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The 3,7-diazabicyclo[3.3.1]nonane scaffold for subtype selective nicotinic acetylcholine receptor ligands. Part 2. Carboxamide derivatives with different spacer motifs

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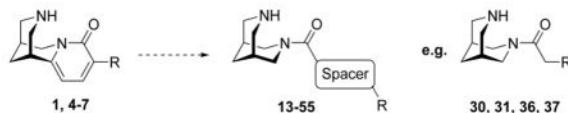
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Abstract

3,7-Diazabicyclo[3.3.1]nonane (bispidine) based nicotinic acetylcholine receptor (nAChR) ligands have been synthesized and evaluated for nAChRs interaction. Diverse spacer motifs were incorporated between the hydrogen bond acceptor (HBA) part and a variety of substituted (hetero)aryl moieties. Bispidine carboxamides bearing spacer motifs often showed high affinity in the low nanomolar range and selectivity for the $\alpha 4\beta 2^*$ nAChR. Compounds **15**, **25**, and **47** with K_i values of about 1 nM displayed the highest affinities for $\alpha 4\beta 2^*$ nAChR. All evaluated compounds are partial agonists or antagonists at $\alpha 4\beta 2^*$, with reduced or no effects on $\alpha 3\beta 4^*$ with the exception of compound **15** (agonist), and reduced or no effect at $\alpha 7$ and muscle subtypes.

Graphical Abstract



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Supplementary data

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

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Keywords

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

1. Introduction

(Di)azabicyclic templates dominate compound libraries for nicotinic acetylcholine receptors (nAChRs).¹ nAChRs are pentameric cation channels found in the central and peripheral nervous systems, as well as in non-neuronal cells and serve as interesting targets especially for various brain diseases.^{2–5} These (di)azabicyclic templates display cationic/HB cores important for the interaction with the receptors. An additional pharmacophoric point, a hydrogen bond acceptor (HBA) motif, is often introduced as a pyridine moiety and less often as carbonyl functionality or as heteroaryls.^{6,7} The bulkiness of ring structures containing the potentially charged nitrogen and moieties attached to the HBA system influence both affinity and functionality.⁸ The diazabicyclic scaffold 3,7-diazabicyclo[3.3.1]nonane (bispidine) originated from the natural product and nAChR ligand cytisine **1** (Fig. 1). It is a privileged scaffold and has been used for the development of nAChR compounds.^{6,7,8–15} In our previous 3,7-diazabicyclo[3.3.1]nonane project, we explored the influence of different non-heteroaryl based HBA systems.⁷ We also reported that 3,7-diazabicyclo[3.3.1]nonane is active on nAChRs and that some 3,7-diazabicyclo[3.3.1]nonane carboxamides showed selectivity for the $\alpha 4\beta 2^*$ nAChR. Herein, we extend the previous study by introducing spacer motifs like methylene, ethylene, ethenylene, ethynylene or (hetero)aryls attached to the HBA system to explore the chemical space for nAChRs further (Fig. 1). Diverse substituents were connected to the spacer motifs.

Firstly, we synthesized and tested four cytisine derivatives including the *in vivo* active 3-(pyridine-3-yl)-cytisine (3PC) **5** displaying at least one rotatable bond and compared them with their analogously substituted 3,7-diazabicyclo[3.3.1]nonane carboxamides to get insight into the influence of a spacer motif.^{16–18} We have recently shown that 3-(pyridine-3-yl)-cytisine (3PC) **5** serves as an interesting lead for the development of antidepressants.^{16–18} Now, we want to “open” the “chemical space” of cytisine to have the possibility to obtain compounds with better subtype selectivity pattern than cytisine derivatives along with a much simpler synthetic approach. Secondly, we prepared and tested a series of carboxamides bearing different spacer motifs providing additional possible interaction points with nAChRs and their consequences on affinity and functionality for further profiling projects.

2. Results and discussion

2.1. Chemistry

Like previously described by us, (-)-cytisine was isolated from seeds and pods of *Laburnum anagyroides*.^{16,17} The dried and milled plant material was extracted with PE to remove lipids. Then (-)-cytisine was extracted with a mixture of $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_3$ (90:10:5) for 8 hours. After filtration and concentration of this solution, it was extracted with HCl (1N) and, subsequently, rendered alkaline, and extracted with CH_2Cl_2 until completion. The alkaloid **1**

was finally purified by column chromatography on silica gel with a mixture of CHCl₃ and MeOH (6:1) or by preparative HPLC using a C₁₈-RP stationary phase and a MeOH-H₂O gradient.

The *N*-*t*-boc protection group was introduced by adding di-*tert*-butyl dicarbonate ((Boc)₂O) to a solution of (-)-cytisine **1** and Na₂CO₃ in a mixture of CH₂Cl₂ and H₂O. The solution was heated to reflux for 2 h and *N*-*t*-boc-cytisine **2** was obtained in good yields after extraction and recrystallization in PE. Alternatively, *N*-*t*-boc-cytisine **2** was synthesized by adding portions of (Boc)₂O to a solution of **1** and Na₂CO₃ in a mixture of CH₂Cl₂ and H₂O until the (-)-cytisine spot **1** has disappeared on TLC. After extracting the product **2** it was purified by preparative HPLC using a C₁₈-RP column and a MeOH-H₂O gradient.

The reaction of *N*-*t*-boc-cytisine **2** with *N*-bromosuccinimide (NBS) for 2 h under reflux in CH₂Cl₂ afforded a mixture of isomeric bromo-*N*-*t*-boc-cytisine derivatives bearing the bromo substituents in the 3 or the 5 position of the pyridone moiety. These isomers could be separated by preparative HPLC using a C₁₈-RP column and a MeOH-H₂O gradient. Only 3-bromo-*N*-*t*-boc-cytisine **3** was used for this project.

The cytisine derivatives **4** – **7** were synthesized in a two-step process incorporating a cross-coupling reaction and the *N*-*t*-boc-deprotection step. The coupling of aromatic or heteroaromatic moieties to the cytisine backbone was achieved by using the Suzuki-Miyaura reaction in a microwave synthesizer. The palladium catalyst Pd(PPh₃)₄ was added to a solution of 3-bromo-*N*-*t*-boc-cytisine **3**, the appropriate boronic acid and an inorganic base in a mixture of DME or DMF and H₂O. Microwave irradiation (30 W) at 80 °C was used for 30 to 90 minutes to synthesize the according *N*-*t*-boc protected cytisine derivatives **Boc-4** – **Boc-7**. These products were purified on preparative HPLC using a C₁₈-RP column and a MeOH-H₂O gradient.

The *N*-*t*-boc protection group of **Boc-4** – **Boc-7** was directly removed by using microwave irradiation (150 W) at 150 °C for 30 minutes in pure H₂O. The solvent of the final cytisine products **4** – **7** was removed by lyophilisation for at least 24 h.

The 3,7-diazabicyclo[3.3.1]nonane (bispidine) scaffold was synthesized using the method described previously, where *N*-benzyl-*N'*-*t*-boc-bispidinone **9** was obtained by a double Mannich reaction from commercially available *tert*-butyl 4-oxopiperidine carboxylate **8**, benzylamine, and paraformaldehyde and reduced to the key intermediate *N*-benzyl-*N'*-*t*-boc-bispidine **10**.^{7,13} The cleavage of the *N*-benzyl protecting group from *N*-benzyl-*N'*-*t*-boc-bispidine **10** was achieved by using palladium on activated charcoal (Pd/C) 5 % under a hydrogen atmosphere. The resulting *N*-*t*-boc-bispidine **12** was now used as the starting material for all carboxamides described.

In general, all *N*-*t*-boc protected intermediates **Boc-13** – **Boc-55** were purified by flash chromatography on silica gel and analyzed by LC-MS. When the purity was above 90–95 % these intermediates were *N*-*t*-boc deprotected without further analysis. The *N*-*t*-boc deprotected final compounds **13** – **55** were purified by flash chromatography and have been analyzed in more details.

Using the method previously described, intermediates **Boc-13** – **Boc-28** were synthesized by using carbonyldiimidazole (CDI) as a coupling reagent or via carboxylic acid chlorides/aminolysis or via DCC (N,N'-dicyclohexylcarbodiimide) coupling reaction.^{7,13}

After removal of the N-*t*-boc protecting group final compounds were often obtained as oils. For purification purposes and to improve stability, compounds **13–55** were transferred into their corresponding fumaric acid salts **13F–55F**. Products **13F–55F** have been obtained in excellent purity (mostly > 99 %).

2.2. Biological activity and SAR

Radioligand binding assays as previously described were performed to determine the affinities (K_i values) of cytosine **1** (standard ligand and starting material), cytosine derivatives **4–7** (Table 1) and the bispidine derivatives **13–55** (Table 2).^{19–21}

Cytosine derivatives in comparison with their analogously substituted 3,7-diazabicyclo[3.3.1]nonane based carboxamides—In the past, we and several other research groups studied structure-activity relationships (SAR) around the intact cytosine template to gain insights into nAChR affinity and functional selectivity.^{1,16,17,22}

3-Phenyl-cytosine **4** exhibited an affinity for the $\alpha 4\beta 2^*$ subtype ($K_i = 128$ nM) what is about 1000 times lower than cytosine **1**, but with enhanced subtype selectivity. The introduction of a heteroaryl substituent provided compounds with high affinity for $\alpha 4\beta 2^*$ (**5** (3PC): $K_i = 0.91$ nM; **6**: $K_i = 3.9$ nM). The pyridyl ring can function as an additional HBA system enhancing the affinity for $\alpha 4\beta 2^*$ when comparing with ligand **4**, but decreasing the subtype selectivity for e.g. $\alpha 3\beta 4$ (**5** (3PC): $K_i = 119$ nM; **6**: $K_i = 436$ nM). Compound **7**, bearing an additional 3,4-methylenedioxy substituent at the phenyl ring, displayed similar affinity for $\alpha 4\beta 2^*$ ($K_i = 110$ nM) like 3-phenyl-cytosine **4** ($K_i = 128$ nM) along with high subtype selectivity.

Compounds **30**, **31**, **36**, and **37** (Table 2) can be directly compared to cytosine derivatives **4–7**. They can be seen as simplified and more flexible cytosine analogs, but lacking the pyridone ring system of **1** (table 1). Compounds **30** and **37** ($K_i = 57.6$ and 13.2 nM, respectively) showed higher affinity for the $\alpha 4\beta 2^*$ nAChR than their more rigid cytosine analogs **4** and **7** ($K_i = 128$ and 110 nM, respectively). In contrast, cytosine derivatives **5** and **6** ($K_i = 0.91$ and 3.9 nM) bearing a pyridine substituent displayed slightly higher affinity for the $\alpha 4\beta 2^*$ nAChR than their more flexible bispidine analogs **31** and **36** ($K_i = 11.2$ and 14.4 nM, respectively). 3,7-Diazabicyclo[3.3.1]nonane based carboxamides can therefore provide easier synthetically accessible nAChR ligands with high $\alpha 4\beta 2^*$ affinity and enhanced subtype selectivity.

3,7-Diazabicyclo[3.3.1]nonane based carboxamides with methylene spacer—

The introduction of the methylene spacer into compound **29** ($K_i = 454$ nM for $\alpha 4\beta 2^*$) increased the affinity for the $\alpha 4\beta 2^*$ subtype by about 8-fold (**30**; $K_i = 58$ nM). Compound **30** showed also high subtype selectivity. The perfluorinated compound **34** failed to interact with nAChRs tested. Other compounds bearing a methylene spacer (compounds **13**, **31** and **35–38**) between the amide bond and the (hetero)aryl substituents also exhibited high

affinity in the low nanomolar range for the $\alpha 4\beta 2^*$ nAChR. Compound **35** substituted with a methylsulfonyl moiety in the para position of the phenyl ring showed a K_i value of 22.9 nM for the $\alpha 4\beta 2^*$ subtype, and no affinity for e.g. $\alpha 3\beta 4^*$ nAChR. The 3-methyl-5-isoxazolyl derivative **13** ($K_i = 46.9$ nM) bearing a substituent which can be considered as a bioisosteric replacement of the phenyl ring displayed similar K_i values for $\alpha 4\beta 2^*$. For compounds **31** (3-pyridyl), **36** (4-pyridyl) and **37** (3,4-methylenedioxyphenyl) K_i values of 11.2 nM (**31**), 14.4 nM (**36**) and 13.2 nM (**37**), respectively, were obtained. These moieties have additional hydrogen bond acceptors which might be beneficial for increasing the affinity for $\alpha 4\beta 2^*$ nAChR further. Compound **38** with the bulkier 2-naphthyl moiety exhibited a K_i value in the low nanomolar range ($K_i = 10.2$ nM) for this receptor subtype. These results indicate that the introduction of a methylene spacer is tolerated by the $\alpha 4\beta 2^*$ subtype and can increase the affinity for this subtype.

3,7-Diazabicyclo[3.3.1]nonane based carboxamides with an ethylene, oxymethylene, or cyclopropyl spacer—The homolog ethylene spacer in compound **32** did not change the affinity for $\alpha 4\beta 2^*$ nAChR ($K_i = 52.5$ nM) comparing with the methylene spacer compound **30** (Table 2). Compound **32** also displayed an affinity for the $\alpha 3\beta 4^*$ subtype ($K_i = 395.8$ nM), but no affinity for the $\alpha 7^*$ nAChR. The introduction of a 3-pyridyl ring (compound **39**) increased the affinity for the $\alpha 4\beta 2^*$ subtype only slightly ($K_i = 39$ nM), whereas the introduction of three methoxy groups in the meta- and the para positions (compound **14**) resulted in a drop of affinity for this receptor subtype ($K_i = 232.6$ nM). Compound **33**, bearing a 2-chloro aryl moiety and an oxymethylene spacer displayed lower affinity for the $\alpha 4\beta 2^*$ subtype ($K_i = 548$ nM) compared to compound **32**. This shows, that either a small electron withdrawing group in the ortho position of the aromatic ring or a heteroatom in the spacer motif can decrease affinity for $\alpha 4\beta 2^*$ nAChR. In contrast, compound **15**, bearing a cyclopropyl ring with a trans substitution pattern as a spacer motif displayed high affinity for the $\alpha 4\beta 2^*$ nAChR ($K_i = 1.2$ nM), but also for the $\alpha 3\beta 4^*$ subtype ($K_i = 81.1$ nM). The rigidity of the cyclopropyl spacer could be beneficial for high affinity for the $\alpha 4\beta 2^*$ nAChR subtype, but different trans and cis arrangements needs to be explored in the future to evaluate the possibility to reduce $\alpha 3\beta 4^*$ interaction and maintain $\alpha 4\beta 2^*$ activity.

3,7-Diazabicyclo[3.3.1]nonane based carboxamides with a ethylene spacer—Bispidine derivative **16**, with a cinnamic acid coupled to the bispidine backbone, showed affinity in the nanomolar range ($K_i = 55.1$ nM) for $\alpha 4\beta 2^*$ nAChR, but lacked affinity for any of the other nAChR subtypes tested. This spacer motif exhibited more rigidity compared to its more flexible ethylene spacer (compound **32**). The K_i values of both compounds (**32** vs. **16**) are almost identical ($K_i = 55.1$ vs. 52.5 nM, respectively). The introduction of an electron donating methoxy substituent into the ortho position of the phenyl ring (compound **17**) showed lower affinity for the $\alpha 4\beta 2^*$ subtype ($K_i = 171.8$ nM) compared to its unsubstituted cinnamic acid derivative **16**. However, when small electron withdrawing groups were introduced in the meta (chloro: **18**, bromo: **19**, nitro: **20**) or para position (fluoro: **40**), compounds with higher affinity for the $\alpha 4\beta 2^*$ subtype (**18**: $K_i = 23.7$ nM; **19**: $K_i = 24.6$ nM; **20**: $K_i = 38.9$ nM; **40**: $K_i = 20.7$ nM) were obtained. Also, compound **21** with an electron donating methoxy group in the para position displayed a slightly higher affinity

($K_i = 39.6$ nM) for the $\alpha 4\beta 2^*$ subtype compared to compound **16**. So, small electron withdrawing groups in the meta or para position increase the affinity for the $\alpha 4\beta 2^*$ subtype and it seems that the position of the small electron withdrawing or donating substituent might be more important than its electronic properties.

The affinity for the $\alpha 4\beta 2^*$ nAChR subtype was decreased when the phenyl ring of compound **16** was replaced by smaller five-membered, aromatic rings systems, such as furanyl (compound **22**) or thiophenyl (compounds **23** and **24**). K_i values were 287.5 nM for the 2-furanyl (**22**), 96.9 nM for the 2-thiophenyl (**23**), and 57.1 nM for the 3-thiophenyl derivative (**24**). When the phenyl ring of compound **16** was replaced by a 3-pyridyl (**41**) or a 4-pyridyl moiety (**25**), the affinity increased for the $\alpha 4\beta 2^*$ subtype (**41**: $K_i = 32.6$ nM; **25**: 1.03 nM). The K_i values of the 3-pyridyl compound **41** and its less rigid counterpart (compound **39**, $K_i = 39$ nM) are very similar for $\alpha 4\beta 2^*$, indicating that both spacer motifs allow similar orientation in the binding pocket. When the simple phenyl moiety of compound **16** was extended by a fused 3,4-methylenedioxy moiety (compound **26**), a K_i value of 36.9 nM was obtained for the $\alpha 4\beta 2^*$ nAChR subtype. The extension to a 1-naphthyl ring system (compound **27**), however, decreased the affinity for the $\alpha 4\beta 2^*$ subtype ($K_i = 296.6$ nM).

