Title: Design, synthesis and biological evaluation of N-methyl-N-[(1,2,3-triazol-4-yl)alkyl]propargylamines as novel monoamine oxidase B inhibitors

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Keywords: Click-chemistry; monoamine oxidase B; Alzheimer's disease; irreversible inhibition

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Abstract: Different azides and alkynes have been coupled via Cu-catalyzed 1,3-dipolar Huisgen cycloaddition to afford a novel family of N1- and C5-substituted 1,2,3-triazole derivatives that feature the propargylamine group typical of irreversible MAO-B inhibitors at the C4-side chain of the triazole ring. All the synthesized compounds were evaluated against human MAO-A and MAO-B. Structure–activity relationships and molecular modelling were utilized to gain insight into the structural and chemical features that enhance the binding affinity and selectivity between the two enzyme isoforms. Several lead compounds, in terms of potency (submicromolar to low micromolar range), MAO-B selective recognition, and brain permeability, were identified. One of these leads (MAO-B IC50 of 3.54 μM, selectivity MAO-B/MAO-A index of 0.04) was further subjected to reversibility and time-dependence inhibition studies, which disclosed a slow and irreversible inhibition of human MAO-B. Overall, the results support the suitability of the 4-triazolylalkyl propargylamine scaffold for exploring the design of multipotent anti-Alzheimer compounds endowed with irreversible MAO-B inhibitory activity.
Design, synthesis and biological evaluation of \(N\)-methyl-\(N\)-[(1,2,3-triazol-4-yl)alkyl]propargylamines as novel monoamine oxidase B inhibitors


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Abstract

Different azides and alkynes have been coupled via Cu-catalyzed 1,3-dipolar Huisgen cycloaddition to afford a novel family of $N_1$- and $C_5$-substituted 1,2,3-triazole derivatives that feature the propargylamine group typical of irreversible MAO-B inhibitors at the $C_4$-side chain of the triazole ring. All the synthesized compounds were evaluated against human MAO-A and MAO-B. Structure–activity relationships and molecular modelling were utilized to gain insight into the structural and chemical features that enhance the binding affinity and selectivity between the two enzyme isoforms. Several lead compounds, in terms of potency (submicromolar to low micromolar range), MAO-B selective recognition, and brain permeability, were identified. One of these leads (MAO-B IC$_{50}$ of 3.54 μM, selectivity MAO-B/MAO-A index of 0.036) was further subjected to reversibility and time-dependence inhibition studies, which disclosed a slow and irreversible inhibition of human MAO-B. Overall, the results support the suitability of the 4-triazolylalkyl propargylamine scaffold for exploring the design of multipotent anti-Alzheimer compounds endowed with irreversible MAO-B inhibitory activity.

Keywords

Click-chemistry; monoamine oxidase B; Alzheimer’s disease; irreversible inhibition
1. Introduction

Alzheimer’s disease (AD) is one of the most relevant age-related neurodegenerative disorders currently representing the fourth leading cause of death and afflicting over 46.8 million people worldwide.\textsuperscript{1,2} Its clinical manifestation is mainly reflected in a progressive loss of memory and cognitive functions, often in association with behavioral disturbances and depression.\textsuperscript{3} Its complex and multifaceted etiopathology, which involves massive loss of cholinergic neurons,\textsuperscript{4} oxidative stress,\textsuperscript{5-7} metal dyshomeostasis,\textsuperscript{8} excitotoxicity,\textsuperscript{9} neurofibrillary tangles and β-amyloid aggregate deposition,\textsuperscript{10,11} has precluded so far the discovery of effective disease-modifying drugs. Currently approved drugs, namely, three acetylcholinesterase (AChE) inhibitors (rivastigmine, galantamine, and donepezil),\textsuperscript{12-14} and an N-methyl-D-aspartate receptor antagonist (memantine),\textsuperscript{15} primarily exert palliative effects. On the other hand, the failure in clinical trials of a number of drug candidates designed against targets mainly involved in β-amyloid biology has shifted drug discovery efforts toward the compounds hitting less explored biological targets alone or in combination with other key targets, i.e. the so-called multi-target-directed ligands (MTDLs).\textsuperscript{16-18}

In this context, monoamine oxidase (MAO, E.C.1.4.3.4) has emerged as a promising target because of the neuroprotective properties exerted by their inhibitors.\textsuperscript{2,19-21} MAO is a flavin adenine dinucleotide (FAD)-containing enzyme that catalyzes the degradation of biogenic and xenobiotic amines. Two isoforms, namely MAO-A and MAO-B, have been characterized by their amino acid sequence, tissue distribution, substrate specificity and inhibitor sensitivity.\textsuperscript{22-24} MAO-A, preferentially degrading serotonin, adrenaline and noradrenaline, is irreversibly inhibited by clorgyline, whereas MAO-B, specifically responsible for the oxidative deamination of phenylethylamine and benzylamine, is irreversibly inhibited by (R)-(−)-deprenyl (selegiline) (Figure 1). These trends reflect structural differences in the binding sites as revealed by high-resolution X-ray structures.\textsuperscript{25-29} In particular, a key structural feature in shaping the substrate cavity is the replacement of the pair Phe208/Ile335 in MAO-A by Ile199/Tyr326 in MAO-B, leading to the distinction between “substrate” and “entrance” sites in MAO-B. The replacement of Ile180/Asn181 and Val210 in MAO-A by Leu17/Cys172 and Thr201 in MAO-B are additional differences in the binding sites, which may modulate the selective inhibition by certain MAO inhibitors.\textsuperscript{30}
The neuroprotection exerted by MAO inhibitors may stem not only from the increased amine neurotransmission, but also from preventing the formation of neurotoxic species, which may lead to neuronal damage,\textsuperscript{31,32} and from the anti-apoptotic properties of the propargylamine group present in some MAO inhibitors.\textsuperscript{33,34} Interestingly, the levels of MAO-B increase with age and its activity is elevated in AD patients, which results in increased brain levels of neurotoxic free radicals.\textsuperscript{20} In this context, the development of MAO-B-inhibitor-based MTDLs emerges as a promising strategy for the design of neuroprotective agents with potential disease-modifying activity towards AD and other neurodegenerative disorders, such as Parkinson disease.\textsuperscript{35,36}

