4, 30.1, 49.4, 49.6, 50.5, 54.5, 127.6, 134.6, 137.7, 140.4, 148.6, 151.9, 174.3, 174.9. LC/ESI-MS: positive mode *m/z* = 232.3 ([M + H]⁺). Purity (> 99.4 %). IR (KBr, cm⁻¹) 3433, 1701, 1635, 984, 969. Anal. (C₁₃H₁₇N₃O*1.0C₄H₄O₄*0.6H₂O) C, H, N.

4.52. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(5-bromopyridin-3-yl)methanone fumaric acid salt (51F)

The N-*t*-boc protected compound was obtained by using the general procedure B with 5-bromopyridine-3-carboxylic acid (303 mg, 1.5 mmol) for 12 h. A mixture of CH₂Cl₂ and MeOH (40:1) was used for the chromatographic purification. After removal of the solvents a clear oil (166 mg, 41 %) was obtained. The N-*t*-boc protection group of this oil (210 mg, 0.51 mmol) was cleaved using the general procedure E with anhydrous ZnBr₂ (231 mg, 1.0 mmol) for 48 h and a yellowish oil **51** (142 mg, 89 %) was obtained after extraction. This oil **51** (81 mg, 0.26 mmol) was transferred to its fumaric acid salt **51F** by using the general procedure G with fumaric acid (30 mg, 0.26 mmol). Compound **51F** (84 mg, 75 %) was obtained as a white solid in 27 % yield over three steps; mp 186–187 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.01 (br m, 2H), 2.25 (br s, 1H), 2.44 (br s, 1H), 3.36 (br m, ³H), 3.45 (br d, *J* = 13.4 Hz, 1H), 3.52 (br d, *J* = 12.6 Hz, 1H), 3.59 (br d, *J* = 13.2 Hz, 1H), 3.83 (br d, *J* = 13.0 Hz, 1H), 4.52 (br d, *J* = 13.9 Hz, 1H), 6.68 (s, 1.84H), 8.18 (dd, *J* = 2.1, 1.9 Hz, 1H), 8.61 (d, *J* = 1.7 Hz, 1H), 8.79 (d, *J* = 2.1 Hz, 1H). ¹³C NMR (125 MHz, D₂O) δ 27.9, 28.4, 30.0, 49.4, 49.5, 50.4, 54.5, 123.4, 135.3, 137.6, 141.2, 148.0, 154.4, 173.2, 174.5. LC/ESI-MS: positive mode *m/z* = 310.3 and 312.3 ([M + H]⁺). Purity (> 99.5 %). IR (KBr, cm⁻¹) 3440, 1697, 1639, 984, 969. Anal. (C₁₃H₁₆BrN₃O*0.92C₄H₄O₄*0.6H₂O) C, H, N.

4.53. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(quinolin-2-yl)methanone fumaric acid salt (52F)

The N-*t*-boc protected compound was obtained by using the general procedure B with 2-quinolinecarboxylic acid (173 mg, 1 mmol) for 72 h. A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a clear oil (210 mg, 55 %) was obtained. The N-*t*-boc protection group of this oil (180 mg, 0.47 mmol) was cleaved using the general procedure E with anhydrous ZnBr₂ (213 mg, 0.94 mmol) for 72 h and a yellowish oil **52** (130 mg, 98 %) was obtained after extraction. This oil **52** (60 mg, 0.21 mmol) was transferred to its fumaric acid salt **52F** by using the general procedure G with fumaric acid (25 mg, 0.21 mmol). Compound **52F** (49 mg, 56 %) was obtained as a white solid in 30 % yield over three steps; mp 145–150 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.06 (br m, 2H), 2.13 (br s, 1H), 2.46 (br s, 1H), 3.40–3.49 (br m, 4H), 3.65 (br m, 2H), 3.83 (br d, *J* = 13.4 Hz, 1H), 4.56 (br d, *J* = 12.9 Hz, 1H), 6.62 (s, 2.0H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.72 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 7.87 (ddd, *J* = 8.5, 6.9, 1.4 Hz,

1H), 7.98 (d, $J = 8.5$, 1H), 8.01 (d, $J = 8.1$ Hz, 1H), 8.52 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (125 MHz, D_2O) δ 28.4, 28.6, 30.9, 50.0, 50.1, 50.3, 53.3, 122.5, 130.6, 131.2, 131.3, 134.2, 137.5, 142.3, 148.7, 155.1, 174.4, 174.6. LC/ESI-MS: positive mode $m/z = 282.5$ ($[\text{M} + \text{H}]^+$). Purity ($> 99.7\%$). IR (KBr, cm^{-1}) 3433, 1702, 1641, 973. Anal. ($\text{C}_{17}\text{H}_{19}\text{N}_3\text{O} \cdot 1.0\text{C}_4\text{H}_4\text{O}_4 \cdot 0.75\text{H}_2\text{O}$) C, H, N.

4.54. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(quinolin-4-yl)methanone fumaric acid salt (53F)

The N-*t*-boc protected compound was obtained by using the general procedure B with 4-quinolinecarboxylic acid (173 mg, 1 mmol) for 72 h. A mixture of CH_2Cl_2 and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a clear oil (177 mg, 46 %) was obtained. The N-*t*-boc protection group of this oil (150 mg, 0.39 mmol) was cleaved using the general procedure E with anhydrous ZnBr_2 (177 mg, 0.79 mmol) for 72 h and a yellowish oil **53** (98 mg, 89 %) was obtained after extraction. This oil **53** (45 mg, 0.16 mmol) was transferred to its fumaric acid salt **53F** by using the general procedure G with fumaric acid (19 mg, 0.16 mmol). Compound **53F** (49 mg, 67 %) was obtained as a white solid in 30 % yield over three steps; mp 168–170 °C (dec). ^1H NMR (500 MHz, D_2O) δ 2.00 (br m, 2H), 2.09 (br s, 1H), 2.50 (br s, 1H), 3.30–3.42 (br m, 4H), 3.45–3.60 (br m, ^3H), 4.65 (br d, $J = 13.9$ Hz, 1H), 6.63 (s, 2.0H), 7.73 (d, $J = 8.2$ Hz, 1H), 7.79 (m, 1H), 7.83 (d, $J = 4.7$ Hz, 1H), 7.96 (m, 1H), 8.17 (d, $J = 8.5$ Hz, 1H), 9.01 (d, $J = 4.7$ Hz, 1H). ^{13}C NMR (125 MHz, D_2O) δ 27.7, 28.1, 29.8, 48.7, 49.2, 50.5, 53.3, 121.1, 126.7, 127.5, 129.8, 132.1, 135.0, 137.6, 146.8, 147.9, 152.0, 174.1, 174.9. LC/ESI-MS: positive mode $m/z = 282.3$ ($[\text{M} + \text{H}]^+$). Purity ($> 99.7\%$). IR (KBr, cm^{-1}) 3424, 1700, 1646, 985, 967. Anal. ($\text{C}_{17}\text{H}_{19}\text{N}_3\text{O} \cdot 1.0\text{C}_4\text{H}_4\text{O}_4 \cdot 1.45\text{H}_2\text{O}$) C, H, N.

4.55. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(quinolin-6-yl)methanone fumaric acid salt (54F)

The N-*t*-boc protected compound was obtained by using the general procedure B with 6-quinolinecarboxylic acid (173 mg, 1 mmol) for 72 h. A mixture of CH_2Cl_2 and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a clear oil (303 mg, 79 %) was obtained. The N-*t*-boc protection group of this oil (270 mg, 0.71 mmol) was cleaved using the general procedure E with anhydrous ZnBr_2 (319 mg, 1.4 mmol) for 72 h and a clear oil **54** (191 mg, 96 %) was obtained after extraction. This oil **54** (45 mg, 0.16 mmol) was transferred to its fumaric acid salt **54F** by using the general procedure G with fumaric acid (19 mg, 0.16 mmol). Compound **54F** (27 mg, 40 %) was obtained as a white solid in 30 % yield over three steps; mp 162–165 °C (dec). ^1H NMR (500 MHz, D_2O) δ 2.02 (br m, 2H), 2.21 (br s, 1H), 2.47 (br s, 1H), 3.34–3.48 (br m, 4H), 3.53–3.61 (br m, 2H), 3.86 (br d, $J = 12.7$ Hz, 1H), 4.59 (br d, $J = 13.9$ Hz, 1H), 6.58 (s, 2.0H), 7.79 (dd, $J = 8.4$, 4.7 Hz, 1H), 7.95 (dd, $J = 8.7$, 1.9 Hz, 1H), 8.18 (d, $J = 1.8$ Hz, 1H), 8.19 (d, $J = 8.9$, 1H), 8.68 (d, $J = 8.1$ Hz, 1H), 9.00 (dd, $J = 4.7$, 1.4 Hz, 1H). ^{13}C NMR (125 MHz, D_2O) δ 28.0, 28.4, 30.1, 49.4, 49.6, 50.6, 54.7, 125.4, 129.0, 130.4, 130.8, 132.3, 136.7, 137.8, 144.2, 146.8, 152.7, 175.7, 176.4. LC/ESI-MS: positive mode $m/z = 282.5$ ($[\text{M} + \text{H}]^+$). Purity ($> 99.9\%$). IR (KBr, cm^{-1}) 3426, 1701, 1633, 969. Anal. ($\text{C}_{17}\text{H}_{19}\text{N}_3\text{O} \cdot 1.0\text{C}_4\text{H}_4\text{O}_4 \cdot 1.5\text{H}_2\text{O}$) C, H, N.