3,7-Diazabicyclo[3.3.1]nonane based carboxamides with an ethynylene spacer

—Compound **42** displayed a 5-times higher affinity for the $\alpha 4\beta 2^*$ nAChR subtype ($K_i = 10.9$ nM) than its more flexible analogs **32** and **16**. The introduction of an electron donating methoxy group (compound **43**) caused a drop in affinity for $\alpha 4\beta 2^*$ ($K_i = 241.9$ nM). A similar observation was made for compound **17**, which means that ortho substitutions are less tolerated by the receptor. Small electron donating or withdrawing groups at meta and/or para positions (compounds **44–50**) increased the affinity for the $\alpha 4\beta 2^*$ subtype (up to about 11 fold). E.g. a methoxy group in the meta or para position increased the affinity slightly (**44**: $K_i = 6.3$ nM; **45**: $K_i = 7.8$ nM) and a di-substitution (compound **46**) resulted in an even higher affinity for the $\alpha 4\beta 2^*$ subtype ($K_i = 2.1$ nM). The combination of a 3-chloro/4-methoxy substitution (compound **47**) resulted in a compound with the highest affinity in this compound library ($K_i = 0.991$ nM). Compound **48**, bearing a 4-methyl group displayed the same affinity ($K_i = 10.9$ nM) for the $\alpha 4\beta 2^*$ nAChR subtype as the unsubstituted compound **42**. 3-Fluoro substitution (compound **49**) also provided a ligand with high affinity for $\alpha 4\beta 2^*$ (K_i value of 7.1 nM). The affinity of compound **50** (3,4-methylenedioxy substituent; $K_i = 3.13$ nM) is similar to its ring open 3,4-dimethoxy analog **46** ($K_i = 2.1$ nM), and both compounds possess about a 10-fold higher affinity than its analog bearing a vinyl spacer (**26**). A 1-naphthyl moiety (compound **51**) decreased affinity for the $\alpha 4\beta 2^*$ subtype ($K_i = 46$ nM) compared to compound **42**. A similar observation has been made with compounds **27** vs. **16**. In summary, bispidine compounds bearing an ethynylene spacer moiety along with substitutions in the meta- and/or para position are well tolerated by the $\alpha 4\beta 2^*$ nAChR subtype.

3,7-Diazabicyclo[3.3.1]nonane based carboxamides with an (hetero)aryl

spacer—As previously reported, the biphenyl derivative **28** has a K_i value of 39.9 nM for $\alpha 4\beta 2^*$ nAChR, and about 1,100 nM for the $\alpha 3\beta 4^*$ subtype.⁷ In line with the observations for

compounds **31** and **36** vs. **30**, **39** vs. **32**, and **41** and **25** vs. **16**, the replacement of the phenyl moiety by 3- or 4-pyridyls increased the affinity for the $\alpha 4\beta 2^*$ nAChR subtype (3-pyridyl-phenyl derivative **52**: $K_i = 25$ nM; 4-pyridyl-phenyl derivative **53**: $K_i = 7.1$ nM). Additionally, the replacement of the phenyl ring by an imidazolyl ring (compound **54**) also increased affinity for the $\alpha 4\beta 2^*$ subtype ($K_i = 5.6$ nM). The phenyl group is tolerated as a spacer motif for $\alpha 4\beta 2^*$ nAChRs. Compound **55**, where a 4-pyridyl substituent was connected via a thiazole spacer with the bispidine amide backbone, did not show any affinity for nAChRs. Similar observations have been made on the previous set of bispidine compounds, when heteroatoms in close proximity to the HBA system caused a dramatic drop in affinity.⁷

In summary, various spacer moieties like methylene, ethylene, ethenylene, ethynylene or phenyl, between the HBA motif and (hetero)aryl moieties are tolerated by the $\alpha 4\beta 2^*$ nAChR subtype, even with high affinity and subtype selectivity.

Most compounds showed partial agonism/antagonism in initial characterization assays using previously described electrophysiological experiments with diverse nAChRs expressed in *Xenopus oocytes* (Figure 2).^{7,23–25} Compounds **35**, **15**, **46**, **47**, **50**, **52**, **53**, and **54** produced the strongest antagonistic effects for $\alpha 4\beta 2^*$ receptors. Compound **35** was further evaluated and recently discovered as an *in vivo* active, highly selective agent with antidepressive effect in a mouse model.²⁶ Compound **15** was the most potent agonist at $\alpha 3\beta 4^*$ in this compound series. No strong effects were observed for $\alpha 7$ subtype. Compound **46** had some antagonistic effect at the muscle subtype. In general, spacer motifs lead to compounds with partial agonist/antagonist profiles with the strongest effects observed for $\alpha 4\beta 2^*$ nAChRs. In contrast, the cyclopropyl spacer (*trans* form) produced compound **15** with an additional $\alpha 3\beta 4^*$ agonistic profile.

2.3. Physicochemical properties and drug-likeness

Physicochemical properties and druglikeness parameters ClogP, TPSA, and logBB were calculated using ACD/ADME Suite 5.0 (ACD/Labs) software. Most compounds are in the range for CNS druglikeness parameter values (M_r : 250 and 350; ClogP: between 1–3; PSA < 75). Additional parameters important for CNS compounds have been calculated (Table 3; supplementary data) for those compounds showing nanomolar affinity for $\alpha 4\beta 2^*$ ($K_i < 1,000$ nM).²⁷ Most active compounds showed “good” values (see Table 3; supplementary data). There were no correlations between affinity and ClogP or TPSA values or rotatable bonds. Most compounds have 2–3 rotatable bonds due to their spacer motif which had an influence on their functionality like stated above. For the likelihood of blood brain barrier (BBB) penetration, logBB values were calculated can be from logP and TPSA values where logBB values below -0.5 would reflect very poor or no BBB penetration and > 0.7 very high penetrants. 3,7-diazabicyclo[3.3.1]nonane carboxamides bearing the ethenylene or ethynylene spacer could function as Michael acceptors, properties which should be avoided for potential drug candidates for chronic treatment. Results derived from these compounds serve as a basis for further compound profiling projects and therefore an important part in this early SAR study.

3. Conclusions

In summary, we synthesized and evaluated a small set of cytosine (**4–7**) derivatives and a series of 3,7-diazabicyclo[3.3.1]nonane carboxamide (**13–55**) for their affinities at various nAChRs. Selected compounds were screened for agonist and antagonist functionality. Most compounds displayed $\alpha 4\beta 2^*$ subtype selectivity regarding their affinities measured.

Cytosine derivatives **4–7** were compared with the four analogously substituted bispidine derivatives **30**, **31**, **36**, and **37**. Their affinities for the $\alpha 4\beta 2^*$ nAChR were in the same range. It seems that the impact of flexibility/rigidity on $\alpha 4\beta 2^*$ affinity is of minor importance. The introduction of an additional hydrogen bond acceptor (HBA) motif, e.g. pyridyl groups, increased the affinity for the $\alpha 4\beta 2^*$ subtype in both sets of derivatives.

The incorporation of spacer moieties like methylene, ethylene, ethenylene, ethynylene or phenyl at the 3,7-diazabicyclo[3.3.1]nonane carboxamide template increased the affinity for the $\alpha 4\beta 2^*$ nAChR. Heteroaryl substituents with HBA functionality increased the affinity for $\alpha 4\beta 2^*$ nAChR further.

Compounds **15**, **25**, and **47** with K_i values of about 1 nM showed the highest affinities for $\alpha 4\beta 2^*$ nAChR.

From the electrophysiology point of view, all evaluated compounds displayed partial agonism or antagonism at $\alpha 4\beta 2^*$, reduced or no effects on $\alpha 3\beta 4^*$ with the exception of compound **15** (agonist), and reduced or no effect at $\alpha 7$ and muscle type.

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 apparatus (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).

4.1. General procedure A: Suzuki cross-coupling reaction with 3-bromo-N-tboc-cytisine

3-Bromo-N-tboc-cytisine (100 mg, 0.27 mmol), the appropriate boronic acid (0.41 mmol), a base (0.6 mmol), DME (3 mL) and H₂O (1 mL) were added into a 10 mL microwave glass tube. The solution was washed with argon for 10 min. After the addition of Pd(PPh₃)₄ (30 mg, 0.027 mmol) the reaction vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation of 30 W was used and the temperature ramped from rt to 80 °C. Once 80 °C was reached the reaction mixture was held for 30 to 90 min. before the mixture was allowed to cool to rt. The reaction vessel was opened and the solvents were evaporated under reduced pressure. The brown residue was extracted on a C-18 SPE column eluting with a mixture of MeOH/H₂O 70:30 or 60:40 v/v and the aqueous solution was concentrated under reduced pressure, subsequently. The residue was purified on a preparative HPLC system using RP C-18 silica gel and appropriate MeOH/H₂O gradients. The chromatograms were scanned at 254 nm and the appropriate fractions were collected. The fractions containing the desired products were concentrated under reduced pressure on a rotary evaporator.

4.2. General procedure B: Cleavage of the N-tboc protecting group from N-tboc protected cytisine derivatives

The concentrated aqueous solution of the N-tboc protected cytisine derivative (approx. 70 mL) was put into a 80 mL microwave glass tube, sealed and placed into the microwave cavity. Microwave irradiation of 150 W was used and the temperature ramped from rt to 150 °C. Once 150 °C was reached the reaction mixture was held for 30 min. before the mixture was allowed to cool to rt. The reaction vessel was opened and the solvent was evaporated by lyophilization for at least 24 h.

4.3. Isolation of (1R,5S)-1,2,3,4,5,6-hexahydro-1,5-methano-8H-pyrido[1,2-a][1,5]diazocin-8-one [(-)-Cytisine] (1)

Seeds and pods of *Laburnum anagyroides watereri* were collected in the Cologne-Bonn area (Germany) in the months September and October. The plant material was air-dried at least for 3 months and ground to a powder consistence. The plant material was extracted with

CH₂Cl₂/MeOH/aq. NH₃ (10:4:1) through homogenization by Ultra-turrax for 8 hours. The evaporated solvents were replaced, exactly the same amounts of each solvent were added to the homogenate during the extraction. The homogenate was centrifuged (2,000 x min, 40 min) and the supernatant collected. The dark green solution was concentrated under reduced pressure to the final volume of 500 ml and extracted with 1M HCl (3 x 100 ml). The aqueous acid solution was rendered alkaline with 26% NH₄OH (pH 11–12) and the free base extracted with CH₂Cl₂ (10 x 100 ml). The organic layers were collected and the solvent evaporated in vacuo. The dark green/brownish residue was purified by column chromatography on silica gel column with CHCl₃/MeOH (6:1). The alkaloid **1** was recrystallized from perchloroethylene or directly used in the next step (synthesis of N-tboc-cytisine **2**). Isolated yields ranged from 0.11 to 0.48 % of **1** calculated from the dry weight; mp 155–156 °C. ¹H NMR (500 MHz, CDCl₃) δ 1.65 (br s, 2H), 2.03 (br s, 1H), 2.62 (br s, 1H), 2.70–2.75 (m, 4H), 3.57 (dd, *J* = 15.7, 6.6 Hz, 1H), 3.77 (d, *J* = 15.4 Hz, 1H), 5.77 (d, *J* = 6.9 Hz, 1H), 6.17 (d, *J* = 9.1 Hz, 1H), 7.05 (dd, *J* = 9.1, 6.9 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 25.6, 27.0, 34.9, 49.1, 52.3, 53.3, 104.2, 115.7, 138.1, 150.7, 162.8. LC/ESI-MS: positive mode *m/z* = 190.9 ([M + H]⁺). Purity (> 99.9 %). IR (KBr, cm⁻¹) 3316, 3282, 3084, 3032, 1650, 1541, 1443, 1141, 821, 737. Anal. (C₁₁H₁₄N₂O*0.25H₂O) C, H, N.

4.4. 8-oxo-1,5,6,8-tetrahydro-2H,4H-1,5-methano-pyrido[1,2-a][1,5]diazocine-3-carboxylic acid tert-butyl ester [N-tboc-cytisine] (**2**)

Cytisine **1** (500 mg, 2.63 mmol), di-tert-butyl dicarbonate (688 mg, 3.15 mmol, 1.2 eq) and Na₂CO₃ (334 mg, 3.15 mmol, 1.2 eq) were stirred in 25 ml CH₂Cl₂ and 6 ml H₂O at 60 °C for 2 hours. The reaction mixture was allowed to cool to rt and 10 ml of concentrated NaCl solution was added. The organic layer was dried over MgSO₄ and the solvent was evaporated. Product **2** was recrystallized from PE and obtained as an off-white crystalline powder (590–690 mg, 77–90 %); mp 149–150 °C. ¹H NMR (500 MHz, CDCl₃) δ 1.30 (s, 9H), 1.87 (m, 1H), 1.93 (m, 1H), 2.38 (br s, 1H), 2.94–3.05 (m, 3H), 3.79 (dd, *J* = 15.7, 6.6 Hz, 1H), 4.00–4.19 (m olv, 2H), 4.14 (d, *J* = 15.4 Hz, 1H), 6.03 (br s, 1H), 6.41 (d, *J* = 9.1 Hz, 1H), 7.24 (dd, *J* = 9.1, 6.3 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 26.1, 27.5, 28.0, 34.8, 48.9, 50.5, 51.6, 80.3, 105.8, 117.1, 138.9, 148.7, 154.5, 163.4. LC/ESI-MS: positive mode *m/z* = 291.3 ([M + H]⁺). Purity (> 99.9 %). IR (KBr, cm⁻¹) 3217, 3099, 1687, 1654, 1465, 1445, 1421, 1364, 818, 760, 572. Anal. (C₁₆H₂₂N₂O₃) C, H, N.

4.5. 9-bromo-8-oxo-1,5,6,8-tetrahydro-2H,4H-1,5-methano-pyrido[1,2-a][1,5]diazocine-3-carboxylic acid tert-butyl ester [3-Bromo-N-tboc-cytisine] (**3**)

N-tboc-cytisine **2** (1 g, 3.44 mmol) and N-bromosuccinimide (613 mg, 3.44 mmol, 1 eq) were stirred in 30 ml CH₂Cl₂ at 60 °C for 2 hours. The reaction mixture was allowed to cool to rt and the solvent was evaporated in vacuo. The oily residue was dissolved in 150 ml MeOH/H₂O (60:40) and the two isomers were separated and purified by preparative HPLC. Product **3** was obtained in 38–52 % yield as a white crystalline powder; mp 131 °C. ¹H NMR (500 MHz, CDCl₃) δ 1.30 (s, 9H), 1.94 (t, *J* = 13.2 Hz, 2H), 2.40 (br s, 1H), 2.99–3.06 (m, 3H), 3.85 (dd, *J* = 15.5, 6.3 Hz, 1H), 4.06–4.35 (m ovl, 2H), 4.23 (d, *J* = 15.8 Hz, 1H), 5.96 (br s, 1H), 7.64 (dd, *J* = 7.6 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 26.0, 27.4, 28.0, 34.7, 49.2, 50.2, 51.4, 80.6, 105.7, 112.5, 140.8, 148.5, 154.4, 159.4. LC/ESI-MS: positive

mode m/z = 369.0 and 371.0 ($[M + H]^+$). Purity (> 99.9 %). IR (KBr, cm^{-1}) 3092, 2974, 1692, 1648, 1587, 1423, 1365, 1237, 1129, 760. Anal. ($\text{C}_{16}\text{H}_{21}\text{BrN}_2\text{O}_3 \cdot 0.25\text{H}_2\text{O}$) C, H, N.

4.6. 9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyridino[1,2-a]diazocin-8-one [3-Phenyl-cytisine] (4)

The Suzuki reaction was performed according to general procedure A with 3-bromo-N-tboc-cytisine **3** (100 mg, 0.27 mmol), phenylboronic acid (50 mg, 0.41 mmol), Na_2CO_3 (64 mg, 0.6 mmol), $\text{Pd}(\text{PPh}_3)_4$ (30 mg, 0.027 mmol), DME and H_2O . The reaction time was 30 min. For the SPE purification a mixture of MeOH/ H_2O 70:30 v/v (100 mL) was used. After the HPLC purification, general procedure B was used for the N-tboc deprotection. Final product **4** was obtained as a white solid (42 mg, 58 %). mp 139.8–140.6 °C. ^1H NMR (500 MHz, CDCl_3) δ 1.96 (br s, 2H), 2.34 (br s, 1H), 2.91 (br s, 1H), 3.02 (br d, J = 12.3 Hz, 2H), 3.07 (dd, J = 12.3, 2.2 Hz, 1H), 4.19 (d, J = 15.5 Hz, 1H), 6.09 (d, J = 7.2 Hz, 1H), 7.29 (tt, J = 7.2, 1.3 Hz, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.46 (d, J = 7.2 Hz, 1H), 7.69 (dt, J = 7.2, 1.3 Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 26.3, 27.9, 35.7, 50.2, 53.0, 54.0, 105.0, 127.2, 127.4, 128.0, 128.6, 137.0, 137.4, 150.3, 162.1. HRMS (EI) calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$ 266.1419, found 266.1426.

4.7. 9-pyridin-3-yl-1,2,3,4,5,6-hexahydro-1,5-methano-pyridino[1,2-a]diazocin-8-one [3-(Pyridin-3'-yl)cytisine] (5)

The Suzuki reaction was performed according to general procedure A with 3-bromo-N-tboc-cytisine **3** (100 mg, 0.27 mmol), 3-pyridineboronic acid (49 mg, 0.41 mmol), K_3PO_4 (126 mg, 0.6 mmol), $\text{Pd}(\text{PPh}_3)_4$ (30 mg, 0.027 mmol), DME and H_2O . The reaction time was 60 min. For the SPE purification a mixture of MeOH/ H_2O 60:40 v/v (100 mL) was used. After the HPLC purification, general procedure B was used for the N-tboc deprotection. Final product **5** was obtained as a yellow solid (48 mg, 66 %). mp 79.8–81.6 °C. ^1H NMR (500 MHz, CDCl_3) δ 1.96 (br s, 2H), 2.36 (br s, 1H), 2.95 (br s, 1H), 2.99–3.03 (m, 2H), 3.06 (dd, J = 12.0, 2.2 Hz, 1H), 3.11 (d, J = 12 Hz, 1H), 3.94 (dd, J = 15.6, 6.9 Hz, 1H), 4.16 (d, J = 15.6 Hz, 1H), 6.11 (d, J = 7.3 Hz, 1H), 7.29 (ddd, J = 7.9, 4.7, 0.9 Hz, 1H), 7.49 (d, J = 7.3 Hz, 1H), 8.16 (ddd, J = 7.9, 2.2, 1.6 Hz, 1H), 8.49 (dd, J = 4.7, 1.6 Hz, 1H), 8.78 (d, J = 1.6 Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ 26.2, 27.8, 35.7, 50.3, 53.0, 53.9, 105.0, 122.8, 123.9, 133.2, 136.1, 137.2, 148.2, 149.1, 151.5, 161.9. HRMS (EI) calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}$ 267.1371, found 267.1376.