Most efforts have been addressed toward the design of MTDLs targeting AChE and/or butyrylcholinesterase (BuChE) and MAO. A successful example is ladostigil (Figure 1), a dual inhibitor of MAO-B and AChE that combines the carbamate moiety of the AChE inhibitor rivastigmine with the indolamine moiety of the selective MAO-B inhibitor rasagiline, and shows neuroprotective and anti-apoptotic activities.\textsuperscript{37,38} A novel series of MAO/ChE inhibitors that combine the N-benzylpiperidine moiety of the AChE inhibitor donepezil with the indolyl propargylamine of the potent MAO-B inhibitor PF9601N has been reported.\textsuperscript{39} Within this series, the most promising MDTL compound (ASS234, 6 in Figure 1) also showed anti-aggregating activity on β-amyloid, antioxidant and antiapoptotic behaviour, and crossed easily the blood-brain barrier (BBB).\textsuperscript{40} Other strategies have relied on the hybridization of coumarins with either N-benzyl-N-
alkyloxy groups\textsuperscript{41} or tacrine,\textsuperscript{42} leading to multipotent inhibitors of both MAO and ChEs, or alternatively have pursued the development of MTDLs targeting both MAO inhibition and additional activities, such as metal chelation.\textsuperscript{43,44} Also, natural products endowed with MAO and ChEs inhibitory activities have been recently reported.\textsuperscript{45} Although the development of MAO-inhibitor-based MTDLs is very attractive, it is challenged by the need to keep a good balance among potencies against multiple targets and optimal ADME-T properties.\textsuperscript{46-50} Furthermore, the success of this strategy depends on the suitability of an efficient synthetic approach, which should afford the fusion or linkage of chemical scaffolds while minimizing drastic alterations in the activity against the multiple targets. In this context, the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) enables the synthesis of a virtually unlimited source of ligands containing the 1,4-disubstituted 1,2,3-triazole core.\textsuperscript{51-54} The CuAAC reaction between libraries of azides and alkynes featuring different pharmacophoric moieties has been used for the synthesis of triazole-linked hybrid compounds as MTDLs.\textsuperscript{55-65} Azide-alkyne cycloaddition reactions have also been used for the synthesis of high-affinity multisite enzyme inhibitors inside the biological target, in the absence of copper catalysis, i.e. the so-called \textit{in situ} click chemistry.\textsuperscript{66-70} In these compounds the triazole ring is used not only as a non-hydrolyzable, non-oxidizable, and non-reducible robust linker between the pharmacophoric moieties, but also provides favourable physicochemical properties and potential interactions with the biological target.\textsuperscript{71}

In this context, as the first step of a program directed to the synthesis of MAO-B-inhibitor-based anti-Alzheimer MTDLs, here we have explored the CuAAC-mediated synthesis of a series of 1,2,3-triazole derivatives, featuring the propargylamine group of typical irreversible MAO-B inhibitors in the side chain at position 4, while the overall hydrophobicity has been modulated through different lipophilic substituents at positions 1 and 5 (Scheme 1). To determine the therapeutic potential of the target compounds and their usefulness as the MAO-B pharmacophoric moiety of novel families of MTDLs, we have assessed the \textit{in vitro} inhibitory activity of the novel compounds against human MAO-B and MAO-A. Molecular modelling studies have been performed to rationalize the differences in inhibitory potency and selectivity between the MAO isoforms, and the mechanism of action of these compounds has been studied by reversibility and time-dependence inhibition studies. Finally, the brain penetration of the novel compounds has been examined through the widely used parallel artificial membrane permeability assay (PAMPA-BBB).
Scheme 1. General structure of the target \( N \)-methyl-\( N \)-[(1,2,3-triazol-4-yl)alkyl]propargylamines.

### 2. Results and Discussion

#### 2.1. Design and synthesis of the target \( N \)-methyl-\( N \)-[(1,2,3-triazol-4-yl)alkyl]propargylamines

We initially planned the synthesis of the 1-ethyltriazolylmethyl and 1-ethyltriazolylethyl propargylamines 31 and 32 (Scheme 2), unsubstituted at position 5 of the triazole ring, and their 5-methyl-substituted analogues 51 and 52, as the early simple prototypes to validate the suitability of the CuAAC-assisted synthetic methodology to deliver 1,4-disubstituted and 1,4,5-trisubstituted 1,2,3-triazole scaffolds featuring the propargylamine group of irreversible MAO inhibitors. These compounds are quite polar (LogP of 0.43, 0.84, 0.65, and 1.06, respectively) due to the presence of the triazole ring. However, the substrate cavity of MAO is highly hydrophobic, and accordingly MAO inhibitors are usually more lipophilic molecules (LogP in the range 2-4 for compounds depicted in Figure 1). Thus, to counterbalance the high polarity conferred by the triazole ring, we envisaged a second generation of derivatives that featured more lipophilic benzyl or phenethyl substituents at position 1 (i.e. compounds 33 and 34, respectively, Scheme 2) or at position 5 of the triazole ring (i.e. the 1-methyl-5-butyl-substituted compound 54). We also planned the synthesis of derivatives of the 1-benzyl-substituted compound 33 bearing different alkyl groups at position 5. However, the moderate acidity of the α-nitrogen benzylic protons of the substituent at position 1 of the triazole ring interfered with the alkylation of the position 5 (see below). To avoid these synthetic issues, we envisaged the synthesis of compounds 55, 56, and 57 (Scheme 2), bearing a phenyl group instead of a benzyl group at position 1 of the
triazole ring and ethyl, propyl, or butyl substituents at position 5. Finally, we also explored the isomerization of the benzene ring of compound 33 from the substituent at position 1 of the triazole ring to the side chain at position 4, i.e. between the triazole ring and the propargylamine moiety (compounds 82 and 83, Scheme 3).