4.56. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-cyclopentylethanone fumaric acid salt (55F)

The N-*t*-boc protected compound was obtained by using the general procedure C with cyclopentylacetic acid (128 mg, 1 mmol) for 12 h. A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (258 mg, 77 %) was obtained. The N-*t*-boc protection group of this solid (200 mg, 0.59 mmol) was cleaved using the general procedure D for 2 h and a white solid **55** (122 mg, 89 %) was obtained after extraction. This solid **55** (122 mg, 0.52 mmol) was transferred to its fumaric acid salt **55F** by using the general procedure G with fumaric acid (60 mg, 0.52 mmol). Compound **55F** (152 mg, 84 %) was obtained as a white solid in 58 % yield over three steps; mp 162–164 °C (dec). ¹H NMR (400 MHz, D₂O) δ 1.06–1.24 (br m, 2H), 1.46–1.68 (br m, 4H), 1.68–1.84 (br m, 2H), 1.93 (br d, *J* = 13.5 Hz, 1H), 1.99 (br d, *J* = 13.7 Hz, 1H), 2.13 (br sept, *J* = 7.6 Hz, 1H), 2.31 (br s, 2H), 2.33–2.42 (br m, 1H), 2.63–2.72 (br m, 1H), 3.05 (br d, *J* = 13.3 Hz, 1H), 3.26–3.54 (br m, 5H), 4.15 (br d, *J* = 13.0 Hz, 1H), 4.41 (br d, *J* = 13.7 Hz, 1H), 6.68 (s, 1.88H). ¹³C NMR (100 MHz, D₂O) δ 25.0, 25.8, 26.2, 28.0, 32.5, 33.0, 36.4, 40.2, 46.4, 47.9, 48.3, 50.2, 135.3, 172.0, 178.7. ESI-MS: positive mode *m/z* = 237.3 ([M + H]⁺). HRMS for C₁₄H₂₄N₂O: calc *m/z* = 237.1961, found *m/z* = 237.1979. Purity (> 99 %). IR (KBr, cm⁻¹) 2947, 2914, 2864, 1654, 1400, 1216, 977. Anal. (C₁₄H₂₄N₂O*0.9C₄H₄O₄*0.5H₂O) C, H, N.

4.57. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(4-hydroxyphenyl)methanone hydrochloric acid salt (56H)

The N-*t*-boc protected compound was obtained by using the general procedure C with 4-hydroxybenzoic acid (138 mg, 1 mmol) for 24 h. DMAP was not used for this reaction and the solvent was changed to THF. After the reaction was finished the precipitate was filtered off, washed with THF (3 × 5 mL), and dried in a desiccator. A white solid (330 mg, 95 %) was obtained. The N-*t*-boc protection group of this solid (300 mg, 0.87 mmol) was cleaved using the general procedure D for 2 h and compound **56H** was obtained as a white solid (210 mg, 86 %) filtering and washing the precipitate with dry Et₂O (3 × 2 mL) as a white solid in 81 % yield over two steps; mp > 320 °C (dec). ¹H NMR (400 MHz, D₂O) δ 2.01 (br m, 2H); 2.33 (br s, 2H); 3.31–3.52 (br m, 6H); 4.24 (br s, 2H); 6.98 (d, *J* = 8.2 Hz, 2H); 7.41 (d, *J* = 8.3 Hz, 2H). ¹³C NMR (100 MHz, D₂O) δ 26.1, 28.1, 47.9, 115.9, 126.8, 129.9, 158.5, 175.5. ESI-MS: positive mode *m/z* = 247.3 ([M + H]⁺). HRMS for C₁₄H₁₈N₂O₂: calc *m/z* = 247.1441, found *m/z* = 247.1436. Purity (> 99.5 %). IR (cm⁻¹) 3084, 2665, 2570, 1607, 1574, 1430, 1255, 1095, 847. Anal. (C₁₄H₁₈N₂O₂*1.0HCl*1.0H₂O) C, H, N.

4.58. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(pyrazin-2-yl)methanone fumaric acid salt (57F)

The N-*t*-boc protected compound was obtained by using the general procedure C with pyrazinecarboxylic acid (124 mg, 1 mmol) for 12 h. A mixture of CH₂Cl₂ and MeOH (40:1) was used for the chromatographic purification. After removal of the solvents a white solid (285 mg, 86 %) was obtained. The N-*t*-boc protection group of this solid (231 mg, 0.69 mmol) was cleaved using the general procedure D with anhydrous ZnBr₂ (469 mg, 2.1 mmol) for 12 h and a yellowish oil **57** (160 mg, 99 %) was obtained after extraction. This oil

57 (160 mg, 0.69 mmol) was transferred to its fumaric acid salt **57F** by using the general procedure G with fumaric acid (80 mg, 0.69 mmol). Compound **57F** (187 mg, 76 %) was obtained as a orange solid in 65 % yield over three steps; mp 154–156 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.06 (br m, 2H), 2.22 (br s, 1H), 2.45 (br s, 1H), 3.37–3.47 (br m, 4H), 3.55 (br d, *J* = 12.2 Hz, 1H), 3.72 (br d, *J* = 12.3 Hz, 1H), 4.00 (br d, *J* = 13.1 Hz, 1H), 4.50 (br d, *J* = 13.2 Hz, 1H), 6.68 (s, 2.0H), 7.48 (m, 1H), 8.77 (m, 1H), 8.91 (m, 1H). ¹³C NMR (125 MHz, D₂O) δ 28.4, 28.6, 30.9, 49.8, 50.2, 50.3, 54.0, 137.6, 146.8, 147.2, 148.8, 150.8, 172.4, 174.4. LC/ESI-MS: positive mode *m/z* = 233.4 ([M + H]⁺). Purity (> 99.7 %). IR (KBr, cm⁻¹) 3446, 1701, 1639, 985, 967. Anal. (C₁₂H₁₆N₄O*1.0C₄H₄O₄*0.5H₂O) C, H, N.

4.59. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(6-chloropyridin-3-yl)methanone fumaric acid salt (58F)

The N-*t*-boc protected compound was obtained by using the general procedure C with 6-chloropyridine-3-carboxylic acid (158 mg, 1 mmol) for 12 h. A mixture of CH₂Cl₂ and MeOH (9:1) was used for the chromatographic purification. After removal of the solvents a white solid was obtained. The N-*t*-boc protection group of this solid (340 mg, 0.92 mmol) was cleaved using the general procedure D 4 h and a clear oil **58** (244 mg, 98 %) was obtained after extraction. This oil **58** (244 mg, 0.91 mmol) was transferred to its fumaric acid salt **58F** by using the general procedure G with fumaric acid (105 mg, 0.91 mmol). Compound **58F** (228 mg, 67 %) was obtained as a white solid in 63 % yield over three steps; mp 154–157 °C (dec). ¹H NMR (400 MHz, D₂O) δ 2.01 (br m, 2H), 2.25 (br s, 1H), 2.44 (br s, 1H), 3.30–3.40 (br m, ³H), 3.42–3.64 (br m, ³H), 3.85 (br d, *J* = 12.9 Hz, 1H), 4.53 (br d, *J* = 13.9 Hz, 1H), 6.67 (s, 1.86H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.97 (dd, *J* = 2.4, 8.3 Hz, 1H), 8.50 (d, *J* = 2.2 Hz, 1H). ¹³C NMR (100 MHz, D₂O) δ 24.7, 25.2, 26.9, 46.2, 46.4, 47.3, 51.4, 124.6, 129.8, 134.4, 138.6, 147.3, 151.8, 170.8, 171.4. ESI-MS: positive mode *m/z* = 266.3 ([M + H]⁺). HRMS for C₁₃H₁₆ClN₃O: calc *m/z* = 266.1055, found *m/z* = 266.1045. Purity (> 99.5 %). IR (cm⁻¹) 2854, 1640, 1581, 1405, 1357, 1105, 970, 640. Anal. (C₁₃H₁₆ClN₃O*0.75C₄H₄O₄*1.2H₂O) C, H, N.