4.8. 9-pyridin-4-yl-1,2,3,4,5,6-hexahydro-1,5-methano-pyridino[1,2-a]diazocin-8-one [3-(Pyridin-4'-yl)cytisine] (6)

The Suzuki reaction was performed according to general procedure A with 3-bromo-N-tboc-cytisine **3** (100 mg, 0.27 mmol), 4-pyridineboronic acid (49 mg, 0.41 mmol), K_3PO_4 (126 mg, 0.6 mmol), $\text{Pd}(\text{PPh}_3)_4$ (30 mg, 0.027 mmol), DME and H_2O . The reaction time was 90 min. For the SPE purification a mixture of MeOH/ H_2O 60:40 v/v (100 mL) was used. After the HPLC purification, general procedure B was used for the N-tboc deprotection. Final product **6** was obtained as a yellow solid (45 mg, 62 %). mp n.d. °C. ^1H NMR (500 MHz, CDCl_3) δ 1.96 (br s, 2H), 2.36 (br s, 1H), 2.94 (br s, 1H), 3.00 (ddd, J = 12.3, 2.5, 1.2 Hz, 1H), 3.04 (d, J = 12.3 Hz, 1H), 3.07 (dd, J = 12.3, 2.5 Hz, 1H), 3.11 (dd, J = 12.3, 2.5 Hz,

1H), 3.95 (dd, $J = 15.8, 6.6$ Hz, 1H), 4.16 (d, $J = 15.8$ Hz, 1H), 6.13 (d, $J = 7.4$ Hz, 1H), 7.57 (d, $J = 7.4$ Hz, 1H), 7.67 (dd, $J = 6.1, 1.6$ Hz, 2H), 8.57 (dd, $J = 6.1, 1.6$ Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 26.2, 27.8, 35.8, 50.3, 53.0, 53.9, 104.9, 122.8, 123.9, 137.8, 144.9, 149.6, 152.6, 161.5. HRMS (EI) calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}$ 267.1371, found 267.1379.

4.9. 9-(benzo[1,3]dioxol-5-yl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyridino[1,2-a]diazocin-8-one [3-(3',4'-Methylenedioxyphenyl)cytisine] (7)

The Suzuki reaction was performed according to general procedure A with 3-bromo-N-tboc-cytisine **3** (100 mg, 0.27 mmol), 3,4-methylenedioxyphenylboronic acid (68 mg, 0.41 mmol), Na_2CO_3 (64 mg, 0.6 mmol), $\text{Pd}(\text{PPh}_3)_4$ (30 mg, 0.027 mmol), DME and H_2O . The reaction time was 30 min. For the SPE purification a mixture of MeOH/ H_2O 70:30 v/v (100 mL) was used. After the HPLC purification, general procedure B was used for the N-tboc deprotection. Final product **7** was obtained as an off-white solid (30 mg, 36 %). mp 259.1–261.6 °C. ^1H NMR (500 MHz, CDCl_3) δ 1.95 (br s, 2H), 2.34 (br s, 1H), 2.90 (br s, 1H), 3.00 (br d, $J = 12.0$ Hz, 2H), 3.06 (dd, $J = 12.0, 2.2$ Hz, 1H), 3.11 (d, $J = 12.0$ Hz, 1H), 3.93 (dd, $J = 15.7, 6.6$ Hz, 1H), 4.16 (d, $J = 15.7$ Hz, 1H), 5.94 (br s, 2H), 6.05 (d, $J = 7.3$ Hz, 1H), 6.81 (d, $J = 8.2$ Hz, 1H), 7.12 (dd, $J = 8.2, 1.6$ Hz, 1H), 7.26 (d, $J = 1.6$ Hz, 1H), 7.38 (d, $J = 7.3$ Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ 26.4, 27.9, 35.7, 50.2, 53.0, 54.0, 100.9, 104.9, 108.0, 109.4, 122.1, 127.1, 131.4, 136.4, 146.8, 147.3, 149.9, 162.1. HRMS (EI) calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$ 310.1317, found 310.1324.

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

Methyl iodide (570 mg, 4 mmol) was added to a stirred solution of **12** (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 Et_3N (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 CH_2Cl_2 and MeOH - 40:1, 20:1 or 9:1).

4.11. General procedure D: Synthesis of N-tboc protected bispidinecarboxamides

The appropriate carboxyl chloride (1 mmol), either neat or dissolved in dry toluene (1–2 mL), was added dropwise to a stirred solution of N-tboc-bispidine **11** (230 mg, 1 mmol) and Et_3N (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 CH_2Cl_2 and MeOH - 40:1, 20:1 or 9:1).

4.12. General procedure E: Synthesis of N-tboc protected bispidinecarboxamides

The appropriate carboxylic acid (1 mmol) and N-tboc-bispidine **11** (248 mg, 1.1 mmol) were dissolved in dry CH_2Cl_2 (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 CH_2Cl_2 (2 mL). The solvent of the filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography (silica gel, mixtures of CH_2Cl_2 and MeOH - 40:1, 20:1 or 9:1).

4.13. General procedure F: 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 of CH₂Cl₂ (3–5 x 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.

4.14. General procedure G: 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 x 20 mL). The combined organic layers were washed with saturated NaHCO₃ solution (10 mL), water (10 mL), dried over MgSO₄, and filtered. The product was obtained after evaporating the solvent under reduced pressure.

4.15. General procedure H. Formation of fumaric acid salts of bispidine derivatives

The amine (0.2 – 1.0 mmol) was dissolved in a mixture of Et₂O 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 x 5 mL) and dry Et₂O (5 mL). The solid was dissolved in water (20–30 mL), and freeze-dried.

4.16. General procedure I. 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 Et₂O (10 mL) were added and the mixture was kept at 4–8 °C overnight. The solid was filtered off, washed with dry Et₂O (3 x 5 mL), dissolved in water (20–30 mL), and freeze-dried.

4.17. (1R,5S)-tert-butyl 7-benzyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (9)

Compound **9** was obtained following the synthetic procedures published by Stead et al.{{2 Stead,D. 2005;}} A solution of *tert*-butyl 4-oxopiperidine-1-carboxylate **8** (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 x 80 mL). The combined aqueous layers were extracted with Et₂O (3 x 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 **9** (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.

4.18. (1R,5S)-tert-butyl 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (**10**)

A solution of **9** (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 x 150 mL). The combined organic layers were washed with saturated solution (1 x 30 mL), water (2 x 30 mL), dried with NaHCO₃MgSO₄ 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 **10** 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). ¹³C NMR (125 MHz, CDCl₃) 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 ([M + H]⁺). Purity (> 99.5 %). IR (KBr, cm⁻¹) 1681. Anal. (C₁₉H₂₈N₂O₂) C, H, N.

4.19. (1R,5S)-tert-butyl 3,7-diazabicyclo[3.3.1]nonane-3-carboxylate fumaric acid salt (**11F**)

200 mg of Pd/C (5 %) was added to a solution of **10** (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 **10** was used for further syntheses. General procedure H was used to transfer this clear oil **10** (161 mg, 0.71 mmol) into a white solid, its fumaric acid salt **11F** (200 mg, 82 %); mp 170 °C (dec). ¹H NMR (500 MHz, D₂O) 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). ¹³C 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 ([M + H]⁺). Purity (> 99.9 %). IR (KBr, cm⁻¹) 3438, 1691, 1657, 985. Anal. (C₁₂H₂₂N₂O₂*1.0C₄H₄O₄*0.1H₂O) C, H, N.

4.20. (1R,5S)-tert-butyl 7-(1H-imidazole-1-carbonyl)-3,7-diazabicyclo[3.3.1]nonan-3-carboxylate (12)

N-*t*Boc-bispidine **11** (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 CH₂Cl₂ and MeOH - 20:1). Evaporation of the solvents afforded a white solid **12** (1.98 g, 6.2 mmol, 93 %); mp 143 °C (dec). ¹H NMR (500 MHz, CDCl₃) 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.

4.21. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-(3-methylisoxazol-5-yl)ethanone fumaric acid salt (13F)

The *N*-*t*boc protected compound was obtained by using the general procedure C with 3-methyl-5-isoxazoleacetic acid (141 mg, 1 mmol) for 48 h. A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a yellowish oil (234 mg, 67 %) was obtained. The *N*-*t*boc protection group of this oil (180 mg, 0.52 mmol) was cleaved using the general procedure G with anhydrous ZnBr₂ (348 mg, 1.55 mmol) for 72 h and an off-white solid **13** (126 mg, 98 %) was obtained after extraction. This solid **13** (74 mg, 0.30 mmol) was transferred to its fumaric acid salt **13F** by using the general procedure I with fumaric acid (34 mg, 0.30 mmol). Compound **13F** (79 mg, 71 %) was obtained as a white solid in 46 % yield over three steps; mp 168–169 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.96 (br m, 1H), 2.02 (br m, 1H), 2.29 (s, 3H), 2.35 (br s, 2H), 3.13 (br d, *J* = 13.9 Hz, 1H), 3.30–3.40 (br m, 2H), 3.46 (br d, *J* = 13.2 Hz, 1H), 3.53 (br d, *J* = 13.3 Hz, 2H), 4.05 (br d, *J* = 17.0 Hz, 1H), 4.13 (br d, *J* = 16.7 Hz, 2H), 4.39 (br d, *J* = 13.9 Hz, 1H), 6.26 (s, 1H), 6.69 (s, 2.0H). ¹³C NMR (125 MHz, D₂O) δ 13.3, 28.0, 28.4, 30.1, 35.3, 49.1, 50.2, 50.5, 52.4, 108.1, 137.6, 164.7, 168.7, 174.4, 174.5. LC/ESI-MS: positive mode *m/z* = 250.4 ([M + H]⁺). Purity (> 99.5 %). IR (KBr, cm⁻¹) 3474, 3139, 1704, 1657, 970. Anal. (C₁₃H₁₉N₃O₂*1.0C₄H₄O₄*0.6H₂O) C, H, N.

4.22. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(3,4,5-trimethoxyphenyl)propan-1-one fumaric acid salt (14F)

The *N*-*t*boc protected compound was obtained by using the general procedure C with 3-(3,4,5-trimethoxyphenyl)propionic acid (140 mg, 1 mmol) for 48 h. A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a clear oil (375 mg, 84 %) was obtained. The *N*-*t*boc protection group of this oil (270 mg, 0.60 mmol) was cleaved using the general procedure F for 12 h and an off-white solid **14** (192 mg, 92 %) was obtained after extraction. This solid **14** (96 mg, 0.28 mmol) was transferred to its fumaric acid salt **14F** by using the general procedure I with fumaric acid (32 mg, 0.28 mmol). Compound **14F** (96 mg, 73 %) was obtained as a white solid in 56 % yield over three steps; mp 124–126 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.83 (br d, *J* = 13.5 Hz, 1H), 1.95 (br d, *J* = 13.4 Hz, 1H), 2.21 (br s, 1H), 2.29 (br s, 1H), 2.71 (br m, 1H),

2.84–3.01 (br m, 5H), 3.29 (br m, 2H), 3.42 (br m, 2H), 3.76 (s, 3H), 3.85 (s, 6H), 4.01 (br d, $J = 13.2$ Hz, 1H), 4.39 (br d, $J = 13.9$ Hz, 1H), 6.63 (s, 2H), 6.67 (s, 2.0H). ^{13}C NMR (125 MHz, D_2O) δ 28.0, 28.4, 30.2, 34.1, 37.9, 48.8, 50.1, 50.5, 52.2, 58.9, 63.8, 108.9, 137.5, 138.1, 140.7, 155.3, 174.4, 180.0. LC/ESI-MS: positive mode $m/z = 349.1$ ($[\text{M} + \text{H}]^+$). Purity ($> 99.9\%$). IR (KBr, cm^{-1}) 3440, 1707, 1641, 973. Anal. ($\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_4 \cdot 1.0\text{C}_4\text{H}_4\text{O}_4 \cdot 0.75\text{H}_2\text{O}$) C, H, N.

4.23. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl((1R,2R)-2-phenylcyclopropyl)methanone fumaric acid salt (15F)

The *N*-*t*-boc protected compound was obtained by using the general procedure C with *trans*-2-phenylcyclopropane-1-carboxylic acid (162 mg, 1 mmol) for 48 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 (326 mg, 88 %) was obtained. The *N*-*t*-boc protection group of this oil (250 mg, 0.67 mmol) was cleaved using the general procedure F for 12 h and a clear oil **15** (177 mg, 97 %) was obtained after extraction. This oil **15** (67 mg, 0.25 mmol) was transferred to its fumaric acid salt **15F** by using the general procedure I with fumaric acid (29 mg, 0.25 mmol). Compound **15F** (28 mg, 28 %) was obtained as a white solid in 24 % yield over three steps; mp 101–102 °C (dec). ^1H NMR (500 MHz, D_2O) δ (rotamers present) 1.41–1.73 (br m, 2H), 1.90–2.03 (br m, 2H), 2.23–2.60 (br m, 4H), 3.11 (br d, $J = 14.0$ Hz, 1H), 3.28–3.58 (br m, 5H), 4.26–4.43 (br m, 2H), 6.67 (s, 1.6H), 7.19–7.45 (m, 5H). ^{13}C NMR (125 MHz, D_2O) δ (rotamers present) 17.6, 27.3, 28.1, 28.4, 28.6, 30.3, 49.5, 50.3, 50.6, 52.3, 128.9, 129.6, 131.7, 137.6, 143.3, 174.5, 179.2. LC/ESI-MS: positive mode $m/z = 271.3$ ($[\text{M} + \text{H}]^+$). Purity ($> 99.7\%$). IR (KBr, cm^{-1}) 3433, 3028, 1705, 1637, 1459, 983, 972. Anal. ($\text{C}_{17}\text{H}_{22}\text{N}_2\text{O} \cdot 0.8\text{C}_4\text{H}_4\text{O}_4 \cdot 1.25\text{H}_2\text{O}$) C, H, N.

4.24. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-phenylprop-2-en-1-one fumaric acid salt (16F)

The *N*-*t*-boc protected compound was obtained by using the general procedure C with *trans*-3-phenylacrylic acid (148 mg, 1 mmol) for 48 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 (256 mg, 72 %) was obtained. The *N*-*t*-boc protection group of this solid (240 mg, 0.67 mmol) was cleaved using the general procedure G with anhydrous ZnBr_2 (303 mg, 1.35 mmol) for 72 h and a white solid **16** (150 mg, 87 %) was obtained after extraction. This solid **16** (73 mg, 0.28 mmol) was transferred to its fumaric acid salt **16F** by using the general procedure I with fumaric acid (33 mg, 0.28 mmol). Compound **16F** (40 mg, 37 %) was obtained as a white solid in 23 % yield over three steps; mp 155–159 °C (dec). ^1H NMR (500 MHz, D_2O) δ 2.02 (br m, 2H), 2.38 (br s, 2H), 3.20 (br d, $J = 13.7$ Hz, 1H), 3.32–3.42 (br m, 2H), 3.46–3.59 (br m, 3H), 4.38 (br d, $J = 12.7$ Hz, 1H), 4.49 (br d, $J = 13.8$ Hz, 1H), 6.68 (s, 1.8H), 7.16 (d, $J = 15.6$ Hz, 1H), 7.49 (m, 3H), 7.59 (d, $J = 15.6$ Hz, 1H), 7.68 (m, 2H). ^{13}C NMR (125 MHz, D_2O) δ 28.2, 28.5, 30.3, 49.4, 50.3, 50.6, 52.4, 120.5, 130.9, 132.0, 133.3, 137.5, 137.6, 146.5, 173.9, 174.5. LC/ESI-MS: positive mode $m/z = 257.4$ ($[\text{M} + \text{H}]^+$). Purity ($> 99.8\%$). IR (KBr, cm^{-1}) 3433, 3059, 1650, 1616, 1451, 975. Anal. ($\text{C}_{16}\text{H}_{20}\text{N}_2\text{O} \cdot 0.9\text{C}_4\text{H}_4\text{O}_4 \cdot 1.2\text{H}_2\text{O}$) C, H, N.

4.25. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(2-methoxyphenyl)prop-2-en-1-one fumaric acid salt (17F)

The *N*-*t*-boc protected compound was obtained by using the general procedure C with *trans*-3-(2-methoxyphenyl)acrylic acid (178 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 (335 mg, 87 %) was obtained. The *N*-*t*-boc protection group of this oil (275 mg, 0.71 mmol) was cleaved using the general procedure G with anhydrous ZnBr₂ (481 mg, 2.13 mmol) for 48 h and a white solid **17** (192 mg, 94 %) was obtained after extraction. This solid **17** (142 mg, 0.50 mmol) was transferred to its fumaric acid salt **17F** by using the general procedure I with fumaric acid (58 mg, 0.50 mmol). Compound **17F** (149 mg, 72 %) was obtained as a white solid in 59 % yield over three steps; mp 141–144 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.97 (br m, 1H), 2.03 (br m, 1H), 2.36 (br s, 2H), 3.17 (br d, *J* = 12.9 Hz, 1H), 3.31–3.40 (br m, 2H), 3.47–3.58 (br m, 3H), 3.92 (s, 3H), 4.33 (br d, *J* = 12.8 Hz, 1H), 4.48 (br d, *J* = 13.4 Hz, 1H), 6.66 (s, 2.0H), 7.07 (dd, *J* = 7.7, 7.5 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.14 (d, *J* = 15.7 Hz, 1H), 7.46 (m, 1H), 7.64 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.83 (d, *J* = 15.7 Hz, 1H). ¹³C NMR (125 MHz, D₂O) δ 28.2, 28.5, 30.3, 49.4, 50.3, 50.6, 52.4, 58.7, 115.0, 120.9, 124.1, 126.2, 131.5, 134.8, 137.5, 141.5, 160.6, 174.1, 174.4. LC/ESI-MS: positive mode *m/z* = 287.1 ([M + H]⁺). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3432, 3044, 1705, 1645, 1462, 976. Anal. (C₁₇H₂₂N₂O₂*1.0C₄H₄O₄*0.75H₂O) C, H, N.