After evaluation of MAO-A and MAO-B inhibitory activity of the first and second generation compounds, 33 emerged as the most selective MAO-B inhibitor, with a one-digit micromolar potency against MAO-B, 27-fold higher than against MAO-A, whereas compound 83 turned out to be the most potent inhibitor of both MAO isoforms, with submicromolar potencies but essentially without any selectivity (see below). In light of these results and on the basis of molecular modelling studies, we inferred that a total number of three methylenes might afford the optimal length between the terminal aromatic ring and the propargylamine nitrogen atom to confer selectivity towards MAO-B. To check this hypothesis, as a third generation we planned the synthesis of compound 36 (Scheme 2), an isomeric derivative of 33, and compound 84 (Scheme 3), with a total number of three methylenes from the terminal aromatic ring (phenyl in 36, triazole in 84) to the propargylamine nitrogen atom. For comparison purposes, we also envisaged the synthesis of compound 35 (Scheme 2), the shorter homologue of 33 with a total number of two methylenes in the tether.

The synthesis of the target compounds was undertaken through synthetic sequences involving as the key step a CuAAC reaction between alkyl or phenyl azides and alkynes bearing an amino or a cyano group to enable the subsequent installation of the propargylamine moiety (Scheme 1). The synthesis of the 5-unsubstituted triazolylmethyl and triazolylethyl propargylamines 31–36 was carried out through a four-step synthetic sequence, starting from the copper-catalyzed Huisgen 1,3-dipolar cycloaddition of the known N-Boc-protected amines 7 and 8 with ethyl, benzyl, and phenethyl azide, generated in situ by reaction of NaN₃ with the corresponding alkyl halide, which afforded the 1-substituted triazole derivatives 9–16 in moderate to good yields (49–78%, Scheme 2). Subsequent methylation of the N-Boc-protected aliphatic nitrogen atom of compounds 9–16 with Mel in anhydrous THF, in the presence of NaH, followed by acidic deprotection of the resulting compounds 17–24 afforded the secondary amines 25–30 in general in excellent yields. The final propargylation of amines 25–30 on reaction with propargyl bromide in acetone in the presence of Cs₂CO₃ led to propargylamines 31–36 in 22–89% yield (Scheme 2). Thus, the target compounds
31–36 were obtained in 5–58% overall yield without the need of any column chromatography purification, with the sole exception of the last step for 31, 35 and 36.

Scheme 2. Reagents and conditions: (i) CuSO₄·5H₂O, ascorbic acid, Na₂CO₃, H₂O/DMF, rt, overnight, 49–78% yield; (ii) MeI, NaH, THF, rt, 1.5–15 h, 81–97% yield; (iii) H₃PO₄, CH₂Cl₂, rt, 1.5–4 h, 38–98% (25–30), 67–100% (44–50); (iv) propargyl bromide, Cs₂CO₃, acetone, rt for 2–15 h, or 0 °C for 2–2.5 h, or 0 °C for 30 min and then rt for 3 h, 22–89% (31–36), 53–95% (51–57); (v) R₅⁻Hal, n-BuLi, THF, −78 °C, 1 h, then −78 °C → rt, and rt, 2 h, 43–98%.

For the synthesis of the 5-alkyl-substituted triazolylmethyl and triazolylethyl propargylamines 51, 52, and 54, apart from the intermediates 17 and 18, the triazole
derivative 21 was also prepared in good yield using the same CuAAC-N-methylation protocol (Scheme 2). Alkylation of compounds 17, 18, and 21 with the appropriate alkyl halide using n-BuLi as the base afforded the corresponding 5-alkylated compounds 37, 38, and 40, respectively, in excellent yields (90–97%). However, when we subjected the 1-benzyl-substituted intermediate 19 to the same alkylation reaction conditions with methyl iodide as the alkylating agent, we did not obtain the expected 1-benzyl-5-methyl-substituted derivative but the 1-(α-methylbenzyl)-5-methyl-substituted derivative 39 in 79% yield, resulting from the double alkylation at the position 5 of the triazole ring and at the moderately acidic α-nitrogen benzylic position of the substituent at position 1 (Scheme 2). Treatment of intermediate 19 with ethyl bromide or n-butyl bromide as the alkylating agents and n-BuLi or the more hindered t-BuLi as the base yielded inseparable mixtures of 5-monoalkylated and α,5-dialkylated products. To avoid double alkylation, we prepared the 1-phenyl-substituted intermediate 22, which was alkylated with ethyl bromide, n-propyl bromide, and n-butyl bromide using n-BuLi as the base, to afford the expected 5-alkyl-substituted derivatives 41, 42, and 43 in 98%, 96%, and 43% yield, respectively (Scheme 2). The acidic N-Boc deprotection of 5-alkyl-substituted compounds 37–43 afforded the secondary amines 44–50 in good yields (67% to quantitative yield). Propargylation of amines 44–50 had to be performed by monitoring the reaction course at different reaction temperatures and times to avoid the formation of dipropargylated products. For example, reaction of amine 44 with propargyl bromide in the presence of Cs₂CO₃ at rt overnight yielded the dipropargylated derivative as the major reaction product (92% yield), whereas on reaction at 0 °C for 2 h only the desired monopropargylated product, 51, was obtained, in 62% yield. Thus, by selecting the most appropriate reaction temperature and time, the target 5-alkyl-substituted triazolylmethyl and triazolylethyl propargylamines 51–57 were synthesized (19–44% overall yield over the five-step sequence).