4.60. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(1-methyl-1H-pyrrol-2-yl)methanone fumaric acid salt (59F)

The N-*t*-boc protected compound was obtained by using the general procedure C with 1-methyl-2-pyrrolicarboxylic acid (125 mg, 1 mmol) for 12 h. A mixture of CH₂Cl₂ and MeOH (40:1) was used for the chromatographic purification. After removal of the solvents an off white solid (325 mg, 98 %) was obtained. The N-*t*-boc protection group of this solid (297 mg, 0.89 mmol) was cleaved using the general procedure E with anhydrous ZnBr₂ (602 mg, 2.7 mmol) for 12 h and a yellowish oil **59** (201 mg, 97 %) was obtained after extraction. This oil **59** (201 mg, 0.86 mmol) was transferred to its fumaric acid salt **59F** by using the general procedure G with fumaric acid (100 mg, 0.86 mmol). Compound **59F** (226 mg, 67 %) was obtained as an off white solid in 64 % yield over three steps; mp 136–137 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.01 (br m, 2H), 2.35 (br s, 2H), 3.36–3.44 (br m, 4H), 3.54 (br d, *J* = 13.4 Hz, 2H), 3.72 (s, ³H), 4.47 (br d, *J* = 14.0 Hz, 2H), 6.22 (dd, *J* = 3.9, 2.6 Hz, 1H), 6.55 (dd, *J* = 3.9, 1.6 Hz, 1H), 6.72 (s, 2.4H), 6.95 (dd, *J* = 2.2, 1.7 Hz, 1H). ¹³C NMR (125 MHz, D₂O) δ 28.4, 30.7, 38.0, 50.3, 110.0, 117.4, 127.1, 137.5, 170.5, 173.9.

LC/ESI-MS: positive mode $m/z = 234.4$ ($[M + H]^+$). Purity (99 %). IR (KBr, cm^{-1}) 3434, 1709, 1617, 972. Anal. ($\text{C}_{13}\text{H}_{19}\text{N}_3\text{O} \cdot 1.2\text{C}_4\text{H}_4\text{O}_4 \cdot 0.95\text{H}_2\text{O}$) C, H, N.

4.61. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(1Hindol-2-yl)methanone fumaric acid salt (60F)

The N-*t*-boc protected compound was obtained by using the general procedure C with indole-2-carboxylic acid (161 mg, 1 mmol) for 12 h. A mixture of CH_2Cl_2 and MeOH (40:1) was used for the chromatographic purification. After removal of the solvents a white solid (353 mg, 96 %) was obtained. The N-*t*-boc protection group of this solid (340 mg, 0.92 mmol) was cleaved using the general procedure D for 4 h and a clear oil **60** (244 mg, 98 %) was obtained after extraction. This oil **60** (244 mg, 0.91 mmol) was transferred to its fumaric acid salt **60F** by using the general procedure G with fumaric acid (105 mg, 0.91 mmol). Compound **60F** (228 mg, 67 %) was obtained as a white solid in 63 % yield over three steps; mp 198–200 °C (dec). ^1H NMR (500 MHz, D_2O) δ 1.97 (br m, 2H), 2.28 (br s, 2H), 3.25–3.34 (br m, ^3H), 3.39–3.47 (br m, ^3H), 4.51 (br d, $J = 16.3$ Hz, 2H), 6.62 (s, 1.5H), 6.91 (d, $J = 0.7$ Hz, 1H), 7.20 (ddd, $J = 8.0, 7.1, 0.9$ Hz, 1H), 7.36 (ddd, $J = 8.2, 7.0, 1.1$ Hz, 1H), 7.55 (dd, $J = 8.3, 0.8$, 1H), 7.75 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR (125 MHz, D_2O) δ 28.3, 30.4, 50.2, 109.8, 115.0, 123.5, 125.0, 127.7, 129.6, 131.8, 137.7, 138.9, 169.4, 175.0. LC/ESI-MS: positive mode $m/z = 270.3$ ($[M + H]^+$). Purity (> 99.2 %). IR (KBr, cm^{-1}) 3422, 1701, 1617, 970. Anal. ($\text{C}_{16}\text{H}_{19}\text{N}_3\text{O} \cdot 0.75\text{C}_4\text{H}_4\text{O}_4 \cdot 1.0\text{H}_2\text{O}$) C, H, N.

4.62. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(1Hindol-3-yl)methanone fumaric acid salt (61F)

The N-*t*-boc protected compound was obtained by using the general procedure C with indole-3-carboxylic acid (161 mg, 1 mmol) for 12 h. A mixture of CH_2Cl_2 and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (85 mg, 23 %) was obtained. The N-*t*-boc protection group of this solid (135 mg, 0.37 mmol) was cleaved using the general procedure D for 2 h and a yellowish oil **61** (97 mg, 99 %) was obtained after extraction. This oil **61** (96 mg, 0.36 mmol) was transferred to its fumaric acid salt **61F** by using the general procedure G with fumaric acid (41 mg, 0.36 mmol). Compound **61F** (76 mg, 56 %) was obtained as a white solid in 13 % yield over three steps; mp 185–190 °C (dec). ^1H NMR (500 MHz, D_2O) δ 1.98 (br m, 2H), 2.28 (br s, 2H), 3.30–3.35 (br m, 2H), 3.40–3.48 (br m, 4H), 4.46 (br d, $J = 13.5$ Hz, 2H), 6.62 (s, 1.6H), 7.27 (ddd, $J = 8.1, 7.1, 1.1$ Hz, 1H), 7.32 (ddd, $J = 8.2, 7.1, 1.2$ Hz, 1H), 7.58 (d, $J = 7.9$ Hz, 1H), 7.70 (s, 1H), 7.79 (d, $J = 7.9$, 1H). ^{13}C NMR (125 MHz, D_2O) δ 28.4, 30.5, 50.3, 52.0, 111.0, 115.2, 123.2, 124.1, 125.8, 128.9, 132.0, 137.7, 138.5, 173.9, 175.1. LC/ESI-MS: positive mode $m/z = 270.3$ ($[M + H]^+$). Purity (> 99.8 %). IR (KBr, cm^{-1}) 3398, 1701, 1600, 985. Anal. ($\text{C}_{16}\text{H}_{19}\text{N}_3\text{O} \cdot 0.8\text{C}_4\text{H}_4\text{O}_4 \cdot 1.1\text{H}_2\text{O}$) C, H, N.

4.63. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(1Hindol-5-yl)methanone (62)

The N-*t*-boc protected compound was obtained by using the general procedure C with Indole-5-carboxylic acid (161 mg, 1 mmol) for 12 h. A mixture of CH_2Cl_2 and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents an off-white solid (364 mg, 98 %) was obtained. The N-*t*-boc protection group of this solid (200 mg,

0.54 mmol) was cleaved using the general procedure D for 4 h and compound **62** was obtained as a white solid (138 mg, 95 %) after extraction, in 93 % yield over two steps; mp 225–226 °C. ¹H NMR (400 MHz, CDCl₃) δ 1.88–1.96 (br m, 4H), 2.95–3.40 (br m, 6H), 4.14 (br s, 1H), 4.73 (br s, 1H), 6.55 (s, 1H), 7.18 (dd, *J* = 1.4, 8.3 Hz, 1H), 7.22 (t, *J* = 2.7 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.67 (s, 1H), 8.99 (br s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 28.8, 32.4, 51.3, 103.1, 111.4, 119.9, 121.0, 125.7, 127.6, 127.9, 136.4, 172.7. ESI-MS: positive mode *m/z* = 271.3 ([M + H]⁺). Purity (> 99 %). IR (cm⁻¹) 3316, 2859, 1614, 1580, 1425, 1233, 930, 886.