4.26. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(3-chlorophenyl)prop-2-en-1-one fumaric acid salt (18F)

The *N*-*t*-boc protected compound was obtained by using the general procedure C with *trans*-3-(3-chlorophenyl)acrylic acid (182 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 white solid (287 mg, 73 %) was obtained. The *N*-*t*-boc protection group of this solid (225 mg, 0.58 mmol) was cleaved using the general procedure G with anhydrous ZnBr₂ (389 mg, 1.73 mmol) for 48 h and a white solid **18** (160 mg, 96 %) was obtained after extraction. This solid **18** (103 mg, 0.35 mmol) was transferred to its fumaric acid salt **18F** by using the general procedure I with fumaric acid (41 mg, 0.35 mmol). Compound **18F** (88 mg, 62 %) was obtained as a white solid in 43 % yield over three steps; mp 141–144 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.99 (br m, 1H), 2.04 (br m, 1H), 2.37 (br s, 2H), 3.18 (br d, *J* = 13.7 Hz, 1H), 3.36 (br m, 2H), 3.52 (br m, 3H), 4.33 (br d, *J* = 12.9 Hz, 1H), 4.47 (br d, *J* = 13.9 Hz, 1H), 6.65 (s, 1.58H), 7.11 (d, *J* = 15.6 Hz, 1H), 7.39–7.46 (m, 2H), 7.48 (d, *J* = 15.6 Hz, 1H), 7.54 (m, 1H), 7.66 (m, 1H). ¹³C NMR (125 MHz, D₂O) δ 28.2, 28.5, 30.3, 49.4, 50.2, 50.5, 52.4, 121.7, 129.3, 130.4, 132.8, 133.3, 137.1, 137.6, 139.4, 144.9, 173.4, 174.4. LC/ESI-MS: positive mode *m/z* = 291.4 ([M + H]⁺). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3427, 3058, 1702, 1649, 1475, 971. Anal. (C₁₆H₁₉ClN₂O*0.79C₄H₄O₄*1.15H₂O) C, H, N.

4.27. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(3-bromophenyl)prop-2-en-1-one fumaric acid salt (19F)

The *N*-*t*-boc protected compound was obtained by using the general procedure C with *trans*-3-(3-bromophenyl)acrylic acid (178 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

white solid (337 mg, 77 %) was obtained. The *N*-*t*-boc protection group of this solid (285 mg, 0.65 mmol) was cleaved using the general procedure G with anhydrous ZnBr₂ (442 mg, 1.96 mmol) for 48 h and a white solid **19** (206 mg, 94 %) was obtained after extraction. This solid **19** (132 mg, 0.39 mmol) was transferred to its fumaric acid salt **19F** by using the general procedure I with fumaric acid (46 mg, 0.39 mmol). Compound **19F** (97 mg, 55 %) was obtained as a white solid in 40 % yield over three steps; mp 142–144 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.00 (br m, 2H), 2.37 (br s, 2H), 3.18 (br d, *J* = 12.5 Hz, 1H), 3.30–3.41 (br m, 2H), 3.45–3.58 (br m, 3H), 4.31 (br d, *J* = 12.3 Hz, 1H), 4.46 (br d, *J* = 13.1 Hz, 1H), 6.64 (s, 1.7H), 7.09 (d, *J* = 15.6 Hz, 1H), 7.34 (m, 1H), 7.45 (d, *J* = 15.6 Hz, 1H), 7.57 (m, 1H), 7.80 (m, 1H). ¹³C NMR (125 MHz, D₂O) δ 28.2, 28.5, 30.3, 49.4, 50.2, 50.5, 52.4, 121.7, 125.2, 129.7, 133.3, 133.5, 135.7, 137.5, 139.6, 144.8, 173.4, 174.5. IR (KBr, cm⁻¹) 3423, 3054, 1703, 1649, 1474, 971. Anal. (C₁₆H₁₉BrN₂O*0.85C₄H₄O₄*0.9H₂O) C, H, N.

4.28. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(3-nitrophenyl)prop-2-en-1-one fumaric acid salt (**20F**)

The *N*-*t*-boc protected compound was obtained by using the general procedure C with *trans*-3-(3-nitrophenyl)acrylic acid (193 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 yellow solid (294 mg, 73 %) was obtained. The *N*-*t*-boc protection group of this solid (230 mg, 0.57 mmol) was cleaved using the general procedure G with anhydrous ZnBr₂ (387 mg, 1.72 mmol) for 48 h and a yellow solid **20** (170 mg, 98 %) was obtained after extraction. This solid **20** (120 mg, 0.40 mmol) was transferred to its fumaric acid salt **20F** by using the general procedure I with fumaric acid (46 mg, 0.40 mmol). Compound **20F** (97 mg, 57 %) was obtained as a yellow solid in 41 % yield over three steps; mp 184–187 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.03 (br m, 2H), 2.40 (br s, 2H), 3.22 (br d, *J* = 14.0 Hz, 1H), 3.32–3.43 (br m, 2H), 3.47–3.62 (br m, 3H), 4.38 (br d, *J* = 13.2 Hz, 1H), 4.50 (br d, *J* = 13.7 Hz, 1H), 6.64 (s, 1.7H), 7.27 (d, *J* = 15.6 Hz, 1H), 7.58 (d, *J* = 15.6 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 8.24 (ddd, *J* = 8.3, 2.3, 0.9 Hz, 1H), 8.45 (t, *J* = 1.9 Hz, 1H). ¹³C NMR (125 MHz, D₂O) δ 28.2, 28.5, 30.3, 49.4, 50.2, 50.5, 52.4, 123.2, 125.3, 127.4, 133.0, 137.2, 137.6, 139.1, 143.8, 151.1, 173.1, 174.5. LC/ESI-MS: positive mode *m/z* = 302.0 ([M + H]⁺). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3423, 3082, 1702, 1652, 1529, 1443, 983, 974. Anal. (C₁₆H₁₉N₃O₃*0.85C₄H₄O₄*1.5H₂O) C, H, N.

4.29. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-one fumaric acid salt (**21F**)

The *N*-*t*-boc protected compound was obtained by using the general procedure C with *trans*-3-(4-methoxyphenyl)acrylic acid (178 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 white solid (249 mg, 64 %) was obtained. The *N*-*t*-boc protection group of this solid (240 mg, 0.62 mmol) was cleaved using the general procedure G with anhydrous ZnBr₂ (418 mg, 1.86 mmol) for 24 h and a white solid **21** (175 mg, 98 %) was obtained after extraction. This solid **21** (175 mg, 0.61 mmol) was transferred to its fumaric acid salt **21F** by using the general procedure I with fumaric acid (71 mg, 0.61 mmol). Compound **21F** (194 mg, 76 %) was obtained as a white solid in 48 % yield over three steps; mp 169–170 °C

(dec). ^1H NMR (500 MHz, D_2O) δ 2.00 (br m, 2H), 2.36 (br s, 2H), 3.12–3.19 (br m, 1H), 3.31–3.40 (br m, 2H), 3.45–3.58 (br m, 3H), 3.87 (s, 3H), 4.35 (br d, $J = 12.0$ Hz, 1H), 4.47 (br d, $J = 13.5$ Hz, 1H), 6.65 (s, 2.0H), 6.99 (d, $J = 15.5$ Hz, 1H), 7.03 (ddd, $J = 8.8, 3.0, 2.0$ Hz, 2H), 7.53 (d, $J = 15.5$ Hz, 1H), 7.62 (ddd, $J = 8.7, 2.9, 1.9$ Hz, 2H). ^{13}C NMR (125 MHz, D_2O) δ 28.2, 28.5, 30.3, 49.4, 50.3, 50.6, 52.3, 58.3, 117.4, 117.9, 130.5, 132.8, 137.6, 146.3, 163.6, 174.0, 174.5. LC/ESI-MS: positive mode $m/z = 287.4$ ($[\text{M} + \text{H}]^+$). Purity (> 99.8 %). IR (KBr, cm^{-1}) 3427, 3032, 1737, 1650, 1604, 979. Anal. ($\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2 \cdot 1.0\text{C}_4\text{H}_4\text{O}_4 \cdot 0.75\text{H}_2\text{O}$) C, H, N.

4.30. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(furan-2-yl)prop-2-en-1-one fumaric acid salt (22F)

The N-*t*-boc protected compound was obtained by using the general procedure C with *trans*-3-(furan-2-yl)acrylic acid (138 mg, 1 mmol) for 72 h. A mixture of CH_2Cl_2 and MeOH (40:1) was used for the chromatographic purification. After removal of the solvents an orange solid (176 mg, 51 %) was obtained. The N-*t*-boc protection group of this solid (175 mg, 0.51 mmol) was cleaved using the general procedure G with anhydrous ZnBr_2 (341 mg, 1.52 mmol) for 12 h and an orange oil **22** (84 mg, 68 %) was obtained after extraction. This oil **22** (84 mg, 0.34 mmol) was transferred to its fumaric acid salt **22F** by using the general procedure I with fumaric acid (40 mg, 0.34 mmol). Compound **22F** (65 mg, 51 %) was obtained as an orange solid in 18 % yield over three steps; mp 142–144 °C (dec). ^1H NMR (500 MHz, D_2O) δ 2.00 (br m, 1H), 2.09 (br m, 1H), 2.32 (br s, 2H), 3.30–3.40 (br m, 4H), 3.51 (br s, 2H), 4.48 (br s, 2H), 6.58 (dd, $J = 3.4, 1.7$ Hz, 1H), 6.72 (s, 2.0H), 6.77 (d, $J = 3.4$ Hz, 1H), 7.05 (d, $J = 15.2$ Hz, 1H), 7.45 (d, $J = 15.2$ Hz, 1H), 7.65 (d, $J = 1.7$ Hz, 1H). ^{13}C NMR (125 MHz, D_2O) δ 27.7, 29.5, 49.0, 113.7, 115.8, 116.5, 131.4, 136.5, 146.3, 153.2, 171.1, 171.7. LC/ESI-MS: positive mode $m/z = 247.4$ ($[\text{M} + \text{H}]^+$). Purity (> 99 %). IR (KBr, cm^{-1}) 3426, 3095, 1679, 1648, 1608, 984, 968. Anal. ($\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2 \cdot 1.0\text{C}_4\text{H}_4\text{O}_4 \cdot 0.75\text{H}_2\text{O}$) C, H, N.

4.31. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(thiophen-2-yl)prop-2-en-1-one fumaric acid salt (23F)

The N-*t*-boc protected compound was obtained by using the general procedure C with *trans*-3-(thiophen-2-yl)acrylic acid (154 mg, 1 mmol) for 24 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 (220 mg, 61 %) was obtained. The N-*t*-boc protection group of this oil (170 mg, 0.47 mmol) was cleaved using the general procedure G with anhydrous ZnBr_2 (317 mg, 1.41 mmol) for 48 h and a clear oil **23** (122 mg, 99 %) was obtained after extraction. This oil **23** (44 mg, 0.17 mmol) was transferred to its fumaric acid salt **23F** by using the general procedure I with fumaric acid (19 mg, 0.17 mmol). Compound **23F** (24 mg, 37 %) was obtained as an off-white solid in 22 % yield over three steps; mp 173–178 °C (dec). ^1H NMR (500 MHz, D_2O) δ 1.87–2.06 (br m, 2H), 2.33–2.48 (br m, 2H), 3.13–3.24 (br m, 1H), 3.30–3.58 (br m, 5H), 4.30–4.52 (br m, 2H), 6.67 (s, 2.0H), 6.91 (d, $J = 15.2$ Hz, 1H), 7.15 (dd, $J = 5.1, 3.6$ Hz, 1H), 7.42 (d, $J = 3.6$ Hz, 1H), 7.57 (d, $J = 5.1$, 1H), 7.75 (d, $J = 15.2$, 1H). ^{13}C NMR (125 MHz, D_2O) δ 28.2, 28.5, 30.3, 49.4, 50.3, 50.6, 52.3, 118.6, 131.4, 132.0, 134.5, 137.6, 139.5, 142.4, 173.5, 174.5. LC/ESI-MS: positive mode $m/z = 263.4$ ($[\text{M}$

+ H]⁺). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3441, 3074, 1700, 1638, 1600, 968. Anal. (C₁₄H₁₈N₂OS*1.0C₄H₄O₄*0.6H₂O) C, H, N.

4.32. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(thiophen-3-yl)prop-2-en-1-one fumaric acid salt (24F)

The N-*t*-boc protected compound was obtained by using the general procedure C with *trans*-3-(thiophen-3-yl)acrylic acid (154 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 white solid (312 mg, 86 %) was obtained. The N-*t*-boc protection group of this solid (240 mg, 0.66 mmol) was cleaved using the general procedure G with anhydrous ZnBr₂ (447 mg, 1.98 mmol) for 48 h and a clear oil **24** (168 mg, 97 %) was obtained after extraction. This oil **24** (126 mg, 0.48 mmol) was transferred to its fumaric acid salt **24F** by using the general procedure I with fumaric acid (56 mg, 0.48 mmol). Compound **24F** (129 mg, 70 %) was obtained as a white solid in 58 % yield over three steps; mp 155–159 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.97 (br m, 1H), 2.02 (br m, 1H), 2.36 (br s, 2H), 3.17 (br d, *J* = 12.2 Hz, 1H), 3.30–3.40 (br m, 2H), 3.45–3.58 (br m, 3H), 4.34 (br d, *J* = 12.5 Hz, 1H), 4.47 (br d, *J* = 13.3 Hz, 1H), 6.66 (s, 1.8H), 6.97 (d, *J* = 15.4 Hz, 1H), 7.47 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.52 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.59 (d, *J* = 15.4 Hz, 1H), 7.74 (dd, *J* = 2.8, 1.1 Hz, 1H). ¹³C NMR (125 MHz, D₂O) δ 28.2, 28.5, 30.3, 49.4, 50.3, 50.6, 52.3, 119.6, 128.0, 130.5, 131.8, 137.5, 140.4, 140.5, 174.1, 174.4. LC/ESI-MS: positive mode *m/z* = 263.4 ([M + H]⁺). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3428, 3087, 1705, 1647, 1594, 973. Anal. (C₁₄H₁₈N₂OS*0.9C₄H₄O₄*0.9H₂O) C, H, N.

4.33. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(pyridin-4-yl)prop-2-en-1-one fumaric acid salt (25F)

The N-*t*-boc protected compound was obtained by using the general procedure C with *trans*-3-(pyridin-4-yl)acrylic acid (149 mg, 1 mmol) for 24 h. A mixture of CH₂Cl₂ and MeOH (9:1) was used for the chromatographic purification. After removal of the solvents a white solid (243 mg, 68 %) was obtained. The N-*t*-boc protection group of this solid (185 mg, 0.52 mmol) was cleaved using the general procedure G with anhydrous ZnBr₂ (350 mg, 1.55 mmol) for 48 h and an off-white oil **25** (116 mg, 87 %) was obtained after extraction. This oil **25** (63 mg, 0.24 mmol) was transferred to its fumaric acid salt **25F** by using the general procedure I with fumaric acid (28 mg, 0.24 mmol). Compound **25F** (70 mg, 72 %) was obtained as a white solid in 43 % yield over three steps; mp 155–159 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.02 (br m, 2H), 2.38 (br s, 1H), 2.40 (br s, 1H), 3.24 (br d, *J* = 14.7 Hz, 1H), 3.33–3.41 (br m, 2H), 3.49 (br d, *J* = 13.3 Hz, 1H), 3.54–3.62 (br m, 2H), 4.33 (br d, *J* = 13.2 Hz, 1H), 4.48 (br d, *J* = 13.9 Hz, 1H), 6.58 (s, 2.0H), 7.56 (s, 2H), 8.02 (d, *J* = 6.7 Hz, 1H); 8.70 (d, *J* = 6.2 Hz, 1H). ¹³C NMR (125 MHz, D₂O) δ 28.1, 28.4, 30.2, 49.4, 50.1, 50.4, 52.5, 127.3, 130.4, 138.0, 140.4, 146.6, 152.7, 172.2, 176.2. LC/ESI-MS: positive mode *m/z* = 258.4 ([M + H]⁺). Purity (> 99.9 %). IR (KBr, cm⁻¹) 3427, 3038, 1699, 1653, 1602, 982. Anal. (C₁₅H₁₉N₃O*1.0C₄H₄O₄*1.25H₂O) C, H, N.

4.34. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(benzo[d][1,3]dioxol-5-yl)prop-2-en-1-one fumaric acid salt (26F)

The *N*-*t*-boc protected compound was obtained by using the general procedure C with *trans*-3-(benzo[d][1,3]dioxol-5-yl)acrylic acid (192 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 (284 mg, 71 %) was obtained. The *N*-*t*-boc protection group of this solid (235 mg, 0.59 mmol) was cleaved using the general procedure F for 2 h and an off-white solid **26** (128 mg, 73 %) was obtained after extraction. This solid **26** (128 mg, 0.43 mmol) was transferred to its fumaric acid salt **26F** by using the general procedure I with fumaric acid (49 mg, 0.43 mmol). Compound **26F** (106 mg, 58 %) was obtained as an off-white solid in 30 % yield over three steps; mp 147–148 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.97 (br m, 1H), 2.03 (br m, 1H), 2.37 (s, 2H), 3.16 (br d, *J* = 12.2 Hz, 1H), 3.31–3.41 (br m, 2H), 3.44–3.58 (br m, 3H), 4.34 (br d, *J* = 11.6 Hz, 1H), 4.46 (br d, *J* = 13.2, 1H), 6.02 (s, 2H), 6.65 (s, 2.0H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 15.3 Hz, 1H), 7.12 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.19 (d, *J* = 1.6 Hz, 1H), 7.47 (d, *J* = 15.4 Hz, 1H). ¹³C NMR (125 MHz, D₂O) δ 28.1, 28.5, 30.3, 49.4, 50.3, 50.6, 52.3, 104.6, 109.3, 111.6, 118.0, 127.6, 131.9, 137.5, 146.5, 150.8, 152.0, 173.9, 174.3. LC/ESI-MS: positive mode *m/z* = 301.4 ([M + H]⁺). Purity (> 99.5 %). IR (KBr, cm⁻¹) 3434, 3054, 1706, 1646, 1607, 1448, 976. Anal. (C₁₇H₂₀N₂O₃*1.0C₄H₄O₄*0.75H₂O) C, H, N.