The synthesis of the triazolyl-m-xylyl and triazolyl-p-xylyl propargylamines 82 and 83 and the triazolyl-p-methylphenethyl propargylamine 84 was carried out through the seven–eight-step sequences depicted in Scheme 3. First, the alkynes 64–66, necessary for the CuAAC, were prepared by an initial Negishi coupling between benzyl bromides 58–60 and trimethylsilylacetylene in the presence of n-BuLi and ZnBr₂, under Pd(0) catalysis, followed by desilylation of the protected alkyne derivatives 61–63 with AgOTf in a mixture of CH₂Cl₂/MeOH/H₂O and silica gel column chromatography purification. The CuAAC of methyl azide to alkynes 64–66 afforded the corresponding
triazole derivatives 67–69 in excellent yield (89–95%). LiAlH₄ reduction of the nitrile group of 67 and 68 afforded the corresponding amines 70 and 71 in 49% and 80% yield, respectively. However, the same reaction conditions failed to provide the amine derived from nitrile 69, which could be efficiently reduced to amine 72 by hydrogenation using Raney-Ni as the catalyst. N-Boc protection of the primary amino group of 70–72 afforded the intermediates 73–75. The N-Boc-protected amines 73 and 74 were converted into the target propargylamines 82 and 83 in good yields through the standard N-methylation–acidic deprotection–propargylation protocol, without the need of any additional column chromatography purification (Scheme 3). Because different attempts to methylate the N-Boc-protected amine 75 were fruitless, this compound was alternatively converted into the target propargylamine 84 by direct conversion into the secondary amine 81 upon LiAlH₄ reduction followed by propargylation (Scheme 3).

All the compounds to be subjected to biological evaluation were transformed into the corresponding hydrochloride salts and were chemically characterized through IR, ¹H and ¹³C NMR spectra, and HRMS.

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Scheme notes:
- Series meta: n = 0, 58, 61, 64, 67, 70, 73, 76, 79, 82
- Series para: n = 0, 59, 62, 65, 68, 71, 74, 77, 80, 83
- Series para: n = 1, 60, 63, 66, 69, 72, 75, 78, 81, 84
Scheme 3. Reagents and conditions: (i) trimethylsilylacetylene, THF, n-BuLi, −78 ºC, 30 min, then, ZnBr₂, THF, −78 ºC → 0 ºC, then, 58, 59, or 60, Cl₂Pd(PPh₃)₂, rt, overnight, 44–83% yield; (ii) AgOTf, CH₂Cl₂/MeOH/H₂O, rt, overnight, 63–77% yield; (iii) CuSO₄·5H₂O, ascorbic acid, Na₂CO₃, H₂O/DMF, rt, overnight, 89–95% yield; (iv) LiAlH₄, THF, reflux, 2 h: 70 (49%), 71 (80%), or H₂, Raney-Ni, 7 N NH₃ in MeOH: 72 (quantitative); (v) (Boc)₂O, THF, rt, 3 h, quantitative yield; (vi) MeI, NaH, THF, 60 ºC, 4 h: 76 (84%), 77 (80%); (vii) LiAlH₄, THF, 0 ºC, then 75, reflux, 72 h: 81 (44% yield); (viii) H₃PO₄, CH₂Cl₂, rt, 1.5–3 h: 79 (quantitative), 80 (96%); (ix) propargyl bromide, Cs₂CO₃, acetone, 0 ºC for 3.5 h or 0 ºC for 30 min and then rt for 3 h, 31–65% yield.

2.2. MAO inhibitory activity of the target compounds

The novel N-methyl-N-[(1,2,3-triazol-4-yl)alkyl]propargylamines 31–36, 51–57, and 82–84 were evaluated in vitro against human recombinant MAO-A and MAO-B (hrMAO-A and hrMAO-B). Selegiline and clorgyline were also used as reference compounds. The corresponding IC₅₀ values and selectivity indices (SI; defined as the ratio IC₅₀(MAO-B)/IC₅₀(MAO-A)) are shown in Table 1. The novel compounds turned out to be in most cases moderate to weak MAO inhibitors, with 2–3-digit micromolar IC₅₀ values, with the exceptions of compounds 33, 55, 82 and 83, which exhibited submicromolar or low micromolar potencies against one or both MAO isoforms.

The first generation compounds 31, 32, 51, and 52 were weak inhibitors and showed no selectivity. These trends were not unexpected due to the large polarity of the triazole ring and the small size of these fragment-like compounds. Accordingly, several strategies were explored to modulate both the molecular size and hydrophobicity of the triazole derivatives. The first approach involved the substitution of the ethyl group at position 1 of the triazole ring of the initial prototypes by benzyl and phenethyl groups, which led to increased inhibitory potencies. Thus, the 1-phenethyl-derivative 34 was 2- and 10-fold more potent MAO-A inhibitor than the 1-benzyl- and 1-ethyl-analogues 33 and 32, respectively. In contrast, for MAO-B inhibition, the optimal substitution pattern involved the presence of a 1-benzyl group, with compound 33 being 49- and 106-fold more potent than the 1-phenethyl- and 1-ethyl-analogues 34 and 32, respectively.
Table 1. MAO-A and MAO-B inhibitory activities, selectivity indices, and BBB permeability.