4.64. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(1H-indazol-6-yl)methanone (63)

The N-tboc protected compound was obtained by using the general procedure C with 1H-indazole-6-carboxylic acid (162 mg, 1 mmol) for 12 h. A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (280 mg, 76 %) was obtained. The Ntboc protection group of this solid (160 mg, 0.43 mmol) was cleaved using the general procedure D for 4 h and compound **63** was obtained as an off-white solid (110 mg, 94 %) after extraction, in 71 % yield over two steps; mp 227–229 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 1.45–2.05 (br m, 4H), 2.90–3.40 (br m, 6H), 3.64 (br s, 1H), 4.57 (br s, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.51 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 8.11 (s, 1H), 13.19 (br s, 1H). ¹³C NMR (100 MHz, DMSO-d₆) δ 27.9, 31.6, 46.4, 50.7, 52.0, 108.3, 118.9, 120.6, 122.6, 133.4, 135.1, 139.3, 169.5. ESIMS: positive mode *m/z* = 271.3 ([M + H]⁺). HRMS for C₁₆H₁₉N₃O: calc *m/z* = 270.1601, found *m/z* = 270.1594. Purity (> 99 %). IR (cm⁻¹) 3316, 2859, 1614, 1580, 1425, 1233, 930, 886.

4.65. (1H-imidazol-1-yl)(pyrrolidin-1-yl)methanone (64)

Pyrrolidine (0.78 g, 11 mmol) and CDI (1.95 g, 12 mmol) were dissolved in 20 mL of THF and stirred under reflux for 16 h. After evaporating the solvent under reduced pressure the residue was dissolved in 30 mL of CH₂Cl₂ and washed with water (2 × 10 mL). The organic layer was dried with MgSO₄ and the solvent was removed under reduced pressure.

Compound **64** was obtained as a white solid in 90 % yield without further purification; mp 54–55 °C. ¹H NMR (500 MHz, CDCl₃) δ 1.98 (m, 4H), 3.62 (m, 4H), 7.06 (dd, *J* = 1.4, 0.9 Hz, 1H), 7.34 (t, *J* = 1.4 Hz, 1H), 8.01 (s, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 25.7, 48.0, 117.7, 129.6, 136.8, 149.8. LC/ESI-MS: positive mode *m/z* = 166.1 ([M + H]⁺). Purity (> 99.5 %). IR (KBr, cm⁻¹) 3138, 1672, 1423, 1339. Anal. (C₈H₁₁N₃O) C, H, N.

4.66. (1H-imidazol-1-yl)(morpholino)methanone (65)

Morpholine (0.96 g, 11 mmol) and CDI (1.95 g, 12 mmol) were dissolved in 20 mL of THF and stirred under reflux for 16 h. After evaporating the solvent under reduced pressure the residue was dissolved in 30 mL of CH₂Cl₂ and washed with water (2 × 10 mL). The organic layer was dried with MgSO₄ and the solvent was removed under reduced pressure.

Compound **65** was obtained as a white solid in 65 % yield without further purification; mp 89–90 °C. ¹H NMR (500 MHz, CDCl₃) δ 3.62 (m, 4H), 3.75 (m, 4H), 7.10 (m, 1H), 7.19 (t, *J* = 1.4 Hz, 1H), 7.87 (s, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 46.9, 66.6, 117.9, 130.1, 137.0, 151.0. LC/ESI-MS: positive mode *m/z* = 181.9 ([M + H]⁺). Purity (> 99 %). IR (KBr, cm⁻¹) 3138, 1681, 1433, 1305. Anal. (C₈H₁₁N₃O₂) C, H, N.

4.67. (4-benzylpiperidin-1-yl)(1H-imidazol-1-yl)methanone (66)

4-Benzylpiperidine (1.93 g, 11 mmol) and CDI (1.95 g, 12 mmol) were dissolved in 20 mL of THF and stirred under reflux for 16 h. After evaporating the solvent under reduced pressure the residue was dissolved in 30 mL of CH₂Cl₂ and washed with water (2 × 10 mL). The organic layer was dried with MgSO₄ and the solvent was removed under reduced pressure. Compound **66** was obtained as a white solid in 87 % yield without further purification; mp 64 °C. ¹H NMR (500 MHz, CDCl₃) δ 1.30 (m, 2H), 1.77 (m, 2H), 1.83 (m, 1H), 2.59 (d, *J* = 7.1 Hz, 1H), 2.96 (m, 2H), 4.09 (br d, *J* = 13.1 Hz, 2H), 7.07 (dd, *J* = 1.4, 0.9 Hz, 1H), 7.14 (m, 2H), 7.18 (t, *J* = 1.4 Hz, 1H), 7.22 (m, 1H), 7.29 (m, 2H), 7.84 (t, *J* = 1.0 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 32.0, 38.1, 42.9, 47.0, 118.1, 126.4, 128.5, 129.2, 129.7, 137.0, 139.6, 151.0. LC/ESI-MS: positive mode *m/z* = 270.1 ([M + H]⁺), negative mode *m/z* = 268.0 ([M – H][–]). Purity (> 99.5 %). IR (KBr, cm^{–1}) 3154, 2951, 1680, 1464, 1430. Anal. (C₁₆H₁₉N₃O) C, H, N.

4.68. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(pyrrolidin-1-yl)methanone fumaric acid salt (67F)

(1*H*-pyrrol-1-yl)(Pyrrolidin-1-yl)methanone **64** (182 mg, 1.1 mmol) was dissolved in 2 ml of MeCN and methyl iodide (625 mg, 4.4 mmol) was added. The solution was stirred at rt for 24 h before the volatiles were removed under reduced pressure. The residue was dissolved in 10 ml of CH₂Cl₂ and Et₃N (101 mg, 1 mmol) and *N*-*t*Boc-bispidine **13** (226 mg, 1 mmol) were added. The solution was stirred at rt for another 24 h before it was washed twice with 5 ml of hydrochloric acid (1 M) and once with 5 ml of H₂O. The organic layer was dried with MgSO₄, filtered and the solvent is removed under reduced pressure. The residue was purified by flash chromatography using a mixture of CH₂Cl₂ and MeOH (40:1) and after removal of the solvents a white solid (223 mg, 69 %) was obtained. The *N*-*t*boc protection group of this solid (180 mg, 0.56 mmol) was cleaved using the general procedure D for 3 h and a white solid **67** (120 mg, 97 %) was obtained after extraction. This solid **67** (105 mg, 0.47 mmol) was transferred to its fumaric acid salt **67F** by using the general procedure F. Compound **67F** (109 mg, 67 %) was obtained as a white solid in 45 % yield over three steps; mp 166–169 °C (dec). ¹H NMR (500 MHz, MeOD) δ 1.88–1.93 (br m, 5H), 1.97–2.02 (br m, 1H), 2.17 (br m, 1H), 3.09–3.13 (br m, 2H), 3.29–3.34 (br m, 2H), 3.43–3.47 (br m, 4H), 3.50 (br d, *J* = 12.8 Hz, 2H), 3.81 (br d, *J* = 13.3 Hz, 2H), 6.68 (s, 2.0H). ¹³C NMR (125 MHz, MeOD) δ 26.4, 27.9, 30.5, 48.9, 49.4, 52.1, 136.2, 164.8, 171.5. LC/ESI-MS: positive mode *m/z* = 224.1 ([M + H]⁺). Purity (> 99.4 %). IR (KBr, cm^{–1}) 3441, 1710, 1635, 972. Anal. (C₁₂H₂₁N₃O*1.0C₄H₄O₄*0.25H₂O) C, H, N.