4.35. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(naphthalen-1-yl)prop-2-en-1-one fumaric acid salt (27F)

The *N*-*t*-boc protected compound was obtained by using the general procedure C with *trans*-3-(naphthalene-1-yl)acrylic acid (198 mg, 1 mmol) for 48 h. A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. After removal of the solvents a white solid (344 mg, 85 %) was obtained. The *N*-*t*-boc protection group of this solid (270 mg, 0.66 mmol) was cleaved using the general procedure G with anhydrous ZnBr₂ (449 mg, 1.99 mmol) for 72 h and an off-white solid **27** (196 mg, 96 %) was obtained after extraction. This solid **27** (119 mg, 0.39 mmol) was transferred to its fumaric acid salt **27F** by using the general procedure I with fumaric acid (45 mg, 0.39 mmol). Compound **27F** (103 mg, 61 %) was obtained as a white solid in 50 % yield over three steps; mp 171–174 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.86 (br d, *J* = 13.3 Hz, 1H), 1.97 (br d, *J* = 13.4 Hz, 1H), 2.21 (br s, 1H), 2.32 (br s, 1H), 3.03 (br d, *J* = 13.0 Hz, 1H), 3.20 (br d, *J* = 12.3 Hz, 1H), 3.30 (br d, *J* = 13.0 Hz, 2H), 3.44 (br d, *J* = 13.4 Hz, 2H), 4.15 (br d, *J* = 12.3 Hz, 1H), 4.41 (br d, *J* = 13.4 Hz, 1H), 6.61 (s, 1.9H), 6.96 (d, *J* = 15.3 Hz, 1H), 7.50 (dd, *J* = 7.8, 7.7 Hz, 1H), 7.56 (m, 2H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.91 (dd, *J* = 7.7, 6.7 Hz, 2H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.21 (d, *J* = 15.3 Hz, 1H). ¹³C NMR (125 MHz, D₂O) δ 28.1, 28.4, 30.2, 49.3, 50.2, 50.5, 52.2, 122.8, 126.0, 127.9, 128.6, 129.3, 130.0, 131.6, 133.3, 133.8, 134.5, 136.2, 137.5, 143.0, 173.4, 174.3. LC/ESI-MS: positive mode *m/z* = 307.5 ([M + H]⁺). Purity (> 99.9 %). IR (KBr, cm⁻¹) 3433, 3048, 1701, 1643, 1601, 1458, 970. Anal. (C₂₀H₂₂N₂O*0.95C₄H₄O₄*1.1H₂O) C, H, N.

4.36. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(biphenyl-4-yl)methanone fumaric acid salt (28F)

The N-*t*-boc protected compound was obtained by using the general procedure C 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 F for 12 h and a clear oil **28** (141 mg, 75 %) was obtained after extraction. This oil **28** (60 mg, 0.20 mmol) was transferred to its fumaric acid salt **28F** by using the general procedure I with fumaric acid (23 mg, 0.20 mmol). Compound **28F** (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.

4.37. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(phenyl)methanone fumaric acid salt (29F)

The N-*t*-boc protected compound was obtained by using the general procedure D 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 F for 12 h and an off white solid **29** (138 mg, 99 %) was obtained after extraction. This solid **29** (67 mg, 0.29 mmol) was transferred to its fumaric acid salt **29F** by using the general procedure I with fumaric acid (34 mg, 0.29 mmol). Compound **29F** (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.

4.38. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-phenylethanone fumaric acid salt (30F)

The N-*t*-boc protected compound was obtained by using the general procedure D with phenylacetyl 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 white solid (343 mg, 98 %) was obtained. The N-*t*-boc protection group of this solid (310 mg, 0.90 mmol) was cleaved using the general procedure F for 12 h and an off white solid **30** (210 mg, 97 %) was obtained after extraction. This solid **30** (180 mg, 0.74 mmol) was transferred to its fumaric acid salt **30F** by using the general procedure H. Compound **30F** (158 mg, 66 %) was obtained as a white solid in 62 % yield over three steps; mp 145–147 °C (dec). ¹H NMR (500 MHz, D₂O) δ 1.91 (br m, 1H), 1.97 (br m, 1H), 2.27 (br s, 1H), 2.32 (br s, 1H), 2.78 (br

d, $J = 13.4$ Hz, 1H), 3.27–3.33 (br m, 3H), 3.39 (br d, $J = 12.9$ Hz, 1H), 3.45 (br d, $J = 13.2$ Hz, 1H), 3.85–3.97 (br m, 2H), 4.17 (br d, $J = 13.2$ Hz, 1H), 4.40 (br d, $J = 13.7$ Hz, 1H), 6.69 (s, 0.9H), 7.27–7.45 (m, 5H). ^{13}C NMR (125 MHz, D_2O) δ 28.0, 28.3, 30.2, 43.5, 49.1, 50.2, 50.6, 52.5, 130.2, 131.9, 132.1, 137.3, 138.0, 176.5, 178.8. LC/ESI-MS: positive mode $m/z = 245.4$ ($[\text{M} + \text{H}]^+$). Purity ($> 99\%$). IR (KBr, cm^{-1}) 3443, 3031, 1696, 1640, 1457, 984, 969. Anal. ($\text{C}_{15}\text{H}_{20}\text{N}_2\text{O} \cdot 0.45\text{C}_4\text{H}_4\text{O}_4 \cdot 1.5\text{H}_2\text{O}$) C, H, N.

4.39. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-(pyridine-3-yl)ethanone fumaric acid salt (31F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 2-(pyridine-3-yl)acetic acid (137 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 (262 mg, 76 %) was obtained. The *N*-*t*-boc protection group of this solid (222 mg, 0.64 mmol) was cleaved using the general procedure F for 2 h and a clear oil **31** (143 mg, 90 %) was obtained after extraction. This oil **31** (143 mg, 0.58 mmol) was transferred to its fumaric acid salt **31F** by using the general procedure I with fumaric acid (67 mg, 0.58 mmol). Compound **31F** (96 mg, 47 %) was obtained as a white solid in 32 % yield over three steps; mp 166–168 °C (dec). ^1H NMR (400 MHz, D_2O) δ 1.97 (br d, $J = 13.6$ Hz, 1H), 2.03 (br d, $J = 13.3$ Hz, 1H), 2.36 (br s, 2H), 3.14 (br d, $J = 13.5$ Hz, 1H), 3.30–3.42 (br m, 2H), 3.46 (br d, $J = 13.0$ Hz, 1H), 3.53–3.64 (br m, 2H), 4.04 (br d, $J = 18.1$ Hz, 1H), 4.19 (br d, $J = 12.2$ Hz, 1H), 4.22 (br d, $J = 17.1$ Hz, 1H), 4.38 (br d, $J = 13.9$ Hz, 1H), 6.55 (s, 1.84H), 7.91 (dd, $J = 7.9, 5.8$ Hz, 1H), 8.31 (d, $J = 8.0$ Hz, 1H), 8.61 (s, 1H), 8.67 (d, $J = 5.3$ Hz, 1H). ^{13}C NMR (100 MHz, D_2O) δ 25.8, 26.2, 27.9, 37.9, 47.0, 48.0, 48.2, 49.8, 126.9, 135.3, 142.1, 144.4, 147.0, 174.2, 174.3. ESI-MS: positive mode $m/z = 246.3$ ($[\text{M} + \text{H}]^+$). Purity ($> 99.9\%$). IR (cm^{-1}) 2926, 2859, 1699, 1640, 1219, 1106, 970, 639. Anal. ($\text{C}_{14}\text{H}_{19}\text{N}_3\text{O} \cdot 1.0\text{C}_4\text{H}_4\text{O}_4 \cdot 0.4\text{H}_2\text{O}$) C, H, N.

4.40. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-phenylpropan-1-one fumaric acid salt (32F)

The *N*-*t*-boc protected compound was obtained by using the general procedure D with 3-phenylpropionic acid chloride (169 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 (355 mg, 97 %) was obtained. The *N*-*t*-boc protection group of this solid (340 mg, 0.95 mmol) was cleaved using the general procedure F for 12 h and a clear oil **32** (235 mg, 96 %) was obtained after extraction. This oil **32** (103 mg, 0.40 mmol) was transferred to its fumaric acid salt **32F** by using the general procedure I with fumaric acid (46 mg, 0.40 mmol). Compound **32F** (115 mg, 75 %) was obtained as a white solid in 70 % yield over three steps; mp 153–156 °C (dec). ^1H NMR (500 MHz, D_2O) δ 1.86 (br m, 1H), 1.94 (br m, 1H), 2.22 (br s, 1H), 2.29 (br s, 1H), 2.78 (br m, 1H), 2.88 (br m, 1H), 2.90–2.96 (br m, 1H), 2.99 (br d, $J = 14.0$ Hz, 1H), 3.14 (br d, $J = 13.7$ Hz, 1H), 3.27 (br m, 2H), 3.39 (br m, 2H), 4.02 (br d, $J = 13.5$ Hz, 1H), 4.37 (br d, $J = 14.1$ Hz, 1H), 6.69 (s, 2.0H), 7.30 (m, 3H), 7.38 (m, 2H). ^{13}C NMR (125 MHz, D_2O) δ 28.0, 28.3, 30.1, 33.6, 37.9, 48.8, 50.2, 50.6, 52.2, 129.4, 131.4, 131.7, 137.5, 143.7, 174.4, 180.2. LC/ESI-MS: positive mode $m/z = 259.5$ ($[\text{M} +$

H]⁺). Purity (> 99.8 %). IR (KBr, cm⁻¹) 3433, 3054, 1701, 1645, 1454, 984. Anal. (C₁₆H₂₂N₂O*1.0C₄H₄O₄*0.5H₂O) C, H, N.

4.41. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-(2-chlorophenoxy)ethanone fumaric acid salt (33F)

The N-*t*-boc protected compound was obtained by using the general procedure C with (2-chlorophenoxy)acetic acid (187 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 (186 mg, 47 %) was obtained. The N-*t*-boc protection group of this oil (130 mg, 0.33 mmol) was cleaved using the general procedure F for 12 h and a white solid **33** (95 mg, 98 %) was obtained after extraction. This solid **33** (46 mg, 0.16 mmol) was transferred to its fumaric acid salt **33F** by using the general procedure I with fumaric acid (18 mg, 0.16 mmol). Compound **33F** (40 mg, 62 %) was obtained as a white solid in 29 % yield over three steps; mp 145–149 °C (dec). ¹H NMR (500 MHz, D₂O) δ 2.02 (br m, 2H), 2.34 (br s, 1H), 2.37 (br s, 1H), 3.18 (br d, *J* = 13.4 Hz, 1H), 3.35 (br m, 2H), 3.49 (br d, *J* = 13.1 Hz, 1H), 3.59 (br m, 2H), 4.00 (br d, *J* = 13.2 Hz, 1H), 4.38 (br d, *J* = 13.9 Hz, 1H), 4.85 (br d, *J* = 14.3 Hz, 1H), 5.15 (br d, *J* = 14.6 Hz, 1H), 6.68 (s, 1.8H), 7.07 (m, 2H), 7.33 (m, 1H), 7.50 (dd, *J* = 8.2, 1.3 Hz, 1H). ¹³C NMR (125 MHz, D₂O) δ 28.0, 28.2, 30.2, 49.0, 50.2, 50.5, 51.2, 70.1, 117.2, 124.7, 125.8, 131.2, 133.3, 137.5, 155.5, 174.2, 176.4. LC/ESI-MS: positive mode *m/z* = 295.1 ([M + H]⁺). Purity (>97 %). IR (KBr, cm⁻¹) 3441, 3065, 1662, 1457, 970. Anal. (C₁₅H₁₉ClN₂O₂*0.9C₄H₄O₄*0.8H₂O) C, H, N.

4.42. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-(2,3,4,5,6-pentafluorophenyl)ethanone fumaric acid salt (34F)

The N-*t*-boc protected compound was obtained by using the general procedure E with 2,3,4,5,6-pentafluorophenylacetic acid (226 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 (370 mg, 85 %) was obtained. The N-*t*-boc protection group of this solid (200 mg, 0.46 mmol) was cleaved using the general procedure F for 4 h and a white solid **34** (149 mg, 97 %) was obtained after extraction. This solid **34** (145 mg, 0.43 mmol) was transferred to its fumaric acid salt **34F** by using the general procedure I with fumaric acid (50 mg, 0.43 mmol). Compound **34F** (149 mg, 79 %) was obtained as a white solid in 65 % yield over three steps; mp 176–180 °C (dec.). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.78 (br d, *J* = 13.6 Hz, 1H), 1.84 (br d, *J* = 13.8 Hz, 1H), 2.17 (br s, 1H), 2.20 (br s, 1H), 2.96 (br d, *J* = 13.2 Hz, 1H), 3.15 (br m, 2H), 3.26 (br d, *J* = 13.1 Hz, 1H), 3.39 (br d, *J* = 13.0 Hz, 1H), 3.46 (br d, *J* = 12.7 Hz, 1H), 3.74 (br d, *J* = 17.3 Hz, 1H), 3.96 (br d, *J* = 16.4 Hz, 1H), 4.00 (br d, *J* = 11.7 Hz, 1H), 4.17 (br d, *J* = 13.9 Hz, 1H), 6.48 (s, 1.80H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 26.5, 27.0, 28.6, 29.5, 47.9, 48.8, 49.1, 50.7, 136.4, 172.5, 173.7. LC/ESI-MS: positive mode *m/z* = 335.2 ([M + H]⁺). HRMS (EI) calcd for C₁₅H₁₅F₅N₂O 335.1177, found 335.1186. Purity (> 99 %). IR (cm⁻¹) 1669, 1657, 1506, 1410, 1222, 1004, 974, 642. Anal. (C₁₅H₁₅F₅N₂O*1.0C₄H₄O₄*0.4H₂O) C, H, N.

4.43. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-(4-(methylsulfonyl)phenyl)ethanone fumaric acid salt (35F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 4-(methylsulfonyl)phenylacetic acid (214 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 (296 mg, 70 %) was obtained. The *N*-*t*-boc protection group of this solid (246 mg, 0.58 mmol) was cleaved using the general procedure F for 2 h and a white solid **35** (147 mg, 78 %) was obtained after extraction. This solid **35** (147 mg, 0.46 mmol) was transferred to its fumaric acid salt **35F** by using the general procedure I with fumaric acid (53 mg, 0.46 mmol). Compound **35F** (121 mg, 61 %) was obtained as a white solid in 33 % yield over three steps; mp 188–191 °C (dec). ¹H NMR (400 MHz, D₂O) δ 1.93 (br d, *J* = 13.5 Hz, 1H), 2.01 (br d, *J* = 13.6 Hz, 1H), 2.33 (br s, 2H), 3.11 (br d, *J* = 13.2 Hz, 1H), 3.27 (s, 3H), 3.29–3.39 (br m, 2H), 3.42–3.57 (br m, 3H), 4.03 (s, 2H), 4.16 (br d, *J* = 13.2 Hz, 1H), 4.39 (br d, *J* = 13.9 Hz, 1H), 6.68 (s, 1.90H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H). ¹³C NMR (100 MHz, D₂O) δ 25.8, 26.2, 27.9, 41.0, 44.0, 46.9, 48.0, 48.3, 50.1, 128.0, 131.5, 135.4, 138.1, 142.4, 172.1, 175.5. ESI-MS: positive mode *m/z* = 323.3 ([M + H]⁺). HRMS (EI) calcd for C₁₆H₂₂N₂O₃S 323.1424, found 323.1416. Purity (> 99.9 %). IR (cm⁻¹) 2930, 2857, 2720, 2626, 1652, 1582, 1253, 1144, 962, 751, 634. Anal. (C₁₆H₂₂N₂O₃S *1.0C₄H₄O₄*0.7H₂O) C, H, N.

4.44. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-(pyridine-4-yl)ethanone fumaric acid salt (36F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 2-(pyridine-4-yl)acetic acid (137 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 (276 mg, 80 %) was obtained. The *N*-*t*-boc protection group of this solid (220 mg, 0.64 mmol) was cleaved using the general procedure F for 2 h and a clear oil **36** (128 mg, 82 %) was obtained after extraction. This oil **36** (128 mg, 0.52 mmol) was transferred to its fumaric acid salt **36F** by using the general procedure I with fumaric acid (61 mg, 0.52 mmol). Compound **36F** (157 mg, 74 %) was obtained as a white solid in 48 % yield over three steps; mp 174–175 °C (dec). ¹H NMR (400 MHz, D₂O) δ 1.97 (br d, *J* = 13.6 Hz, 1H), 2.03 (br d, *J* = 13.4 Hz, 1H), 2.37 (br s, 2H), 3.14 (br d, *J* = 13.5 Hz, 1H), 3.30–3.42 (br m, 2H), 3.47 (br d, *J* = 13.2 Hz, 1H), 3.54–3.63 (br m, 2H), 4.15 (br d, *J* = 12.6 Hz, 1H), 4.19–4.32 (m, 2H, exchangeable), 4.38 (br d, *J* = 13.9 Hz, 1H), 6.62 (s, 2.80H), 7.93 (d, *J* = 6.3 Hz, 2H), 8.72 (d, *J* = 6.3 Hz, 2H). ¹³C NMR (100 MHz, D₂O) δ 25.8, 26.2, 27.8, 40.8, 46.9, 48.0, 48.2, 49.9, 129.5, 135.6, 141.5, 157.0, 173.08, 173.14. ESI-MS: positive mode *m/z* = 246.3 ([M + H]⁺). HRMS (EI) calcd for C₁₄H₁₉N₃O 246.1601, found 246.1591. Purity (> 99.9 %). IR (cm⁻¹) 2971, 2848, 1671, 1568, 1404, 1271, 976, 784, 631, 590. Anal. (C₁₄H₁₉N₃O *1.0C₄H₄O₄*1.3H₂O) C, H, N.

4.45. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-(benzo[d][1,3]dioxol-5-yl)ethanone fumaric acid salt (37F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 2-benzo[d][1,3]dioxol-5-yl)acetic acid (180 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 (248 mg, 64 %) was obtained. The *N*-*t*-boc protection group of this solid (207 mg, 0.53 mmol) was cleaved using the general procedure F for 2 h and a white solid **37** (152 mg, 99 %) was obtained after extraction. This solid **37** (152 mg, 0.53 mmol) was transferred to its fumaric acid salt **37F** by using the general procedure I with fumaric acid (61 mg, 0.53 mmol). Compound **37F** (76 mg, 37 %) was obtained as a white solid in 23 % yield over three steps; mp 179–185 °C (dec). ¹H NMR (400 MHz, D₂O) δ 1.91 (br d, *J* = 13.2 Hz, 1H), 1.98 (br d, *J* = 13.4 Hz, 1H), 2.29 (br s, 1H), 2.31 (br s, 1H), 3.08 (br d, *J* = 13.5 Hz, 1H), 3.26–3.50 (br m, 5H), 3.81 (m, 2H), 4.15 (br d, *J* = 13.0 Hz, 1H), 4.39 (br d, *J* = 13.7 Hz, 1H), 5.97 (s, 2H), 6.67 (s, 1.75H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 6.88 (d, *J* = 7.9 Hz, 1H). ¹³C NMR (100 MHz, D₂O) δ 25.8, 26.3, 27.9, 40.8, 46.9, 48.0, 48.4, 50.2, 101.8, 109.3, 110.4, 123.2, 128.7, 135.5, 146.8, 148.1, 172.2, 176.6. ESI-MS: positive mode *m/z* = 289.3 ([M + H]⁺). HRMS (EI) calcd for C₁₆H₂₀N₂O₃ 289.1547, found 289.1550. Purity (> 97 %). IR (cm⁻¹) 2869, 1698, 1659, 1596, 1443, 1398, 1253, 1213, 1192, 1034, 787. Anal. (C₁₆H₂₀N₂O₃*1.1C₄H₄O₄*0.4H₂O) C, H, N.