<table>
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<tr>
<th>Compound</th>
<th>hrMAO-A&lt;sup&gt;a&lt;/sup&gt; IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>hrMAO-B&lt;sup&gt;a&lt;/sup&gt; IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>SI&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Pe (10&lt;sup&gt;-6&lt;/sup&gt; cm s&lt;sup&gt;-1&lt;/sup&gt;)&lt;sup&gt;c&lt;/sup&gt;</th>
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<td></td>
<td></td>
<td></td>
<td>1st generation</td>
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</tr>
<tr>
<td>31</td>
<td>134.7 ± 21.8</td>
<td>248.6 ± 94.5</td>
<td>1.8</td>
<td>nd&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>32</td>
<td>553.5 ± 83.6</td>
<td>373.9 ± 119</td>
<td>0.7</td>
<td>nd&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>51</td>
<td>267.4 ± 30.8</td>
<td>104.7 ± 27.1</td>
<td>0.4</td>
<td>nd&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>52</td>
<td>91.2 ± 13.6</td>
<td>237.6 ± 51.8</td>
<td>2.6</td>
<td>nd&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>33</td>
<td>97.1 ± 30.1</td>
<td>3.54 ± 0.44</td>
<td>0.036</td>
<td>15.6 ± 1.5 (CNS+)</td>
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<td>34</td>
<td>56.1 ± 8.7</td>
<td>172.8 ± 47.8</td>
<td>3.1</td>
<td>14.8 ± 0.9 (CNS+)</td>
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<td>53</td>
<td>47.0 ± 6.9</td>
<td>134.2 ± 25.5</td>
<td>2.9</td>
<td>20.0 ± 0.7 (CNS+)</td>
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<td>54</td>
<td>&lt; 300</td>
<td>94.73 ± 16.3</td>
<td>&lt; 0.32</td>
<td>29.9 ± 0.8 (CNS+)</td>
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<tr>
<td>55</td>
<td>7.5 ± 1.1</td>
<td>213.4 ± 54.0</td>
<td>28.5</td>
<td>17.0 ± 1.9 (CNS+)</td>
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<tr>
<td>56</td>
<td>26.1 ± 4.0</td>
<td>156.8 ± 31.9</td>
<td>6.0</td>
<td>17.2 ± 0.6 (CNS+)</td>
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<tr>
<td>57</td>
<td>17.3 ± 4.5</td>
<td>155.5 ± 25.0</td>
<td>9.0</td>
<td>24.1 ± 1.3 (CNS+)</td>
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<tr>
<td>82</td>
<td>2.12 ± 0.32</td>
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<td>15.6 ± 1.5 (CNS+)</td>
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<td>83</td>
<td>0.53 ± 0.06</td>
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<td>35</td>
<td>&gt; 500</td>
<td>129 ± 42.6</td>
<td>&lt; 0.26</td>
<td>2.3 ± 0.7 (CNS+/−)</td>
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<td>36</td>
<td>&gt; 500</td>
<td>11.2 ± 2.1</td>
<td>&lt; 0.022</td>
<td>0.6 ± 0.1 (CNS−)</td>
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<td>84</td>
<td>27.4 ± 0.1</td>
<td>5.22 ± 0.49</td>
<td>0.19</td>
<td>4.5 ± 0.5 (CNS+/−)</td>
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<tr>
<td>Selegiline</td>
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<td>0.018 ± 0.003</td>
<td>nd&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>Clorgyline</td>
<td>0.020 ± 0.003</td>
<td></td>
<td>0.009</td>
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<sup>a</sup> In vitro inhibitory activities against hr-MAO-A and hr-MAO-B. Experiments performed with Amplex Red fluorimetric method in 96-well plates. Data are the mean of duplicate experiments ± SEM.

<sup>b</sup> SI = IC<sub>50</sub> (MAO-B) / IC<sub>50</sub> (MAO-A).

<sup>c</sup> Permeability values from the PAMPA-BBB assay. Values are expressed as the mean ± SD of three independent experiments.
This latter finding suggests that the size of compound 33 is better suited to fill the binding cavity in MAO-B, as confirmed by the results obtained from restrained docking calculations. Thus, following the strategy used in our previous studies, the propargylamine nitrogen atom was imposed to overly the position of the corresponding atom in the X-ray structures of covalently-bound selegiline and rasagiline (PDB entries 2BYB and 2BK4). By imposing this restraint, we may explore the arrangement of the compound after covalent linkage of the propargylamine unit to the FAD cofactor. Figure 2 shows that 33 superposes well with the structures of the irreversible inhibitor 6 (PDB entry 4CRT), and the reversible ligand 1,4-diphenyl-2-butene (PDB entry 1OJ9), which spans the substrate binding cavity. In particular, it is worth noting that the benzene ring of 33 matches well the position filled by the benzene unit in 1,4-diphenyl-2-butene. In turn, docking of the phenethyl derivative 34 made it necessary to adopt a folded conformation, reflecting some degree of internal strain due to clashes within the cavity (data not shown).
Figure 2. Representation of the docked pose of compound 33 (shown as green-coloured sticks) in the binding cavity of MAO-B (shown as gray cartoon). The surface of the binding cavity is depicted as a gray isocontour. The structures of inhibitor 6 (PDB entry 4CRT; covalently-bound to FAD, also shown as gray-coloured sticks) and the reversible ligand 1,4-diphenyl-2-butene (PDB entry 1OJ9) are shown as white-colored and yellow sticks, respectively.