4.69. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(morpholino)methanone fumaric acid salt (68F)

Morpholino(1*H*-pyrrol-1-yl)methanone **65** (182 mg, 1.1 mmol) was dissolved in 2 ml of MeCN and methyl iodide (625 mg, 4.4 mmol) was added. The solution was stirred at rt for 24 h before the volatiles were removed under reduced pressure. The residue was dissolved in 10 ml of CH₂Cl₂ and Et₃N (101 mg, 1 mmol) and *N*-*t*boc-bispidine **13** (226 mg, 1 mmol) were added. The solution was stirred at rt for another 24 h before it was washed twice with 5 ml of hydrochloric acid (1 M) and once with 5 ml of H₂O. The organic layer was dried with

MgSO₄, filtered and the solvent is removed under reduced pressure. The residue was purified by flash chromatography using a mixture of CH₂Cl₂ and MeOH (9:1) and after removal of the solvents a white solid (336 mg, 99 %) was obtained. The N-*t*boc protection group of this solid (130 mg, 0.38 mmol) was cleaved using the general procedure D for 2 h and a clear oil **68** (87 mg, 95 %) was obtained after extraction. This oil **68** (87 mg, 0.36 mmol) was transferred to its fumaric acid salt **68F** by using the general procedure G with fumaric acid (42 mg, 0.36 mmol). Compound **68F** (57 mg, 44 %) was obtained as an off white solid in 42 % yield over three steps; mp 155–158 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.93 (br m, 1H), 1.98 (br m, 1H), 2.24 (br s, 2H), 3.27 (br m, 2H), 3.35 (br m, 2H), 3.38 (dd, *J* = 4.9, 4.7 Hz, 4H), 3.54 (br d, *J* = 13.2 Hz, 2H), 3.76 (dd, *J* = 4.9, 4.7 Hz, 4H), 3.78 (br m, 2H), 6.73 (s, 1.5H). ¹³C NMR (125 MHz, D₂O) δ 28.8, 31.4, 49.3, 50.4, 53.9, 69.1, 137.5, 168.0, 173.9. LC/ESI-MS: positive mode *m/z* = 240.4 ([M + H]⁺). Purity (> 99.7 %). IR (KBr, cm⁻¹) 3440, 1679, 1637, 985, 967. Anal. (C₁₂H₂₁N₃O₂*0.75C₄H₄O₄*1.5H₂O) C, H, N.

4.70. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(4-benzylpiperidin-1-yl)methanone fumaric acid salt (69F)

(4-Benzylpiperidin-1-yl)(1*H*-pyrrol-1-yl)methanone **66** (296 mg, 1.1 mmol) was dissolved in 2 ml of MeCN and methyl iodide (625 mg, 4.4 mmol) was added. The solution was stirred at rt for 24 h before the volatiles were removed under reduced pressure. The residue was dissolved in 10 ml of CH₂Cl₂ and Et₃N (101 mg, 1 mmol) and N-*t*Boc-bispidine **13** (226 mg, 1 mmol) were added. The solution was stirred at rt for another 24 h before it was washed twice with 5 ml of hydrochloric acid (1 M) and once with 5 ml of H₂O. The organic layer was dried with MgSO₄, filtered and the solvent is removed under reduced pressure. The residue was purified by flash chromatography using a mixture of CH₂Cl₂ and MeOH (40:1) and after removal of the solvents a white solid (355 mg, 83 %) was obtained. The N-*t*boc protection group of this solid (300 mg, 0.70 mmol) was cleaved using the general procedure D for 3 h and a clear oil **69** (191 mg, 83 %) was obtained after extraction. This oil **69** (124 mg, 0.38 mmol) was transferred to its fumaric acid salt **69F** by using the general procedure G with fumaric acid (44 mg, 0.38 mmol). Compound **69F** (124 mg, 72 %) was obtained as a white solid in 50 % yield over three steps; mp 172–175 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.17–1.27 (br m, 2H), 1.69 (br m, 2H), 1.82 (br m, 1H), 1.91 (br d, *J* = 13.6 Hz, 1H), 1.97 (br d, *J* = 13.6 Hz, 1H), 2.21 (br s, 2H), 2.61 (d, *J* = 7.1 Hz, 2H), 2.87 (dt, *J* = 12.4, 1.9 Hz, 2H), 3.22 (br d, *J* = 13.1 Hz, 2H), 3.34 (br d, *J* = 13.1 Hz, 2H), 3.53 (br d, *J* = 13.2 Hz, 2H), 3.70 (br m, 4H), 6.69 (s, 2.0H), 7.27–7.41 (m, 5H). ¹³C NMR (125 MHz, D₂O) δ 27.5, 30.2, 32.8, 38.8, 43.4, 48.1, 49.1, 52.9, 127.6, 129.9, 130.8, 136.2, 142.3, 166.8, 173.0. LC/ESI-MS: positive mode *m/z* = 328.4 ([M + H]⁺). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3441, 1704, 1628, 981, 965. Anal. (C₂₀H₂₉N₃O*1.0C₄H₄O₄*0.5H₂O) C, H, N.

4.71. 1-((1R,5S)-7-methyl-3,7-diazabicyclo[3.3.1]nonan-3-yl)ethanone (70)

Compound **70** was obtained by using general procedure H with iodomethane (92.3 mg). Purification was achieved by flash chromatography using a mixture of CH₂Cl₂ and MeOH (9:1) and after removal of the solvents under reduced pressure the final compound **70** was obtained as a clear oil (47.4 mg, 40 %). ¹H NMR (400 MHz, CDCl₃) δ 1.59 (br m, 1H), 1.68

(br m, 1H), 1.87 (br s, 2H), 2.03 (s, ^3H), 2.09 (s, ^3H), 2.12 (br d, $J = 11.2$ Hz, 1H), 2.20 (br d, $J = 11.0$ Hz, 1H), 2.87 (br m, ^3H), 3.34 (d, $J = 13.1$ Hz, 1H), 3.79 (br d, $J = 13.1$ Hz, 1H), 4.55 (br d, $J = 13.2$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.2, 29.2, 29.6, 31.2, 46.5, 46.9, 51.2, 60.5, 61.0, 81.4, 170.3. ESI-MS: positive mode $m/z = 183.2$ ($[\text{M} + \text{H}]^+$), 205.2 ($[\text{M} + \text{Na}]^+$). Purity ($> 95\%$). IR (cm^{-1}) 2923, 2862, 2775, 1614, 1443, 1259, 997.

4.72. 1-((1R,5S)-7-ethyl-3,7-diazabicyclo[3.3.1]nonan-3-yl)ethanone (71)

Compound **71** was obtained by using general procedure H with iodoethane (101.4 mg). Purification was achieved by flash chromatography using a mixture of CH_2Cl_2 and MeOH (9:1) and after removal of the solvents under reduced pressure the final compound **71** was obtained as a clear oil (74.0 mg, 58 %). ^1H NMR (400 MHz, CDCl_3) δ 0.95 (t, $J = 7.0$ Hz, ^3H), 1.61 (br m, 1H), 1.70 (br m, 1H), 1.84 (br s, 2H), 2.01 (s, ^3H), 2.04–2.26 (br m, 5H), 2.81 (br d, $J = 13.2$ Hz, 1H), 2.96 (br d, $J = 10.7$ Hz, 2H), 3.33 (br d, $J = 12.7$ Hz, 1H), 3.78 (br d, $J = 13.4$ Hz, 1H), 4.60 (br d, $J = 13.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 12.4, 22.2, 29.2, 29.7, 32.1, 46.4, 51.2, 52.7; 58.3; 58.4, 169.8. ESIMS: positive mode $m/z = 197.3$ ($[\text{M} + \text{H}]^+$), 219.2 ($[\text{M} + \text{Na}]^+$). Purity ($> 95\%$). IR (cm^{-1}) 2916, 2864, 2748, 1631, 1445, 1233, 994, 586.

4.73. 1-((1R,5S)-7-propyl-3,7-diazabicyclo[3.3.1]nonan-3-yl)ethanone (72)

Compound **72** was obtained by using general procedure H with 1-iodopropane (110.5 mg). Purification was achieved by flash chromatography using a mixture of CH_2Cl_2 and MeOH (20:1) and after removal of the solvents under reduced pressure the final compound **72** was obtained as a clear oil (91.6 mg, 67 %). ^1H NMR (400 MHz, CDCl_3) δ 0.82 (t, $J = 7.4$ Hz, ^3H), 1.32–1.49 (br m, 2H), 1.69 (br s, 2H), 1.88 (br s, 2H), 2.03 (s, ^3H), 2.06–2.32 (br m, 4H), 2.83 (br d, $J = 13.2$ Hz, 1H), 2.95 (br d, $J = 8.0$ Hz, 2H), 3.32 (br d, $J = 13.4$ Hz, 1H), 3.78 (br d, $J = 13.0$ Hz, 1H), 4.58 (br d, $J = 13.5$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 11.8, 20.0, 22.3, 29.0, 29.5, 31.5, 46.5, 51.2, 61.2, 80.7, 170.0. ESI-MS: positive mode $m/z = 211.3$ ($[\text{M} + \text{H}]^+$). Purity ($> 95\%$). IR (cm^{-1}) 2921, 2858, 2204, 1603, 1431, 1205, 758, 688.