4.46. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-(naphthalene-2-yl)ethanone fumaric acid salt (38F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 2-naphthylacetic acid (186 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 (366 mg, 93 %) was obtained. The *N*-*t*-boc protection group of this solid (309 mg, 0.78 mmol) was cleaved using the general procedure F for 2 h and a white solid **38** (228 mg, 99 %) was obtained after extraction. This solid **38** (228 mg, 0.78 mmol) was transferred to its fumaric acid salt **38F** by using the general procedure I with fumaric acid (90 mg, 0.78 mmol). Compound **38F** (122 mg, 32 %) was obtained as a white solid in 30 % yield over three steps; mp 181–185 °C (dec). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.71 (br d, *J* = 11.8 Hz, 1H), 1.79 (br d, *J* = 12.3 Hz, 1H), 2.10 (br s, 1H), 2.13 (br s, 1H), 2.88 (br d, *J* = 11.9 Hz, 1H), 3.04–3.34 (br m, 5H), 3.83 (br d, *J* = 14.2 Hz, 1H), 3.95 (br d, *J* = 14.5 Hz, 1H), 4.06 (br d, *J* = 10.9 Hz, 1H), 4.25 (br d, *J* = 12.2 Hz, 1H), 6.48 (s, 1.36H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.42 (m, 2H), 7.61 (s, 1H), 7.72–7.86 (m, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 25.4, 25.7, 28.1, 40.6, 45.9, 46.7, 46.8, 49.0, 125.4, 125.9, 127.33, 127.34, 127.4, 127.5, 128.3, 131.7, 133.0, 133.6, 135.1, 167.9, 171.6. ESI-MS: positive mode *m/z* = 295.4 ([M + H]⁺). HRMS (EI) calcd for C₁₉H₂₂N₂O 295.1805, found 295.1808. Purity (> 98 %). IR (cm⁻¹) 2952, 2852, 1656, 1402, 1218, 1104, 980, 796. Anal. (C₁₉H₂₂N₂O*0.8C₄H₄O₄*1.0H₂O) C, H, N.

4.47. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-(pyridine-4-yl)propanone fumaric acid salt (39F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 3-(pyridine-3-yl)propionic acid (151 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 (232 mg, 64 %) was obtained. The *N*-*t*-boc protection group of this solid (190 mg, 0.53 mmol) was cleaved using the general procedure F for 2 h and a clear oil **39** (120 mg, 88 %) was obtained after extraction. This oil **39** (120 mg, 0.46 mmol) was transferred to its fumaric

acid salt **39F** by using the general procedure I with fumaric acid (54 mg, 0.46 mmol). Compound **39F** (127 mg, 65 %) was obtained as a white solid in 37 % yield over three steps; mp 149–155 °C (dec). ¹H NMR (400 MHz, D₂O) δ 1.92 (br d, *J* = 13.6 Hz, 1H), 1.99 (br d, *J* = 13.6 Hz, 1H), 2.31 (br s, 2H), 2.86–3.08 (br m, 3H), 3.15 (q, *J* = 7.0 Hz, 2H), 3.39–3.54 (br m, 3H), 4.06 (br d, *J* = 13.0 Hz, 1H), 4.34 (br d, *J* = 13.8 Hz, 1H), 6.62 (s, 2.78H), 7.98 (dd, *J* = 7.7, 6.2 Hz, 1H), 8.50 (d, *J* = 8.1 Hz, 1H), 8.63 (d, *J* = 5.6 Hz, 1H), 8.70 (s, 1H). ¹³C NMR (100 MHz, D₂O) δ 25.8, 26.1, 27.7, 34.2, 46.6, 48.0, 48.3, 49.6, 127.5, 135.6, 139.7, 141.7, 142.3, 147.5, 173.1, 176.3. ESI-MS: positive mode *m/z* = 260.3 ([M + H]⁺). HRMS (EI) calcd for C₁₅H₂₁N₃O 260.1757, found 260.1751. Purity (> 99.9 %). IR (cm⁻¹) 2949, 2852, 1731, 1642, 1562, 1312, 1180, 985, 787, 641. Anal. (C₁₅H₂₁N₃O*1.4C₄H₄O₄*1.0H₂O) C, H, N.

4.48. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(4-fluorophenyl)prop-2-en-1-one fumaric acid salt (**40F**)

The N-*t*-boc protected compound was obtained by using the general procedure E with *trans*-3-(4-fluorophenyl)acrylic acid (166 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 (242 mg, 65 %) was obtained. The N-*t*-boc protection group of this solid (210 mg, 0.56 mmol) was cleaved using the general procedure F for 2 h and a clear oil **40** (149 mg, 97 %) was obtained after extraction. This oil **40** (149 mg, 0.54 mmol) was transferred to its fumaric acid salt **40F** by using the general procedure I with fumaric acid (63 mg, 0.54 mmol). Compound **40F** (151 mg, 71 %) was obtained as a white solid in 45 % yield over three steps; mp 199–201 °C (dec). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.76 (br d, *J* = 12.5 Hz, 1H), 1.87 (br d, *J* = 12.7 Hz, 1H), 2.07 (br s, 2H), 2.88–3.42 (br m, 6H), 4.34 (br d, *J* = 12.9 Hz, 2H), 6.46 (s, 2.0H), 7.25 (d, *J* = 15.3 Hz, 1H), 7.24–7.28 (m, 2H), 7.41 (d, *J* = 15.5 Hz, 1H), 7.77 (dd, *J* = 8.2, 5.8 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 26.6, 28.4, 46.7, 115.7 (d, *J*_{C,F} = 21.6 Hz), 120.0 (d, *J*_{C,F} = 2.1 Hz), 130.0 (d, *J*_{C,F} = 8.3 Hz), 132.0 (d, *J*_{C,F} = 3.1 Hz), 135.1 (br d, *J*_{C,F} = 1.9 Hz), 139.0, 162.7 (d, *J*_{C,F} = 247.1), 167.5, 167.9. ESI-MS: positive mode *m/z* = 275.1 ([M + H]⁺). HRMS (EI) calcd for C₁₆H₁₉FN₂O 275.1554, found 275.1547. Purity (> 99.9 %). IR (cm⁻¹) 2952, 2851, 2717, 2640, 1732, 1652, 1620, 1558, 1507, 1316, 1217, 972, 826, 787, 645. Anal. (C₁₆H₁₉FN₂O * 1.5C₄H₄O₄) C, H, N.

4.49. (E)-1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(pyridin-3-yl)prop-2-en-1-one fumaric acid salt (**41F**)

The N-*t*-boc protected compound was obtained by using the general procedure E with *trans*-3-(pyridine-3-yl)acrylic acid (149 mg, 1 mmol) for 12 h. A mixture of CH₂Cl₂ and MeOH (20:1) was used for the chromatographic purification. An additional HPLC purification (RP₁₈ silica gel, MeOH-H₂O gradient) was necessary. After removal of the solvents a white solid (238 mg, 67 %) was obtained. The N-*t*-boc protection group of this solid (160 mg, 0.45 mmol) was cleaved using the general procedure F for 4 h and a clear oil **41** (110 mg, 95 %) was obtained after extraction. This oil **41** (92 mg, 0.36 mmol) was transferred to its fumaric acid salt **41F** by using the general procedure I with fumaric acid (41 mg, 0.36 mmol). Compound **41F** (115 mg, 86 %) was obtained as a white solid in 55 % yield over three steps; mp 82–85 °C (dec). ¹H NMR (400 MHz, D₂O) δ 2.03 (br m, 2H),

2.39 (br s, 2H), 3.23 (br d, $J = 13.5$ Hz, 1H), 3.37 (br t, $J = 12.1$ Hz, 2H), 3.46–3.62 (br m, 3H), 4.35 (br d, $J = 13.4$ Hz, 1H), 4.49 (br d, $J = 14.0$ Hz, 1H), 6.58 (s, 1.96H), 7.37 (d, $J = 15.7$ Hz, 1H), 7.59 (d, $J = 15.9$ Hz, 1H), 7.83 (dd, $J = 8.1, 5.5$ Hz, 1H), 8.49 (d, $J = 8.2$ Hz, 1H), 8.65 (d, $J = 5.3$ Hz, 1H), 8.86 (s, 1H). ^{13}C NMR (100 MHz, D_2O) δ 26.0, 26.3, 28.0, 47.2, 48.0, 48.3, 50.2, 123.4, 126.7, 133.8, 135.7, 137.9, 141.0, 144.9, 145.7, 170.5, 173.5. ESI-MS: positive mode $m/z = 258.3$ ($[\text{M} + \text{H}]^+$). HRMS (EI) calcd for $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}$ 258.1601, found 258.1597. Purity (> 99 %). IR (cm^{-1}) 2858, 1699, 1651, 1574, 1418, 1222, 1107, 971, 545. Anal. ($\text{C}_{15}\text{H}_{19}\text{N}_3\text{O} \cdot 0.4\text{C}_4\text{H}_4\text{O}_4 \cdot 7.0\text{H}_2\text{O}$) C, H, N.

4.50. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-2-phenylprop-2-yn-1-one fumaric acid salt (42F)

The N-*t*-boc protected compound was obtained by using the general procedure E with phenylpropionic acid (146 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 (303 mg, 86 %) was obtained. The N-*t*-boc protection group of this solid (250 mg, 0.71 mmol) was cleaved using the general procedure G with anhydrous ZnBr_2 (318 mg, 1.41 mmol) for 48 h and an off-white solid **42** (148 mg, 82 %) was obtained after extraction. This solid **42** (148 mg, 0.58 mmol) was transferred to its fumaric acid salt **42F** by using the general procedure I with fumaric acid (67 mg, 0.58 mmol). Compound **42F** (110 mg, 53 %) was obtained as a white solid in 37 % yield over three steps; mp 151–154 °C (dec). ^1H NMR (400 MHz, DMSO-d_6) δ 1.78 (br d, $J = 13.0$ Hz, 1H), 1.87 (br d, $J = 12.7$ Hz, 1H), 2.07 (br s, 2H), 2.96–3.14 (br m, 4H), 3.24 (br d, $J = 12.8$ Hz, 1H), 3.46 (br d, $J = 13.0$ Hz, 1H), 4.26 (br d, $J = 13.5$ Hz, 1H), 4.37 (br d, $J = 12.0$ Hz, 1H), 6.48 (s, 1.80H), 7.44–7.55 (m, 3H), 7.60–7.65 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.5, 26.0, 28.6, 45.6, 47.3, 47.4, 50.3, 82.5, 89.4, 120.0, 128.9, 130.4, 132.2, 135.0, 154.3, 167.7. ESI-MS: positive mode $m/z = 255.3$ ($[\text{M} + \text{H}]^+$). HRMS (EI) calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$ 255.1492, found 255.1507. Purity (> 99.5 %). IR (cm^{-1}) 3536, 3390, 2218, 1658, 1607, 1425, 980. Anal. ($\text{C}_{16}\text{H}_{18}\text{N}_2\text{O} \cdot 1.0\text{C}_4\text{H}_4\text{O}_4 \cdot 3.0\text{H}_2\text{O}$) C, H, N.

4.51. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(2-methoxyphenyl)prop-2-yn-1-one fumaric acid salt (43F)

The N-*t*-boc protected compound was obtained by using the general procedure E with 3-(2-methoxyphenyl)propionic acid (176 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 (370 mg, 96 %) was obtained. The N-*t*-boc protection group of this solid (370 mg, 0.96 mmol) was cleaved using the general procedure F for 4 h and a white solid **43** (260 mg, 95 %) was obtained after extraction. This solid **43** (260 mg, 0.91 mmol) was transferred to its fumaric acid salt **43F** by using the general procedure I with fumaric acid (106 mg, 0.91 mmol). Compound **43F** (284 mg, 78 %) was obtained as a white solid in 71 % yield over three steps; mp 155–159 °C (dec). ^1H NMR (400 MHz, DMSO-d_6) δ 1.77–1.90 (br m, 2H), 2.20 (br s, 2H), 2.96–3.04 (br m, 1H), 3.07–3.23 (br m, 3H), 3.28 (br d, $J = 13.2$ Hz, 1H), 3.43 (br d, $J = 13.0$ Hz, 1H), 3.78 (s, 3H), 4.21 (br d, $J = 13.8$ Hz, 1H), 4.41 (br d, $J = 13.3$ Hz, 1H), 6.46 (s, 2.00H), 6.97 (t, $J = 7.5$ Hz, 1H), 7.05 (d, $J = 8.4$ Hz, 1H), 7.45 (m, 1H), 7.50 (dd, $J = 7.6, 1.5$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.8, 26.0, 28.2, 46.4,

47.4, 47.5, 51.1, 56.8, 86.7, 89.1, 109.3, 112.5, 121.9, 133.7, 134.9, 136.0, 156.7, 161.8, 169.7. ESI-MS: positive mode $m/z = 285.3$ ($[M + H]^+$). HRMS (EI) calcd for $C_{17}H_{20}N_2O_2$ 285.1598, found 285.1603. Purity (> 99.5 %). IR (cm^{-1}) 2939, 2200, 1712, 1609, 1421, 1254, 968, 762, 728. Anal. ($C_{17}H_{20}N_2O_2 \cdot 1.0C_4H_4O_4 \cdot 1.6H_2O$) C, H, N.

4.52. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(3-methoxyphenyl)prop-2-yn-1-one fumaric acid salt (44F)

The N-*t*-boc protected compound was obtained by using the general procedure E with 3-(3-methoxyphenyl)propionic acid (176 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 clear oil (349 mg, 91 %) was obtained. The N-*t*-boc protection group of this oil (310 mg, 0.81 mmol) was cleaved using the general procedure F for 4 h and a white solid **44** (228 mg, 99 %) was obtained after extraction. This solid **44** (228 mg, 0.80 mmol) was transferred to its fumaric acid salt **44F** by using the general procedure G with fumaric acid (93 mg, 0.80 mmol). Compound **44F** (202 mg, 67 %) was obtained as a white solid in 60 % yield over three steps; mp 123–126 °C (dec). 1H NMR (400 MHz, D_2O) δ 1.97 (br d, $J = 13.5$ Hz, 1H), 2.04 (br d, $J = 13.3$ Hz, 1H), 2.36 (br s, 2H), 3.16 (br d, $J = 14.0$ Hz, 1H), 3.29–3.41 (br m, 2H), 3.45 (br d, $J = 13.0$ Hz, 1H), 3.52–3.59 (br m, 2H), 3.81 (s, 3H), 4.37 (br d, $J = 14.1$ Hz, 1H), 4.55 (br d, $J = 13.5$ Hz, 1H), 6.63 (s, 1.60H), 7.10 (dd, $J = 8.3, 2.5$ Hz, 1H), 7.15 (br s, 1H), 7.23 (d, $J = 7.5$ Hz, 1H), 7.37 (t, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, D_2O) δ 25.6, 26.1, 28.1, 46.5, 47.7, 48.1, 51.5, 56.1, 80.7, 94.2, 118.0, 118.1, 120.9, 126.2, 130.8, 135.3, 157.9, 159.4, 172.1. ESI-MS: positive mode $m/z = 285.4$ ($[M + H]^+$). HRMS (EI) calcd for $C_{17}H_{20}N_2O_2$ 285.1598, found 285.1605. Purity (> 99.5 %). IR (cm^{-1}) 2935, 2863, 2207, 1718, 1703, 1611, 1417, 1231, 1106, 989, 682. Anal. ($C_{17}H_{20}N_2O_2 \cdot 0.84C_4H_4O_4 \cdot 1.4H_2O$) C, H, N.

4.53. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(4-methoxyphenyl)prop-2-yn-1-one fumaric acid salt (45F)

The N-*t*-boc protected compound was obtained by using the general procedure E with 3-(4-methoxyphenyl)propionic acid (176 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 clear oil (377 mg, 98 %) was obtained. The N-*t*-boc protection group of this oil (320 mg, 0.83 mmol) was cleaved using the general procedure F for 4 h and a white solid **45** (236 mg, 99 %) was obtained after extraction. This solid **45** (236 mg, 0.83 mmol) was transferred to its fumaric acid salt **45F** by using the general procedure I with fumaric acid (96 mg, 0.83 mmol). Compound **45F** (272 mg, 83 %) was obtained as a white solid in 81 % yield over three steps; mp 169–174 °C (dec). 1H NMR (400 MHz, $DMSO-d_6$) δ 1.77 (br d, $J = 12.5$ Hz, 1H), 1.86 (br d, $J = 12.8$ Hz, 1H), 2.07 (br s, 2H), 2.98 (br dd, $J = 13.7, 2.8$ Hz, 1H), 3.01–3.12 (br m, 3H), 3.23 (br d, $J = 12.8$ Hz, 1H), 3.41–3.48 (br m, 1H), 3.81 (s, 3H), 4.25 (br d, $J = 13.6$ Hz, 1H), 4.37 (br d, $J = 13.0$ Hz, 1H), 6.47 (s, 1.92H), 7.02 (d, $J = 8.9$ Hz, 2H), 7.57 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, $DMSO-d_6$) δ 25.5, 25.9, 28.5, 45.6, 47.1, 47.3, 50.3, 55.4, 81.7, 90.1, 111.7, 114.6, 134.1, 135.0, 154.6, 160.8, 167.7. ESI-MS: positive mode $m/z = 285.3$ ($[M + H]^+$). HRMS (EI) calcd for $C_{17}H_{20}N_2O_2$ 285.1598, found

285.1594. Purity (> 99 %). IR (cm⁻¹) 2868, 2198, 1717, 1600, 1511, 1254, 1172. Anal. (C₁₇H₂₀N₂O₂*0.95C₄H₄O₄*1.6H₂O) C, H, N.