An alternative strategy explored to modulate the hydrophobicity distribution of triazole derivatives relied on the alkylation of position 5 of the triazole ring (compounds 53–57). However, alkylation did not seem to have a clear effect on MAO inhibitory potency, although this chemical modification was generally beneficial for MAO-A selectivity for compounds bearing large substituents at position 1 (Ph-CH(Me)- or Ph), with selectivity indices in the range 2.9–28.5 (compounds 53, 55-57 in Table 1).

Finally, we also envisaged the isomerization of the benzene ring of compound 33 from the substituent at position 1 of the triazole ring to the side chain at position 4. This approach led to increased MAO-A inhibitory potencies, with compounds 82 and 83 being 46- and 183-fold more potent than 33, and also to increased MAO-B inhibitory activity in the case of 83 (6-fold more potent than 33), bearing a para-disubstituted benzene ring in the side chain at position 4. Docking calculations of compound 83 also led to a binding pose that filled the binding cavity of MAO-B (Figure 3), while docking of the derivative with a meta-disubstituted benzene (compound 82) revealed steric clashes in the substrate binding cavity (data not shown), in agreement with the 100-fold ratio in the IC_{50} values determined for these compounds against hrMAO-B (Table 1).

In agreement with the hypothesis that a total number of three methylenes separating the terminal aromatic ring and the propargylamine nitrogen atom afforded the optimal length to confer selectivity towards MAO-B, third generation compounds 36 and 84 turned out to be selective for MAO-B versus MAO-A inhibition, with IC_{50} values for MAO-B inhibition in the low micromolar range. Compound 36 was found to be more selective MAO-B inhibitor than its shorter homologue 35, and even more selective than its isomer 33 with the same total number of methylenes in the tether (27-fold more potent for MAO-B than for MAO-A inhibition; Table 1). Also, in contrast with compounds 82 and 83, with the inverse selectivity or with no selectivity, compound 84...
was found to be 5-fold more potent for MAO-B than for MAO-A inhibition, albeit with a 9-fold lower potency than its shorter homologue 83.

**Figure 3.** Representation of the docked pose of compound 83 (shown as green-coloured sticks) in the binding cavity of MAO-B (shown as gray cartoon). The surface of the binding cavity is depicted as a gray isocontour. The structures of inhibitor 6 (PDB entry 4CRT; covalently-bound to FAD, also shown as gray-coloured sticks) and the reversible ligand 1,4-diphenyl-2-butene (PDB entry 1OJ9) are shown as white-colored and yellow sticks, respectively.

Overall, compound 83 emerges as the most potent MAO inhibitor of the series, with submicromolar potencies against both MAO-A and MAO-B, and hence, essentially without selectivity, whereas compounds 33, 36, and 84, with a total number of three methylene groups in the tethers that connect their phenyl and triazole rings with the
propargylamine nitrogen atom, emerge as low micromolar selective MAO-B inhibitors of interest as novel leads for AD drug discovery.

2.3. Reversibility and time-dependent inhibition studies

The triazole derivative 33, one the most promising compounds of the series by virtue of its one-digit micromolar inhibitory potency and MAO-B selectivity, was subjected to further studies to gain insight into the type of inhibition of MAO-B. First, we investigated whether the propargylamino group present in 33 led to the irreversible inhibition of the enzyme. As shown in Figure 4, the reversibility assays confirmed that 33 irreversibly inhibited MAO-B, since the inhibition was not reverted after various cycles of consecutive centrifugations and washings with buffer. Furthermore, this finding is in agreement with the time-dependent inhibition of MAO-B resulting from incubation with 33, as shown in Figure 4. Thus, after pre-incubation of hrMAO-B with a 10 μM concentration of 33 for different times ranging from 5 to 360 min, the enzymatic activity showed a slow time-dependent inhibition of MAO-B. These findings mimic the behavior reported for the MTDL inhibitor 6,39 and for the structurally related MAO-B inhibitor PFN9601.81 As previously noted for 6,39 these results suggest that the proper accommodation of 33 in a conformation suitable for covalent attachment to the FAD cofactor may require an a priori conformational rearrangement for the structural adaptation to the peculiar shape of the MAO-B binding pocket.

![Figure 4](image-url)

**Figure 4.** Plot of the enzymatic activity (mFU/min) versus pre-incubation time (min) (left) and plot of the remaining enzymatic activity (as % of control sample) versus pre-incubation time (right) in the study of reversibility of hrMAO-B inhibition by 33.
2.4. Blood-brain barrier permeation assay

Because an essential feature of anti-neurodegenerative drug candidates is the ability to cross the BBB, all the novel compounds were subjected to the well-established PAMPA-BBB assay, as an in vitro model of passive permeation. The in vitro permeability (Pe) of the novel compounds through a lipid extract of porcine brain was determined using a mixture of phosphate-buffered saline (PBS)/EtOH 70:30. Assay validation was carried out by comparison of the experimental and reported permeability values of 14 commercial drugs (see Table S1 in Supplementary Material), which provided a good linear correlation: \( Pe_{\text{exp}} = 1.003 \times Pe_{\text{lit}} - 0.783 \) (\( R^2 = 0.93 \)). Using this equation and the limits established by Di et al. for BBB permeation, the following ranges of permeability were established: \( Pe \left( 10^{-6} \text{ cm s}^{-1} \right) > 5.18 \) for compounds with high BBB permeation (CNS+); \( Pe \left( 10^{-6} \text{ cm s}^{-1} \right) < 2.06 \) for compounds with low BBB permeation (CNS−); and \( 5.18 > Pe \left( 10^{-6} \text{ cm s}^{-1} \right) > 2.06 \) for compounds with uncertain BBB permeation (CNS±). As shown in Table 1, the tested compounds had generally Pe values well above the threshold for high BBB permeation, so that they were predicted to be able to cross the BBB and reach their biological target in the CNS, although unexpectedly the third generation compounds showed lower permeabilities than the rest of compounds, maybe as a consequence of solubility issues.