4.74. Membrane preparation: Preparation of rat brains

Frozen rat brains ($-80\text{ }^\circ\text{C}$) were thawed slowly before the preparation of the P2 rat brain membrane fraction (30–60 min. on ice, afterwards at rt). A single cut just behind the inferior colliculi was done to exclude the cerebellum and the medulla. After the determination of the wet weight (1.32 g on average), the brains were pressed into a pulp using a syringe and homogenized in saccharose buffer with a glass teflon homogenizer (potter, 10 sec.). The tissue was then centrifuged ($1,000 \times g$, 20 min., $4\text{ }^\circ\text{C}$), the supernatant (S1) aspirated with a Pasteur pipette and stored on ice. The P1 pellet was re-suspended in saccharose buffer and the centrifugation was repeated. The supernatant S1' was collected and added to the supernatant S1. The combined supernatants were centrifuged ($25,000 \times g$, 20 min., $4\text{ }^\circ\text{C}$), the supernatant S2 was removed and the pellet P2 collected and diluted with HSS buffer. The buffer volume added was calculated on the basis of the wet weight on a ratio 1:2.

The final pellet was stored in aliquots at $-80\text{ }^\circ\text{C}$. On the day of the experiment, the P2 membrane fraction was thawed, diluted with HSS buffer (30-fold volume), homogenized

and centrifuged ($35,000 \times g$, 10 min., 4 °C). The collected pellet was suspended in HSS buffer and used in the radioligand binding experiment.

4.75. Membrane preparation: Preparation of calf adrenals

Frozen calf adrenals (−80 °C) were placed on ice (30–60 min.) and allowed to thaw slowly before they were cut into small pieces. After determination of the wet weight (4–6 g), the tissue was homogenized in HSS buffer (Ultraturrax at 750 rpm). The homogenate was centrifuged ($30,000 \times g$, 10 min., 4 °C), the pellets collected and washed. This procedure was repeated five times. The buffer volume to re-suspend the pellet was calculated on the basis of the wet weight in a ratio of 1:6.5.

The prepared tissues were stored in aliquots at −80 °C. One hour before the experiments the tissues were slowly thawed, homogenized in HSS buffer and centrifuged ($25,000 \times g$, 20 min., 4 °C). The pellets were re-suspended in fresh HSS buffer and used for radioligand binding assays.

4.76. Membrane preparation: Preparation of Torpedo californica electroplax

Frozen samples of Torpedo californica electric organ (−80 °C) were placed on ice (30–60 min.) and allowed to thaw slowly before the membrane preparation. The tissue was homogenized in ice-cold HSS buffer (Ultraturrax at 750 rpm) and centrifuged ($30,000 \times g$, 10 min., 4 °C). The pellets were collected, washed four times with HSS buffer through re-homogenization and centrifugation at the same settings. The remaining pellets were collected, re-suspended in HSS buffer and stored in aliquots at −80 °C.

One hour before the experiments the tissues were slowly thawed, homogenized in HSS buffer and centrifuged ($25,000 \times g$, 20 min., 4 °C). The pellets were re-suspended in fresh HSS buffer and used for radioligand binding assays.

4.77. Radioligand binding assay: Competition assay using (±)-[³H]epibatidine ([³H]Epi) and rat brain P2 fraction (α4β2* nAChR)

A dilution row of 6–9 concentrations of the test compound was prepared. Each assay sample, with a total volume of 500 μL contained 100 μL of the membrane protein (60 μg), 100 μL of (±)-[³H]Epi (0.5 nM), 100 μL of HSS buffer and 200 μL of the test compound. Non-specific binding was determined in the presence of 300 μM (−)-nicotine tartrate salt. The samples were homogenized and incubated (90 min. at 22 °C). The incubation was terminated by vacuum filtration through glass fiber filters presoaked in 1% PEI solution. The filters were rinsed three times with TRIS buffer, punched out and transferred into 4 mL scintillation vials. The scintillation vials were filled with scintillation cocktail (2 mL) and the radioactivity was measured using a liquid scintillation counter. Assays were carried out in duplicates, triplicates or quadruplicates.

4.78. Radioligand binding assay: Competition assay using [³H]methyllycaconitine ([³H]MLA) and rat brain P2 fraction (α7* nAChR)

A dilution row of 6–9 concentrations of the test compound was prepared. Each assay sample, with a total volume of 250 μL contained 50 μL of the test compound, 100 μL of

[³H]MLA, 100 μ L of P2 membrane protein fraction (60–70 μ g). Non-specific binding was determined in the presence of 1 μ M MLA. The samples were homogenized and incubated (120 min. at 22 °C). The incubation was terminated by vacuum filtration through glass fiber filters presoaked in 1% PEI solution. The filters were rinsed three times with TRIS buffer, punched out and transferred into 4 mL scintillation vials. The scintillation vials were filled with scintillation cocktail (2 mL) and the radioactivity was measured using a liquid scintillation counter. Assays were carried out in duplicates, triplicates or quadruplicates.

4.79. Radioligand binding assay: Competition assay using ($\pm$)-[³H]epibatidine ([³H]Epi) and calf adrenals membrane fraction (α 3 β 4* nAChR)

A dilution row of 6–9 concentrations of the test compound was prepared. Each assay sample, with a total volume of 500 μ L contained 200 μ L of the test compound, 100 μ L of ($\pm$)-[³H]Epi (0.5 nM), 100 μ L of the calf adrenal membrane fraction (60 – 70 μ g) and 100 μ L HSS buffer. Non-specific binding was determined in the presence of 300 μ M (–)-nicotine tartrate salt. The samples were homogenized and incubated (90 min. at 22 °C). The incubation was terminated by vacuum filtration through glass fiber filters presoaked in 1% PEI solution. The filters were rinsed three times with TRIS buffer, punched out and transferred into 4 mL scintillation vials. The scintillation vials were filled with scintillation cocktail (2 mL) and the radioactivity was measured using a liquid scintillation counter. Assays were carried out in duplicates, triplicates or quadruplicates.

4.80. Radioligand binding assay: Competition assay using ($\pm$)-[³H]epibatidine ([³H]Epi) and Torpedo californica electroplax ((α 1)2 β 1 γ 6 nAChR)

A dilution row of 6–9 concentrations of the test compound was prepared. Each assay sample, with a total volume of 500 μ L contained 200 μ L of the test compound, 100 μ L of ($\pm$)-[³H]Epi, 100 μ L of Torpedo californica electroplax (60 – 70 μ g) and 100 μ L HSS buffer. Non-specific binding was determined in the presence of 300 μ M (–)-nicotine tartrate salt. The samples were homogenized and incubated (90 min. at 22 °C). The incubation was terminated by vacuum filtration through glass fiber filters presoaked in 1% PEI solution. The filters were rinsed three times with TRIS buffer, punched out and transferred into 4 mL scintillation vials. The scintillation vials were filled with scintillation cocktail (2 mL) and the radioactivity was measured using a liquid scintillation counter. Assays were carried out in duplicates, triplicates or quadruplicates.

4.81. Heterologous Expression of nAChRs in *Xenopus laevis* Oocytes

Mouse muscle nAChR α 1, β 1, and δ clones used for receptor expression in *Xenopus laevis* oocytes were obtained from Dr. J. Boulter (University of California, Los Angeles, CA), and the mouse ϵ clone was provided by Dr. P. Gardner (University of Massachusetts Medical School, Worcester, MA). Human nAChR clones were obtained from Dr. J. Lindstrom (University of Pennsylvania, Philadelphia, PA). The human Resistance-tocholinesterase 3 (RIC-3) clone, obtained from Dr. M. Treinin (Hebrew University, Jerusalem, Israel), was co-injected with α 7 to improve the level and speed of α 7 receptor expression without affecting the pharmacological properties of the receptors.⁵⁷ Subsequent to linearization and

purification of the plasmid cDNAs, cRNAs were prepared using the mMessage mMachine *in vitro* RNA transfection kit (Ambion, Austin, TX).