4.54. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(3,4-dimethoxyphenyl)prop-2-yn-1-one fumaric acid salt (46F)

The N-*t*-boc protected compound was obtained by using the general procedure E with 3-(3,4-dimethoxyphenyl)propionic acid (206 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 (299 mg, 72 %) was obtained. The N-*t*-boc protection group of this solid (260 mg, 0.63 mmol) was cleaved using the general procedure F for 4 h and a white solid **46** (192 mg, 97 %) was obtained after extraction. This solid **46** (192 mg, 0.61 mmol) was transferred to its fumaric acid salt **46F** by using the general procedure I with fumaric acid (71 mg, 0.61 mmol). Compound **46F** (158 mg, 60 %) was obtained as a white solid in 42 % yield over three steps; mp 152–153 °C (dec). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.78 (br d, *J* = 12.5 Hz, 1H), 1.87 (br d, *J* = 12.9 Hz, 1H), 2.08 (br s, 2H), 2.98 (br dd, *J* = 13.7, 3.1 Hz, 1H), 3.01–3.15 (br m, 3H), 3.24 (br d, *J* = 12.4 Hz, 1H), 3.44 (br dd, *J* = 12.9 Hz, 2.1 Hz, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 4.25 (br d, *J* = 13.4 Hz, 1H), 4.37 (br d, *J* = 12.9 Hz, 1H), 6.46 (s, 2.11H), 7.02 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 1.9 Hz, 1H), 7.22 (dd, *J* = 8.3, 1.9 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 25.5, 25.9, 28.5, 45.6, 47.0, 47.2, 50.3, 55.6, 55.7, 81.4, 90.4, 111.6, 111.9, 114.9, 126.2, 135.0, 148.6, 150.9, 154.6, 167.8. ESI-MS: positive mode *m/z* = 315.4 ([M + H]⁺). HRMS (EI) calcd for C₁₈H₂₂N₂O₃ 315.1703, found 315.1702. Purity (> 99 %). IR (cm⁻¹) 3081, 2202, 1695, 1603, 1514, 1252, 1107. Anal. (C₁₈H₂₂N₂O₃*1.5C₄H₄O₄*0.5H₂O) C, H, N.

4.55. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(3-chloro-4-methoxyphenyl)prop-2-yn-1-one fumaric acid salt (47F)

The N-*t*-boc protected compound was obtained by using the general procedure E with 3-(3-chloro-4-methoxyphenyl)propionic acid (211 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 (412 mg, 98 %) was obtained. The N-*t*-boc protection group of this solid (360 mg, 0.86 mmol) was cleaved using the general procedure F for 4 h and an off-white solid **47** (270 mg, 99 %) was obtained after extraction. This solid **47** (270 mg, 0.85 mmol) was transferred to its fumaric acid salt **47F** by using the general procedure I with fumaric acid (98 mg, 0.85 mmol). Compound **47F** (270 mg, 74 %) was obtained as an off-white solid in 72 % yield over three steps; mp 169–174 °C (dec). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.76–1.89 (br m, 2H), 2.19 (br s, 2H), 3.00 (br d, *J* = 13.4 Hz, 1H), 3.06–3.17 (br m, 2H), 3.21 (br d, *J* = 13.4 Hz, 1H), 3.33 (br d, *J* = 13.2 Hz, 1H), 3.43 (br d, *J* = 13.1 Hz, 1H), 3.82 (s, 3H), 4.20 (br d, *J* = 13.4 Hz, 1H), 4.34 (br d, *J* = 13.3 Hz, 1H), 6.46 (s, 1.96H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.54 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 25.6, 26.3, 28.5, 46.8, 47.8, 48.1, 51.6, 57.3, 82.4, 92.3, 113.5, 114.3, 122.8, 134.7, 134.9, 136.3, 157.7, 157.7, 170.9. ESI-MS: positive mode *m/z* = 319.3 ([M + H]⁺). HRMS (EI) calcd for C₁₇H₁₉ClN₂O₂ 319.1208, found 319.1212. Purity (> 99.5 %). IR (cm⁻¹) 3088, 2205, 1720, 1609, 1426, 1296, 1255, 969. Anal. (C₁₇H₁₉ClN₂O₂*0.8C₄H₄O₄*2.0H₂O) C, H, N.

4.56. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(4-methylphenyl)prop-2-yn-1-one fumaric acid salt (48F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 3-(4-methylphenyl)propionic acid (160 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 (350 mg, 95 %) was obtained. The *N*-*t*-boc protection group of this solid (305 mg, 0.83 mmol) was cleaved using the general procedure F for 4 h and a white solid **48** (217 mg, 98 %) was obtained after extraction. This solid **48** (217 mg, 0.81 mmol) was transferred to its fumaric acid salt **48F** by using the general procedure I with fumaric acid (94 mg, 0.81 mmol). Compound **48F** (244 mg, 78 %) was obtained as a white solid in 75 % yield over three steps; mp 202–207 °C (dec). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.77 (br d, *J* = 12.7 Hz, 1H), 1.87 (br d, *J* = 12.7 Hz, 1H), 2.07 (br s, 2H), 2.35 (s, 3H), 2.98 (br dd, *J* = 13.6 Hz, 1H), 3.01–3.13 (br m, 3H), 3.24 (br d, *J* = 12.8 Hz, 1H), 3.45 (br dd, *J* = 13.1, 1.9 Hz, 1H), 4.25 (br d, *J* = 13.6 Hz, 1H), 4.36 (br d, *J* = 12.9 Hz, 1H), 6.47 (s, 2.00H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 21.2, 25.5, 25.9, 28.6, 45.6, 47.0, 47.2, 50.3, 82.2, 89.8, 116.9, 129.6, 132.2, 135.0, 140.5, 154.5, 167.8. ESI-MS: positive mode *m/z* = 269.4 ([M + H]⁺). HRMS (EI) calcd for C₁₇H₂₀N₂O 269.1648, found 269.1650. Purity (> 99.5 %). IR (cm⁻¹) 3408, 2963, 2867, 2202, 1720, 1605, 1431, 1270, 977. Anal. (C₁₇H₂₀N₂O*1.0C₄H₄O₄*1.7H₂O) C, H, N.

4.57. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(3-fluorophenyl)prop-2-yn-1-one fumaric acid salt (49F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 3-(3-fluorophenyl)propionic acid (164 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 (327 mg, 88 %) was obtained. The *N*-*t*-boc protection group of this solid (290 mg, 0.78 mmol) was cleaved using the general procedure F for 4 h and a white solid **49** (210 mg, 99 %) was obtained after extraction. This solid **49** (210 mg, 0.77 mmol) was transferred to its fumaric acid salt **49F** by using the general procedure I with fumaric acid (90 mg, 0.77 mmol). Compound **49F** (199 mg, 68 %) was obtained as a white solid in 60 % yield over three steps; mp 154–158 °C (dec). ¹H NMR (400 MHz, D₂O+DMSO-*d*₆) δ 1.84 (br m, 2H), 2.20 (br s, 2H), 3.03 (br d, *J* = 13.9 Hz, 1H), 3.09–3.21 (br m, 2H), 3.25 (br d, *J* = 13.1 Hz, 1H), 3.36 (br d, *J* = 14.0 Hz, 1H), 3.45 (br d, *J* = 13.2 Hz, 1H), 4.21 (br d, *J* = 13.9 Hz, 1H), 4.38 (br d, *J* = 13.4 Hz, 1H), 6.47 (s, 1.80H), 7.14–7.25 (m, 1H), 7.25–7.41 (m, 3H). ¹³C NMR (100 MHz, D₂O+ DMSO-*d*₆) δ 26.2, 26.7, 28.8, 47.2, 48.3, 48.6, 52.1, 82.6, 92.9 (d, *J*_{C,F} = 3.4 Hz), 119.8 (d, *J*_{C,F} = 20.8 Hz), 120.5 (d, *J*_{C,F} = 23.6 Hz), 122.5 (d, *J*_{C,F} = 9.4 Hz), 130.3 (d, *J*_{C,F} = 2.7 Hz), 132.4 (d, *J*_{C,F} = 8.7 Hz), 136.4, 158.0, 163.4 (d, *J*_{C,F} = 246.0 Hz), 172.0. ESI-MS: positive mode *m/z* = 273.3 ([M + H]⁺). HRMS (EI) calcd for C₁₆H₁₇N₂O 273.1398, found 273.1401. Purity (> 98 %). IR (cm⁻¹) 3523, 3082, 2867, 2213, 1704, 1610, 1421, 1229, 969, 788. Anal. (C₁₆H₁₇N₂O *0.9C₄H₄O₄*1.9H₂O) C, H, N.

4.58. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-one fumaric acid salt (50F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 3-(benzo[d][1,3]dioxol-5-yl)propionic acid (190 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 yellow oil (347 mg, 87 %) was obtained. The *N*-*t*-boc protection group of this oil (290 mg, 0.73 mmol) was cleaved using the general procedure F for 4 h and an off-white solid **50** (214 mg, 99 %) was obtained after extraction. This solid **50** (214 mg, 0.72 mmol) was transferred to its fumaric acid salt **50F** by using the general procedure I with fumaric acid (83 mg, 0.72 mmol). Compound **50F** (254 mg, 77 %) was obtained as an off-white solid in 66 % yield over three steps; mp 182–186 °C (dec). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.77 (br d, *J* = 13.0 Hz, 1H), 1.88 (br d, *J* = 13.1 Hz, 1H), 2.10 (br s, 2H), 2.98 (br dd, *J* = 13.7, 2.8 Hz, 1H), 3.04–3.16 (br m, 3H), 3.27 (br d, *J* = 12.8 Hz, 1H), 3.43 (br d, *J* = 13.0 Hz, 1H), 4.24 (br d, *J* = 13.4 Hz, 1H), 4.36 (br d, *J* = 13.0 Hz, 1H), 6.11 (s, 2H), 6.51 (s, 2.80H), 7.00 (d, *J* = 7.8 Hz, 1H), 7.18 (dd, *J* = 9.7, 1.6 Hz, 1H), 7.19 (s, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 25.2, 25.6, 28.1, 45.5, 46.6, 46.8, 50.2, 81.2, 89.9, 101.9, 109.0, 111.7, 112.9, 127.9, 134.8, 147.5, 149.3, 154.7, 167.3. ESI-MS: positive mode *m/z* = 299.3 ([M + H]⁺). HRMS (EI) calcd for C₁₇H₁₈N₂O₃ 299.1390, found 299.1393. Purity (> 99 %). IR (cm⁻¹) 3495, 3382, 2196, 1646, 1602, 1425, 1251, 1235, 1038, 977. Anal. (C₁₇H₁₈N₂O₃*1.2C₄H₄O₄*2.5H₂O) C, H, N.

4.59. 1-((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-(naphthalene-1-yl)prop-2-yn-1-one fumaric acid salt (51F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 3-(naphthalene-1-yl)propionic acid (196 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 (108 mg, 27 %) was obtained. The *N*-*t*-boc protection group of this oil (108 mg, 0.27 mmol) was cleaved using the general procedure F for 4 h and a white solid **51** (74 mg, 91 %) was obtained after extraction. This solid **51** (74 mg, 0.24 mmol) was transferred to its fumaric acid salt **51F** by using the general procedure I with fumaric acid (28 mg, 0.24 mmol). Compound **51F** (60 mg, 58 %) was obtained as a white solid in 14 % yield over three steps; mp 171–173 °C (dec). ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.81 (br d, *J* = 12.5 Hz, 1H), 1.89 (br d, *J* = 12.7 Hz, 1H), 2.11 (br s, 1H), 2.14 (br s, 1H), 3.02–3.18 (br m, 4H), 3.28 (br d, *J* = 12.8 Hz, 1H), 3.58 (br d, *J* = 12.7 Hz, 1H), 4.32 (br d, *J* = 13.5 Hz, 1H), 4.48 (br d, *J* = 12.6 Hz, 1H), 6.48 (s, 2.10H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 7.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 8.25 (d, *J* = 8.3 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 25.5, 25.9, 28.5, 45.7, 47.0, 47.1, 50.5, 87.4, 87.5, 117.4, 125.1, 125.6, 127.1, 127.9, 128.8, 130.8, 132.1, 132.6, 132.8, 135.1, 154.5, 167.9. ESI-MS: positive mode *m/z* = 305.4 ([M + H]⁺). HRMS (EI) calcd for C₂₀H₂₀N₂O 305.1648, found 305.1644. Purity (> 99 %). IR (cm⁻¹) 3498, 2840, 2199, 1704, 1635, 1214, 970, 768, 644. Anal. (C₂₀H₂₀N₂O *0.75C₄H₄O₄*1.6H₂O) C, H, N.

4.60. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(4-(pyridin-3-yl)phenyl)methanone fumaric acid salt (52F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 4-(3-pyridyl)benzoic acid (199 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 (403 mg, 99 %) was obtained. The *N*-*t*-boc protection group of this solid (380 mg, 0.93 mmol) was cleaved using the general procedure F for 2 h and a white solid **52** (257 mg, 90 %) was obtained after extraction. This solid **52** (257 mg, 0.84 mmol) was transferred to its fumaric acid salt **52F** by using the general procedure I with fumaric acid (97 mg, 0.84 mmol). Compound **52F** (202 mg, 56 %) was obtained as a white solid in 50 % yield over three steps; mp 149–151 °C (dec). ¹H NMR (400 MHz, D₂O) δ 2.02 (br m, 2H), 2.24 (br s, 1H), 2.45 (br s, 1H), 3.33–3.42 (br m, 3H), 3.46–3.58 (br m, 3H), 3.91 (br d, *J* = 12.3 Hz, 1H), 4.55 (br d, *J* = 12.8 Hz, 1H), 6.56 (s, 2.1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.98 (dd, *J* = 8.1, 5.6 Hz, 1H), 8.65 (d, *J* = 8.2 Hz, 1H), 8.72 (d, *J* = 5.3 Hz, 1H), 9.00 (s, 1H). ¹³C NMR (100 MHz, D₂O) δ 25.8, 26.2, 28.0, 47.2, 47.4, 48.4, 52.5, 127.3, 128.3, 128.6, 135.7, 136.1, 137.2, 138.9, 142.4, 142.7, 143.0, 173.6, 175.0. ESI-MS: positive mode *m/z* = 308.4 ([M + H]⁺). HRMS (EI) calcd for C₁₉H₂₁N₃O 308.1757, found 308.1743. Purity (> 99 %). IR (cm⁻¹) 2855, 2579, 1718, 1604, 1435, 1261, 1099, 970, 633. Anal. (C₁₉H₂₁N₃O * 1.0C₄H₄O₄ * 1.5H₂O) C, H, N.

4.61. (1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl(4-(pyridin-4-yl)phenyl)methanone fumaric acid salt (53F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 4-(4-pyridyl)benzoic acid (199 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 (246 mg, 60 %) was obtained. The *N*-*t*-boc protection group of this solid (180 mg, 0.44 mmol) was cleaved using the general procedure F for 4 h and a white solid **53** (132 mg, 97 %) was obtained after extraction. This solid **53** (132 mg, 0.43 mmol) was transferred to its fumaric acid salt **53F** by using the general procedure I with fumaric acid (50 mg, 0.43 mmol). Compound **53F** (120 mg, 58 %) was obtained as a white solid in 34 % yield over three steps; mp 175–180 °C (dec). ¹H NMR (400 MHz, D₂O) δ 2.02 (br m, 2H), 2.25 (br s, 1H), 2.46 (br s, 1H), 3.34–3.60 (br m, 6H), 3.89 (br d, *J* = 13.2 Hz, 1H), 4.56 (br d, *J* = 14.0 Hz, 1H), 6.58 (s, 3.00H), 7.70 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 2H), 8.32 (d, *J* = 6.7 Hz, 2H), 8.81 (d, *J* = 6.8 Hz, 2H). ¹³C NMR (100 MHz, D₂O) δ 25.8, 26.2, 28.0, 47.1, 47.7, 48.4, 52.5, 125.3, 128.6, 129.1, 135.5, 137.1, 138.0, 142.4, 157.2, 173.0, 174.7. ESI-MS: positive mode *m/z* = 308.4 ([M + H]⁺). HRMS (EI) calcd for C₁₉H₂₁N₃O 308.1757, found 308.1749. Purity (> 99.5 %). IR (cm⁻¹) 2906, 2694, 2601, 1698, 1639, 1255, 1171, 969, 834, 636. Anal. (C₁₉H₂₁N₃O * 1.4C₄H₄O₄ * 0.75H₂O) C, H, N.

4.62. (4-(1H-imidazol-1-yl)phenyl)((1R,5S)-3,7-diazabicyclo[3.3.1]nonan-3-yl)methanone fumaric acid salt (54F)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 4-(1H-imidazol-1-yl)benzoic acid (188 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 (366 mg, 92 %) was obtained. The *N*-*t*-boc protection group of this solid (317 mg, 0.80 mmol) was cleaved using the general procedure F for 2 h and a white solid **54** (209 mg, 88 %) was obtained after extraction. This solid **54** (209 mg, 0.71 mmol) was transferred to its fumaric acid salt **54F** by using the general procedure I with fumaric acid (82 mg, 0.71 mmol). Compound **54F** (149 mg, 36 %) was obtained as a white solid in 29 % yield over three steps; mp 178–181 °C (dec). ¹H NMR (400 MHz, D₂O) δ 2.01 (br m, 2H), 2.25 (br s, 1H), 2.45 (br s, 1H), 3.34–3.64 (br m, 6H), 3.87 (br d, *J* = 12.8 Hz, 1H), 4.54 (br d, *J* = 13.8 Hz, 1H), 6.52 (s, 2.0H), 7.61 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.90 (s, 1H), 9.09 (s, 1H). ¹³C NMR (100 MHz, D₂O) δ 25.8, 26.2, 27.9, 47.2, 47.4, 48.4, 52.5, 121.6, 122.6, 123.3, 129.5, 135.0, 135.9, 136.4, 137.1, 174.2, 174.5. ESI-MS: positive mode *m/z* = 297.4 ([M + H]⁺). HRMS (EI) calcd for C₁₇H₂₀N₄O 297.1710, found 297.1700. Purity (> 99 %). IR (cm⁻¹) 3104, 2910, 2699, 1704, 1635, 1523, 1257, 969, 851, 636. Anal. (C₁₇H₂₀N₄O*0.9C₄H₄O₄*1.0H₂O) C, H, N.