3. Conclusion

The results reported in this study support the feasibility of the CuAAC-mediated synthesis of 1,2,3-triazole derivatives featuring the propargylamine group typical of irreversible MAO-A and MAO-B inhibitors, leading to suitable templates for the design of MAO-B inhibitor-based MTDLs. The synthetic procedures of the 1,4-disubstituted or 1,4,5-trisubstituted 1,2,3-triazole scaffolds involve 4–6-step sequences from the CuAAC of alkyl or phenyl azides with an alkyne bearing an N-Boc-protected primary amino or a cyano group as precursors of the propargylamine warhead. Nevertheless, introduction of lipophilic substitutents were necessary to counterbalance the high polarity conferred by the triazole ring and to modulate the inhibitory activity against the two MAO isoforms. The triazolyl-\( p \)-xylyl propargylamine \(^{83} \) has been found to be a moderately potent nonselective MAO inhibitor, with submicromolar potencies against both human MAO-A and MAO-B. On the other hand, the isomeric 1-benzyltriazolylethyl propargylamine \(^{33} \) and 1-phenethyltriazolylmethyl propargylamine
36, and the triazolyl-p-methylphenethyl propargylamine 84 have emerged as moderately potent and selective MAO-B inhibitor with low micromolar potencies and large selectivity indices, with an appropriate hydrophilic-lipophilic balance (LogP values of 2.1, 1.9, and 2.4, respectively, i.e. in the range of classical MAO inhibitors) and relatively low molecular weight (254–268). Further work will be focused on refining the MAO-B inhibitory potency of these scaffolds by enabling the linkage to a second pharmacophoric moiety to derive novel MTDLs, as well as to develop small-molecule probes for MAO-B imaging in models of neurodegenerative diseases.83

4. Experimental part

4.1. Chemistry. General methods

Melting points were determined in open capillary tubes with a MFB 595010M Gallenkamp melting point apparatus. 400 MHz 1H/100.6 MHz 13C NMR spectra were recorded on a Varian Mercury 400 spectrometer at the Centres Científics i Tecnològics of the University of Barcelona (CCiTUB). The chemical shifts are reported in ppm (δ scale) relative to solvent signals (CD3OD at 3.31 and 49.0 ppm in the 1H and 13C NMR spectra, respectively; CDCl3 at 7.26 and 77.16 ppm in the 1H and 13C NMR spectra, respectively), and coupling constants are reported in Hertz (Hz). Assignments given for the NMR spectra of the new compounds have been carried out by comparison with the NMR data of compounds 10, 25, 34, 37, 52, and 82, which in turn, were assigned on the basis of DEPT, COSY 1H/1H (standard procedures), and COSY 1H/13C (gHSQC or gHMBC sequences) experiments. IR spectra were run on a Perkin-Elmer Spectrum RX I spectrophotometer. Absorption values are expressed as wavenumbers (cm⁻¹); only significant absorption bands are given. Column chromatography was performed on silica gel 60 AC.C (40–60 mesh, SDS, ref 2000027). Thin-layer chromatography was performed with aluminum-backed sheets with silica gel 60 F254 (Merck, ref 1.05554), and spots were visualized with UV light and 1% aqueous solution of KMnO4. High resolution mass spectra were carried out at the CCiTUB with a LC/MSD TOF Agilent Technologies spectrometer. The analytical samples of all of the compounds that were subjected to pharmacological evaluation were dried at 65 °C / 2 Torr (standard conditions).
4.1.1. *N*-([1-ethyl-1H-1,2,3-triazol-4-yl]methyl)amine 9

To a solution of bromoethane (0.53 mL, 774 mg, 7.10 mmol) in H₂O / DMF 1:4 (50 mL), NaN₃ (502 mg, 7.72 mmol), Na₂CO₃ (2.05 g, 19.3 mmol), ascorbic acid (907 mg, 5.15 mmol), CuSO₄·5H₂O (641 mmg, 2.57 mmol) and N-Boc-propargylamine, 7 (1.00 g, 6.44 mmol) were added. The reaction mixture was stirred at rt overnight, diluted with 20% aq. NH₄OH (200 mL), treated with solid EDTA (ca 5 g) and extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with H₂O (3 × 100 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting residue was washed with pentane (3 × 10 mL) and dried under vacuum, to give compound 9 (1.14 g, 78% yield) as a white solid; Rf 0.57 (CH₂Cl₂ / MeOH 9:1); mp 77–78 °C; IR (ATR) ν 3318 (N–H), 1685, 1675 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.40 [s, 9H, C(CH₃)₃], 1.51 (t, J = 7.2 Hz, 3H, 1–CH₂–CH₃), 4.35 (q, J = 7.2 Hz, 2H, 1–CH₂–CH₃), 4.36 (s, 2H, 4–CH₂–NH), 5.21 (broad s, 1H, NH/Boc), 7.50 (s, 1H, 5-H); ¹³C NMR (100.6 MHz, CDCl₃) δ 15.5 (CH₃, 1–CH₂–CH₃), 28.4 [3CH₃, C(CH₃)₃], 36.2 (CH₂, 4–CH₂–N), 45.3 (CH₂, 1–CH₂–CH₃), 79.7 [C, C(CH₃)₃], 121.3 (CH, C₅), 145.6 (C, C₄), 156.0 (C, NCOO); HRMS (ESI), calcd for (C₁0H₁₄N₂O₂ + H⁺) 227.1503, found 227.1493.