Oocytes were surgically removed from mature female *Xenopus laevis* frogs (Nasco, Ft. Atkinson, WI) and injected appropriate nAChR subunit cRNAs as described previously.⁶⁰ Frogs were maintained in the Animal Care Service facility of the University of Florida, and all procedures were approved by the University of Florida Institutional Animal Care and Use Committee. In brief, the frog was first anesthetized for 15–20 min in 1.5 L frog tank water containing 1 g of 3-aminobenzoate methanesulfonate (MS-222) buffered with sodium bicarbonate. The harvested oocytes were treated with 1.25 mg/ml collagenase (Worthington Biochemicals, Freehold, NJ) for 2 h at room temperature in a calcium-free Barth's solution (88 mM NaCl, 1 mM KCl, 2.38 mM NaHCO₃, 0.82 mM MgSO₄, 15 mM HEPES, and 12 mg/l tetracycline, pH 7.6) to remove the follicular layer. Stage V oocytes were subsequently isolated and injected with 50 nl of 5–20 ng nAChR subunit cRNA. Recordings were carried out 1–7 days after injection.

4.82. Two-Electrode Voltage Clamp Electrophysiology

Experiments were conducted using OpusXpress 6000A (Molecular Devices, Union City, CA).⁶⁰ Both, the voltage and current electrodes were filled with 3 M KCl. Oocytes were voltage-clamped at –60 mV. The oocytes were bath-perfused with Ringer's solution (115 mM NaCl, 2.5 mM KCl, 1.8 mM CaCl₂, 10 mM HEPES, and 1 μ M atropine, pH 7.2) at 2 ml/min for $\alpha 7$ receptors and at 4 ml/min for other subtypes. To evaluate the effects of different compounds on ACh-evoked responses of various nAChR subtypes expressed in oocytes, baseline conditions were defined by two initial applications of ACh made before co-applications of experimental compounds with the control ACh. The agonist solutions were applied from a 96-well plate via disposable tips, and the test compounds were co-applied with ACh by the OpusXpress pipette delivery system for acute co-application experiments. Drug applications were 12 s in duration followed by a 181-s washout period for $\alpha 7$ receptors and 8 s with a 241-s washout for other subtypes. A typical recording for each oocyte contained two initial control applications of ACh, an experimental compound application, and then a follow-up control application of ACh to determine the desensitization or rundown of the receptors. The control ACh concentrations were: 30 μ M for $\alpha 1\beta 1\epsilon\delta$, 60 μ M for $\alpha 7$, 100 μ M for $\alpha 3\beta 4$, 30 μ M for $\alpha 4\beta 2$.

Data were collected at 50 Hz, filtered at 20 Hz, analyzed by Clampfit 9.2 (Molecular Devices) and Excel 2003 (Microsoft, Redmond, WA), and normalized to the averaged peak current or net charge response of the two initial ACh controls.⁶¹ Data were expressed as means $\pm$ SEM from at least four oocytes for each experiment and plotted by Kaleidagraph 3.0.2 (Abelbeck Software, Reading, PA).

4.83. Calculation of physicochemical properties

The physicochemical properties have been calculated using ACD/ADME Suite 5.0 and ACD/PhysChem (ACD/Labs).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BBB	blood-brain barrier
CD₃OD	tetradeuteromethanol
CDCl₃	deuteriochloroform
CH₂Cl₂	dichloromethane
CNS	central nervous system
D₂O	deuterium oxide
DCC	N,N'-dicyclohexylcarbodiimide
DMAP	4-(Dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
Et₂O	diethyl ether
Et₃N	triethylamine
EtOAc	ethyl acetate
HBA	hydrogen bond acceptor
HCl	hydrogen chloride
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
HSS	HEPES-buffered salt solution
K₂CO₃	potassium carbonate
KBr	potassium bromide
KMnO₄	potassium permanganate
KOH	potassium hydroxide
MeCN	acetonitrile
MeI	iodomethane

MeOH	methanol
MgSO₄	magnesium sulfate
nAChR	nicotinic acetylcholine receptor
NaHCO₃	sodium hydrogen carbonate
NaOH	sodium hydroxide
Pd/C	palladium on activated charcoal
PE	petroleum ether
PEI	poly(ethyleneimine)
Ro5	rule of five
THF	tetrahydrofuran
TPSA	topological polar surface area
TRIS	Tri(hydroxymethyl)aminomethane
ZnBr₂	zinc bromide

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Figure 1.

Structures of acetylcholine **1**, the natural products nicotine **2**, and cytisine **3**, 3-(pyridine-3-yl)-cytisine (3PC) **4** and the FDA approved drug varenicline **5**.

Figure 2.
3,7-diazabicyclo[3.3.1]nonane based compounds

Figure 3.

Responses of oocytes expressing diverse nAChR subtypes to 1 or 10 μ M of selected compounds (numbering are following the sequence in the tables) relative to ACh control responses. Responses of oocytes expressing diverse nAChRs to compounds co-applied at 1 μ M with ACh compared to responses to ACh alone. Bars above zero indicate additive effects; bars below zero indicate reduced responses.

Scheme 1.

Synthesis of compounds. Reagents and conditions: (a) $(\text{CH}_2\text{O})_n$, BnNH_2 , AcOH, MeOH, [Ar] reflux, 6 h; (b) N_2H_4 (80%), NaOH, diethylene glycol, 125 °C, 2 h, then Dean Stark trap, 140 °C, 8 h; (c) HCl/1,4-dioxane (4M), rt, 12 h; (d) Pd/C (5%), H_2 (2–4 bar), MeOH, rt, 4–24 h; (e) carboxyl chloride, Et_3N , toluene, rt, 2 h; (f) sulfonyl chloride, Et_3N , toluene, rt, 2 h; (g) carbamoyl chloride, Et_3N , toluene, rt, 2 h; (h) CDI, THF, reflux, 2 h = **14**; then MeI, MeCN, THF, rt, 24 h, then R-COOH, Et_3N , MeCN, rt, 12–120 h; (i) R-COOH, DCC, DMAP, CH_2Cl_2 , 0 °C to rt, 12 h; for **Boc-56**: 4-hydroxybenzoic acid, DCC, THF, rt, 24 h;

(j) **64**, **65** or **66**, MeI, MeCN, rt, 24h; then **13**, CH₂Cl₂, Et₃N, rt, 24h.; (k) HCl/1,4-dioxane (4M), rt, 4 h; (l) anhydr. ZnBr₂, CH₂Cl₂, rt, 12–120 h; (m) CDI, THF, reflux, 16 h; (n) alkyl iodide, K₂CO₃, DMF, rt, 12 h

Table 1
Affinities (K_i values $\pm$ SEM) and calculated physicochemical parameters of known nAChR ligands **3–7**

compound	$\alpha 4\beta 2^*$ Ki [nM]	$\alpha 3\beta 4^*$ Ki [nM]	$\alpha 7^*$ Ki [nM]	$(\alpha 1)\beta 1\gamma\delta$ Ki [nM]	M_r	ClogP ^e	TPSA	logBB ^f
3 (Cyt) ^a	0.122	19	250	1,300	190.24	0.17	32.34	-0.25
4 (3PC) ^b	0.91	119	1,100	> 5,000	267.14	1.03	45.23	-0.23
5 (Var) ^c	0.06	240	322	3,540	211.26	0.74	37.81	-0.06
17	385 $\pm$ 6	2,000	19,000	194.27	-0.14	32.34	-0.10
34	2,450 $\pm$ 420	10,000	> 50,000	208.30	0.26	23.55	-0.12

^{a,b} from ref.: 41,44,45;

^c from ref.: 42;

^d from ref.: 44;

^e logP values have been calculated using the ACD/Labs Algorithm;

^f logP calculated with the ACD/Labs Algorithm was used to calculate logBB.

TPSA: topological polar surface area.