4.63. (1*R*,5*S*)-3,7-diazabicyclo[3.3.1]nonan-3-yl(2-(pyridine-4-yl)thiazol-4-yl)methanone fumaric acid salt (**55F**)

The *N*-*t*-boc protected compound was obtained by using the general procedure E with 2-(4-pyridyl)thiazole-4-carboxylic acid (206 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 yellow oil (401 mg, 97 %) was obtained. The *N*-*t*-boc protection group of this oil (401 mg, 0.97 mmol) was cleaved using the general procedure F for 2 h and a yellow oil **55** (252 mg, 83 %) was obtained after extraction. This oil **55** (252 mg, 0.80 mmol) was transferred to its fumaric acid salt **55F** by using the general procedure I with fumaric acid (93 mg, 0.80 mmol). Compound **55F** (119 mg, 35 %) was obtained as an off-white solid in 28 % yield over three steps; mp 124–128 °C (dec). ¹H NMR (400 MHz, D₂O) δ 2.06 (br m, 2H), 2.27 (br s, 1H), 2.45 (br s, 1H), 3.34–3.72 (br m, 6H), 4.33 (br s, 1H), 4.51 (br s, 1H), 6.60 (s, 1.58H), 8.19 (d, *J* = 5.6 Hz, 2H), 8.31 (s, 1H), 8.78 (d, *J* = 5.2 Hz, 2H). ¹³C NMR (100 MHz, D₂O) δ 26.3, 28.6, 47.8, 47.9, 48.0, 52.0, 122.9, 128.9, 135.5, 144.3, 147.1, 150.8, 164.8, 167.9, 173.1. ESI-MS: positive mode *m/z* = 315.4 ([M + H]⁺). HRMS (EI) calcd for C₁₆H₁₈N₄OS 315.1274, found 315.1261. Purity (> 99.5 %). IR (cm⁻¹) 3354, 3201, 2860, 2600, 1704, 1630, 1458, 1406, 1247, 1015, 972, 641. Anal. (C₁₆H₁₈N₄OS*1.0C₄H₄O₄*1.0H₂O) C, H, N.

4.64. 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.

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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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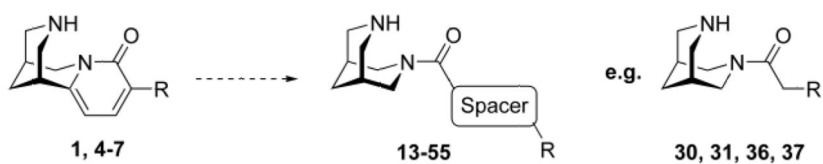


Figure 1. Structures of (-)-cytisine **1**, cytisine derivatives **4–7** and the development of the 3,7-diazabicyclo[3.3.1]nonane based compounds **13–55** incorporating a spacer motif, e.g. compounds **30, 31, 36, and 37**.

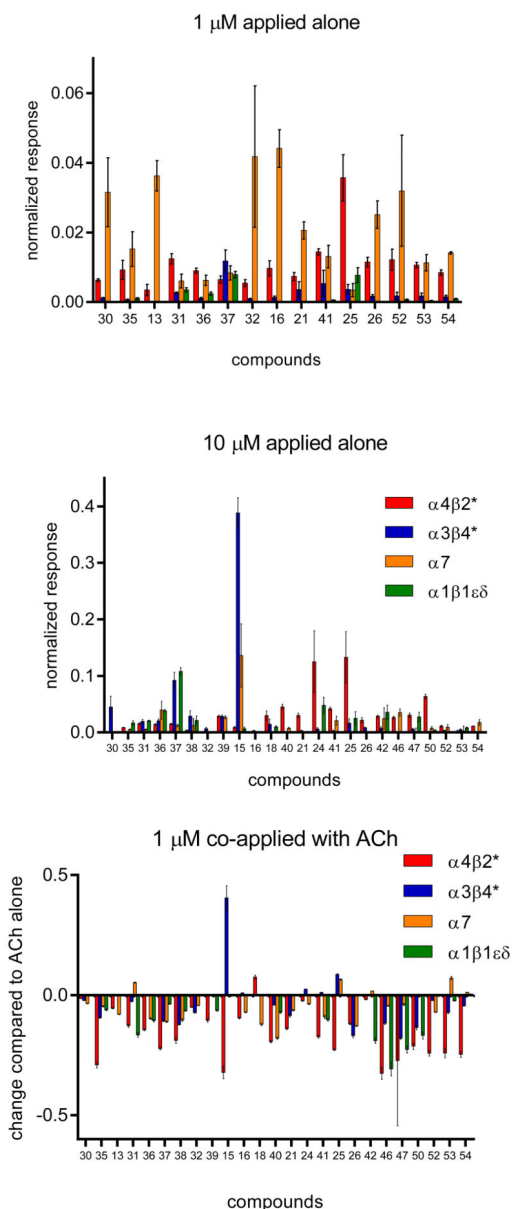
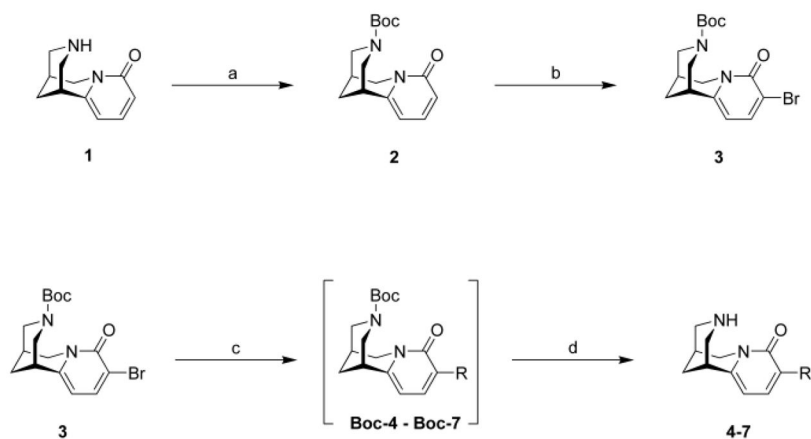
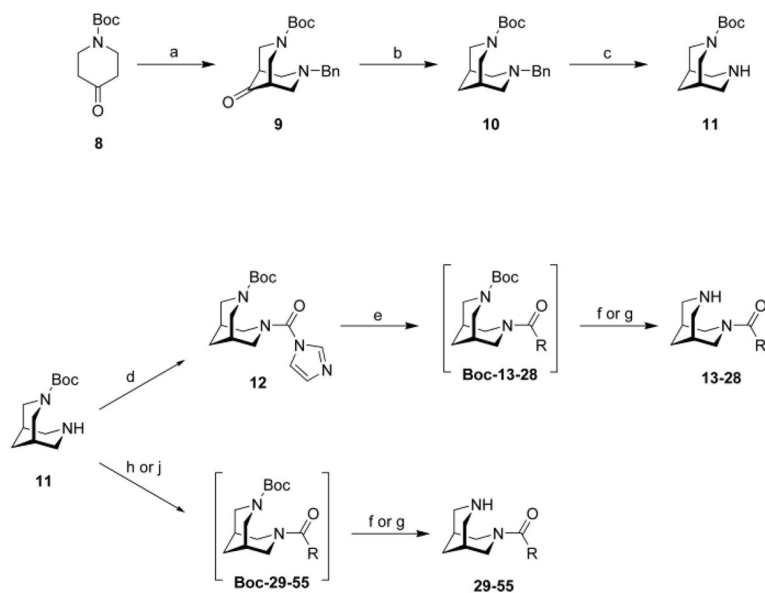


Figure 2. Responses of oocytes expressing diverse nAChR subtypes to 1 or 10 μM of selected compounds (numbering are following the sequence in the tables) relative to ACh control responses. Responses of oocytes expressing diverse nAChRs to compounds co-applied at 1 μM with ACh compared to responses to ACh alone. Bars above zero indicate additive effects; bars below zero indicate reduced responses.

**Scheme 1.**

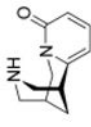
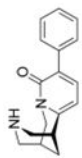
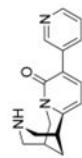
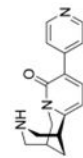
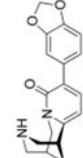
Synthesis of cytosine derivatives. Reagents and conditions: (a) (Boc)₂O, Na₂CO₃, CH₂Cl₂, H₂O, reflux, 2 h; (b) NBS, CH₂Cl₂, reflux, 2 h; (c) R-B(OH)₂, Pd(PPh₃)₄, base, DME or DMF, H₂O [Ar], MW (30 W), 80 °C, 30 to 60 min; (d) H₂O, MW (150 W), 150 °C, 30 min.

**Scheme 2.**

Synthesis of bispidine derivatives. 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, $125\text{ }^\circ\text{C}$, 2 h, then Dean Stark trap, $140\text{ }^\circ\text{C}$, 8 h; (c) Pd/C (5%), H_2 (2–4 bar), MeOH , rt, 4–24 h; (d) CDI , THF , reflux, 2 h; (e) (i) MeI , MeCN , THF , rt, 24 h; (ii) R-COOH , Et_3N , MeCN , rt, 12–120 h; (f) $\text{HCl}/1,4\text{-dioxane}$ (4M), rt, 4 h; (g) anhydr. ZnBr_2 , CH_2Cl_2 , rt, 12–120 h; (h) R-COCl , Et_3N , toluene, rt, 2h; (j) R-COOH , DCC , DMAP , CH_2Cl_2 , $0\text{ }^\circ\text{C}$ to rt, 12 h.

Affinities (K_i values \pm SEM) and calculated physicochemical parameters (logP, TPSA, logBB) of the (-)-cytisine **1** and cytisine derivatives **4–7**

Table 1

Structure	$\alpha_4\beta_2^*$ K_i [nM]	$\alpha_3\beta_4^*$ K_i [nM]	α_7^* K_i [nM]	$(\alpha_1)\beta_1\gamma$ K_i [nM]	Mol. Weight	ClogP ^c	TPSA	logBB ^b
	0.122	18	261	1,300	190.24	0.17	32.34	-0.25
	128	> 10,000	> 10,000	> 10,000	266.34	2.27	32.34	-0.01
	0.91	119	1,100	> 5,000	267.14	1.03	45.23	-0.23
	3.9	436	> 10,000	> 10,000	267.14	0.78	45.23	-0.28
	110	> 10,000	> 10,000	> 10,000	310.35	2.31	50.80	-0.03



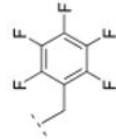
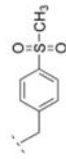
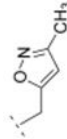
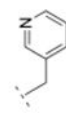
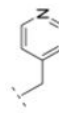
^a logP values have been calculated using the ACD/Labs Algorithm (ACD);

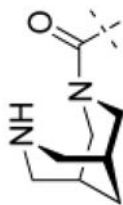
^b logBB was calculated from logP derived from using the ACD/Labs Algorithm (ACD);

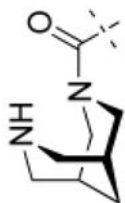
^c data from ref. 16–20.

Affinities (K_i values \pm SEM) and calculated physicochemical parameters (logP, TPSA, logBB) of the bispidine carboxamide derivatives **13–55**

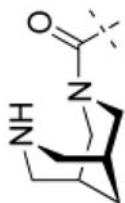
Table 2

Compd.	R =	$\alpha4\beta2^*$ K_i [nM]	$\alpha3\beta4^*$ K_i [nM]	$\alpha7^*$ K_i [nM]	($\alpha1$), ($\beta1$), (γ) K_i [nM]	Mol. Weight	ClogP a	TPSA	logBB b
29		453.6 \pm 14.8	> 5,000	> 10,000	> 10,000	230.31	0.56	32.34	-0.09
30		57.6 \pm 15.4	n. d.	> 10,000	n. d.	244.33	1.57	32.34	0.18
34		> 5,000	n. d.	n. d.	n. d.	334.28	1.75	32.34	0.25
35		22.9 \pm 0.9	> 5,000	> 5,000	> 5,000	322.42	-0.15	74.86	-0.10
13		46.9 \pm 7.2	> 1,000	> 1,000	n. d.	249.31	-0.11	58.37	-0.03
31		11.2 \pm 1.5	> 1,000	> 1,000	> 5,000	245.32	0.08	45.23	-0.01
36		14.4 \pm 2.0	> 1,000	> 1,000	> 5,000	245.32	0.08	45.23	-0.01

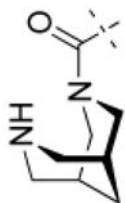




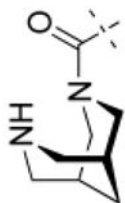
Compd.	R =	α 4 β 2* Ki [nM]	α 3 β 4* Ki [nM]	α 7* Ki [nM]	(α 1) β 1 γ δ Ki [nM]	Mol. Weight	Clog P_{α}	TPSA	logBB b
37		13.2 \pm 1.2	> 1,000	> 1,000	> 5,000	288.34	1.43	50.80	-0.13
38		10.2 \pm 2.1	> 1,000	> 1,000	> 5,000	294.39	2.80	32.34	-0.19
32		52.5 \pm 0.7	395.8	> 10,000	n. d.	258.36	2.08	32.34	0.04
39		39 \pm 3.4	> 5,000	> 5,000	> 5,000	259.35	0.59	45.23	-0.10
14		232.6	> 5,000	> 10,000	n. d.	348.44	1.52	60.03	-0.08
33		548.0 \pm 66.0	> 5,000	> 5,000	> 5,000	294.78	1.75	41.57	-0.23
15		1.2 \pm 0.4	81.1	> 10,000	n. d.	270.37	1.73	32.34	-0.13



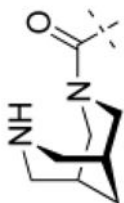
Compd.	R =	$\alpha4\beta2^*$ Ki [nM]	$\alpha3\beta4^*$ Ki [nM]	$\alpha7^*$ Ki [nM]	($\alpha1$), $\beta1$, $\gamma\delta$ Ki [nM]	Mol. Weight	Clog P_{α}	TPSA	logBB b
16		55.1 ± 12.5	> 5,000	> 5,000	> 10,000	256.34	1.87	32.34	-0.24
17		171.8 ± 39.7	n. d.	n. d.	> 10,000	286.37	1.87	41.57	-0.21
18		23.7 ± 3.2	n. d.	> 10,000	n. d.	290.79	2.47	32.34	0.06
19		24.6 ± 4.2	n. d.	> 10,000	n. d.	335.24	2.70	32.34	0.01
20		38.9 ± 4.4	> 1,000	n. d.	> 10,000	301.34	1.77	81.17	-0.51
40		20.7 ± 2.4	> 5,000	> 5,000	> 10,000	274.33	1.87	32.34	-0.03



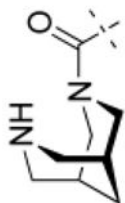
Compd.	R =	α 4 β 2* Ki [nM]	α 3 β 4* Ki [nM]	α 7* Ki [nM]	(α 1) β 1 γ δ Ki [nM]	Mol. Weight	ClogP ^a	TPSA	logBB ^b
21		39.6 ± 5.4	n. d.	n. d.	n. d.	286.37	1.81	41.57	-0.23
22		287.5 ± 25.7	> 1,000	> 1,000	> 5,000	246.30	1.49	45.48	-0.07
23		96.9 ± 20.5	2,000	> 10,000	n. d.	262.37	1.68	60.58	-0.32
24		57.1 ± 12.3	n. d.	> 10,000	n. d.	262.37	1.66	60.58	0.33
41		32.59	> 1,000	> 1,000	> 5,000	257.33	0.62	45.23	-0.23
25		1.03	> 1,000	> 10,000	> 5,000	257.33	0.37	45.23	-0.27



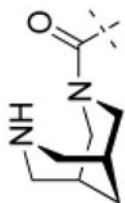
Compd.	R =	$\alpha 4\beta 2^*$ Ki [nM]	$\alpha 3\beta 4^*$ Ki [nM]	$\alpha 7^*$ Ki [nM]	($\alpha 1$), ($\beta 1$), (γ) Ki [nM]	Mol. Weight	Clog P_{α}	TPSA	logBB b
26		36.9 ± 8.0	> 1,000	> 1,000	> 5,000	300.35	1.99	50.80	-0.15
27		296.6 ± 50.7	> 5,000	> 1,000	> 5,000	306.40	3.10	32.34	-0.11
42		10.9 ± 3.4	> 1,000	> 5,000	> 1,000	254.33	2.41	32.34	-0.27
43		241.9	> 1,000	> 1,000	> 5,000	284.35	2.33	41.57	-0.23
44		6.3 ± 1.1	> 1,000	> 1,000	> 5,000	284.35	2.33	41.57	-0.23
45		7.8 ± 2.0	> 1,000	> 1,000	> 5,000	284.35	2.33	41.57	-0.23



Compd.	R =	α 4 β 2* Ki [nM]	α 3 β 4* Ki [nM]	α 7* Ki [nM]	(α 1) β 1 γ δ Ki [nM]	Mol. Weight	ClogP α	TPSA	logBB β
46		2.1 \pm 0.8	> 1,000	> 1,000	> 5,000	314.38	2.15	50.80	-0.24
47		0.991 \pm 0.02	> 1,000	> 1,000	> 5,000	318.80	2.87	41.57	-0.19
48		10.9 \pm 2.1	> 1,000	> 1,000	> 5,000	268.35	2.87	32.34	-0.03
49		7.1 \pm 2.4	> 1,000	> 1,000	> 5,000	272.32	2.46	32.34	-0.17
50		3.1 \pm 1.0	> 1,000	> 1,000	> 5,000	298.34	2.27	50.80	-0.14



Compd.	R =	α 4 β 2* Ki [nM]	α 3 β 4* Ki [nM]	α 7* Ki [nM]	(α 1) β 1 γ δ Ki [nM]	Mol. Weight	Clog P_{α}	TPSA	logBB b
51		46.0 \pm 7.5	> 1,000	> 1,000	> 5,000	304.39	3.64	32.34	-0.09
28		39.9 \pm 7.1	1089.5 \pm 290.5	*c	*c	306.40	2.21	32.34	-0.65
52		25.0 \pm 5.5	> 1,000	> 1,000	> 5,000	307.39	0.90	45.23	-0.85
53		7.1 \pm 1.3	> 1,000	> 1,000	> 5,000	307.39	0.83	45.23	-0.86
54		5.6 \pm 0.9	> 1,000	> 1,000	> 5,000	296.37	0.33	49.64	-0.29



Compd.	R =	$\alpha4\beta2^*$ Ki [nM]	$\alpha3\beta4^*$ Ki [nM]	$\alpha7^*$ Ki [nM]	($\alpha1$)/ $\beta1$ / $\gamma\delta$ Ki [nM]	Mol. Weight	ClogP ^a	TPSA	logBB ^b
55		> 1,000	n.d.	n.d.	n.d.	314.41	1.58	73.47	-0.34

Values are generated from 2–10 independent experiments; n. d. = not determined;

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

^b logBB was calculated from logP derived from using the ACD/Labs Algorithm (ACD);

^c radioligand binding was increased.