Table 2

Affinities (K_i values $\pm$ SEM) and calculated physicochemical parameters (logP, TPSA, logBB) of bispidine, the bispidine intermediates **12** and **13** and of the bispidine carboxamide derivatives **8**, **15–33**, and **43–63**

Compd.	R =	$\alpha_4\beta_2^*$ K_i [nM]	$\alpha_3\beta_4^*$ K_i [nM]	α_7^* K_i [nM]	$(\alpha_1)_2\beta_1\gamma\delta$ K_i [nM]	M_r	ClogP ^b	TPSA	logBB ^c
bispidine	H	600.0 $\pm$ 23	> 1,000	> 1,000	> 1,000	126.20	0.06	24.06	0.01
12		> 10,000	569.6 $\pm$ 150.0	> 5,000	> 10,000	216.32	1.88	15.27	0.23
13		45.0 $\pm$ 5.3	1276.5 $\pm$ 9.3	> 5,000	> 10,000	226.31	1.18	41.57	0.08
8		5.6 $\pm$ 1.4	663.8 $\pm$ 40.1	636 ^a	n. d.	168.24	-0.14	32.34	-0.02
15		4.5 $\pm$ 2.3	328.7 $\pm$ 70.2	> 2,000	> 1,000	182.26	0.39	32.34	0.00
16		3.6 $\pm$ 0.7	265.9 $\pm$ 83.4	> 1,000	> 5,000	196.29	0.92	32.34	0.04
17		50.3 $\pm$ 10.4	828.0 ^a	> 5,000	n. d.	196.29	0.73	32.34	0.04
43		10.8 $\pm$ 0.8	n. d.	n. d.	n. d.	222.33	1.35	32.34	0.11

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55		43.5	n. d.	n. d.	n. d.	236.35	1.88	32.34	0.22
18		> 5,000	> 5,000	> 10,000	> 10,000	236.35	1.92	32.34	0.28
19		453.6 ± 14.8	> 5,000	> 10,000	> 10,000	230.30	0.56	32.34	-0.09
44		> 10,000	> 10,000	> 10,000	> 10,000	244.33	1.02	32.34	-0.13
20		> 10,000	n. d.	n. d.	n. d.	264.75	1.67	32.34	-0.01
21		> 10,000	> 10,000	> 10,000	> 10,000	275.30	0.06	81.17	- 0.52
45		386.4 ± 42.7	> 5,000	n. d.	> 10,000	248.30	0.82	32.34	-0.05
22		> 1,000	n. d.	n. d.	n. d.	264.75	1.36	32.34	- 0.11
46		147.1 ± 6.8	> 3,000	n. d.	> 10,000	298.30	1.62	32.34	0.03
23		> 2,000	> 10,000	> 10,000	> 10,000	275.30	0.47	81.17	-0.47
24		221.0 ± 84.0	> 5,000	> 10,000	> 10,000	244.33	1.02	32.34	- 0.13
25		> 10,000	> 10,000	> 10,000	> 10,000	286.41	2.25	32.34	0.12

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47		39.9 ± 7.1	1089.5 ± 290.5	*	*	306.40	2.21	32.34	-0.65
26		197.3	> 10,000	> 10,000	> 10,000	248.30	0.78	32.34	-0.06
27		130.2	n. d.	> 10,000	n. d.	264.75	1.33	32.34	-0.12
28		138.0 ± 17.3	> 10,000	> 10,000	n. d.	309.20	1.50	32.34	-0.12
56		104.6	n. d.	> 1,000	n. d.	246.30	0.20	52.57	-0.25
48		20.7 ± 8.9	> 10,000	> 10,000	> 5,000	255.31	0.22	56.13	-0.12
49		15.9 ± 3.9	4200	1726	> 5,000	275.30	0.52	81.17	-0.46
29		> 1,000	> 5,000	> 5,000	> 10,000	290.36	1.24	50.80	-0.01
50		454.8 ± 89.4	> 10,000	> 10,000	> 10,000	231.29	-0.60	45.23	-0.07
57		73.2 ± 9.1	> 10,000	> 10,000	> 10,000	232.28	-1.00	58.12	-0.11

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15		291.6 ± 50.1	> 5,000	> 10,000	> 10,000	310.19	0.62	45.23	-0.19
58		194	> 1,000	n. d.	n. d.	265.74	0.24	45.23	-0.42
30		21.4 ± 2.3	2242.5	n. d.	> 10,000	220.27	0.53	45.48	0.04
31		17.6 ± 0.8	> 10,000	> 10,000	> 10,000	236.33	0.88	60.58	-0.11
59		661.6 ± 47.3	n. d.	n. d.	n. d.	233.31	-0.81	37.27	-0.11
60		> 10,000	> 10,000	> 10,000	> 10,000	269.34	0.12	48.13	-0.33
61		> 10,000	> 10,000	> 10,000	> 10,000	269.34	0.49	48.13	-0.39
62		1.800	n. d.	n. d.	n. d.	269.34	0.49	48.13	-0.43
63		205.07	n. d.	n. d.	n. d.	270.33	0.17	61.02	-0.21
32		> 10,000	n. d.	> 10,000	n. d.	280.36	1.79	32.34	-0.37
33		447.2 ± 100.5	> 10,000	> 10,000	n. d.	280.36	1.79	32.34	-0.31

52		> 1,000	n. d.	n. d.	> 10,000	281.35	0.84	45.23	-0.36
53		162.1 ± 38.1	> 5,000	n. d.	> 10,000	281.35	0.66	45.23	-0.39
54		81.3 ± 20.6	> 5,000	> 10,000	n. d.	281.35	0.48	45.23	-0.42

Values are generated from 2–10 independent experiments;

^a n=2;

* = radioligand binding was increased;

n. d. = not determined;

^b ClogP values have been calculated using the ACD/Labs Algorithm;

^c logP calculated with the ACD/Labs Algorithm was used to calculate logBB.

Table 3

Affinities (K_i values $\pm$ SEM) and calculated physicochemical parameters (logP, TPSA, logBB) of the bispidine sulfonamides **34–40**, bispidine urea derivatives **41–42**, **67–69**, and alkylated acetylbispidine derivatives **70–72**

Compd.	R =	$\alpha 4\beta 2^*$ Ki [nM]	$\alpha 3\beta 4^*$ Ki [nM]	$\alpha 7^*$ Ki [nM]	($\alpha 1$) $_2$ ($\beta 1$) $_2$ Ki [nM]	M_r	ClogP ^b	TPSA	logBB ^c
34		> 5,000	n. d.	n. d.	> 10,000	204.29	-0.04	57.79	-0.03
35		> 5,000	> 10,000	> 10,000	n. d.	266.36	1.64	57.79	-0.07
36		970.4	> 10,000	> 10,000	n. d.	291.37	1.58	81.58	0.10
37		858.3 $\pm$ 66.7	> 10,000	> 10,000	n. d.	280.39	2.10	57.79	0.13
38		645.1	> 10,000	> 10,000	n. d.	291.37	1.54	81.58	0.08
39		> 5,000	n. d.	n. d.	n. d.	345.26	2.67	57.79	0.25
40		135.2 $\pm$ 8.1	5,700	> 10,000	> 10,000	311.36	1.84	106.62	-0.20

Compd.	R =	$\alpha 4\beta 2^*$ Ki [nM]	$\alpha 3\beta 4^*$ Ki [nM]	$\alpha 7^*$ Ki [nM]	$(\alpha 1)_2\beta 1\gamma\delta$ Ki [nM]	M_r	ClogP ^b	TPSA	logBB ^c
41		499.3	> 1,000	n. d.	n. d.	197.28	0.32	35.58	-0.01
42		> 3,000	n. d.	n. d.	n. d.	225.33	1.38	35.58	0.13
67		> 5,000	> 10,000	> 10,000	> 10,000	223.31	0.76	35.58	-0.07
68		3800	n. d.	n. d.	n. d.	239.31	-0.22	44.81	-0.07
69		> 10,000	> 10,000	> 5,000	> 5,000	327.46	3.31	35.58	0.50

Compd.	R =	$\alpha 4\beta 2^*$ Ki [nM]	$\alpha 3\beta 4^*$ Ki [nM]	$\alpha 7^*$ Ki [nM]	$(\alpha 1)_2\beta 1\gamma\delta$ Ki [nM]	M_r	ClogP ^b	TPSA	logBB ^c
70	methyl	200	n. d.	n. d.	n. d.	182.26	0.25	23.55	0.03
71	ethyl	> 5,000	n. d.	n. d.	n. d.	196.29	0.78	23.55	0.09
72	n-propyl	> 5,000	n. d.	n. d.	n. d.	210.31	1.31	23.55	0.16

Values are generated from 2–10 independent experiments;

^a n=2;

n. d. = not determined;

^b ClogP values have been calculated using the ACD/Labs Algorithm;

^c logP calculated with the ACD/Labs Algorithm was used to calculate logBB.