4.1.2. *N*-([1-ethyl-1H-1,2,3-triazol-4-yl]ethyl)amine 10

It was prepared as described for 9. From bromoethane (0.65 mL, 949 mg, 8.71 mmol), NaN₃ (618 mg, 9.51 mmol), Na₂CO₃ (2.52 g, 23.8 mmol), ascorbic acid (1.12 g, 6.36 mmol), CuSO₄·5H₂O (790 mg, 3.16 mmol), and N-Boc-3-butylnylamine, 8 (1.34 g, 7.92 mmol), compound 10 (1.48 g, 78% yield) was obtained as a white solid; Rf 0.50 (CH₂Cl₂ / MeOH 9:1); mp 78–80 °C; IR (ATR) ν 3341 (N–H), 1692 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.40 [s, 9H, C(CH₃)₃], 1.51 (t, J = 7.6 Hz, 3H, 1–CH₂–CH₃), 2.87 (t, J = 6.4 Hz, 2H, 4–CH₂–CH₂–NH), 3.44 (dt, J = J’ = 6.4 Hz, 2H, 4–CH₂–CH₂–NH), 4.35 (q, J = 7.6 Hz, 2H, 1–CH₂–CH₃), 5.04 (broad s, 1H, NH/Boc), 7.35 (s, 1H, 5-H); ¹³C NMR (100.6 MHz, CDCl₃) δ 15.6 (CH₃, 1–CH₂–CH₃), 26.3 (CH₂, 4–CH₂–CH₂–N), 28.5 [3CH₃, C(CH₃)₃], 39.9 (CH₂, 4–CH₂–CH₂–N), 45.2 (CH₂, 1–CH₂–CH₃), 79.2 [C, C(CH₃)₃], 120.8 (CH, C₅), 145.5 (C, C₄), 156.1 (C, NCOO); HRMS (ESI), calcd for (C₁₁H₁₉N₂O₂ + H⁺) 241.1659, found 241.1654.

4.1.3. *N*-([1-ethyl-1H-1,2,3-triazol-4-yl]ethyl)amine 11
It was prepared as described for 9. From benzyl bromide (0.75 mL, 1.08 g, 6.31 mmol), NaN₃ (462 mg, 7.11 mmol), Na₂CO₃ (1.88 g, 17.7 mmol), ascorbic acid (834 mg, 4.74 mmol), CuSO₄·5H₂O (590 mg, 2.36 mmol), and N-Boc-3-butylnylamine, 8 (1.00 g, 5.91 mmol), compound 11 (1.27 g, 71% yield) was obtained as a white solid; Rf 0.58 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05); mp 103–105 ºC; IR (ATR) ν 3407 (N–H), 1688 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.38 [s, 9H, C(CH₃)₃], 2.84 (t, J = 6.8 Hz, 2H, 4–CH₂–CH₂–NH), 3.41 (td, J = 6.8 Hz, J’ = 6.0 Hz, 2H, 4–CH₂–CH₂–NH), 5.04 (broad s, 1H, NH/Boc), 5.46 (s, 2H, 1–CH₂–Ph), 7.22 [ddm, J = 7.6 Hz, J’ = 2.0 Hz, 2H, Ph–C2(6) –H], 7.29–7.37 [complex signal, 4H, 5-H, Ph–C3(5)–H, Ph–C4–H]; ¹³C NMR (100.6 MHz, CDCl₃) δ 26.3 (CH₂, 4–CH₂–CH₂N), 28.4 [3CH₃, C(CH₃)₃], 39.8 (CH₂, 4–CH₂–CH₂–N), 54.1 (CH₂, 1–CH₂–Ph), 79.2 [C, C(CH₃)₃], 121.4 (CH, C5), 128.1 (2CH), 128.8 (CH), 129.2 (2CH) (Ph–CH), 134.8 (C, Ph–C1), 145.9 (C, C4), 156.0 (C, NCOO); HRMS (ESI), calcd for (C₁₈H₂₂N₄O₂ + H⁺) 303.1816, found 303.1813.

4.1.4. N-(tert-Butoxycarbonyl)-N-[2-(1-phenethyl-1H-1,2,3-triazol-4-yl)ethyl]amine 12
It was prepared as described for 9. From phenethyl bromide (0.89 mL, 1.21 g, 6.52 mmol), NaN₃ (462 mg, 7.11 mmol), Na₂CO₃ (1.88 g, 17.7 mmol), ascorbic acid (834 mg, 4.74 mmol), CuSO₄·5H₂O (590 mg, 2.36 mmol), and N-Boc-3-butylnylamine, 8 (1.00 g, 5.91 mmol), compound 12 (908 mg, 49% yield) was obtained as a white solid; Rf 0.52 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05); mp 123–125 ºC; IR (ATR) ν 3392 (N–H), 1688 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.43 [s, 9H, C(CH₃)₃], 2.85 (m, 2H, 4–CH₂–CH₂–N), 3.19 (t, J = 7.2 Hz 2H, 1–CH₂–CH₂–Ph), 3.42 (m, 2H, 4–CH₂–CH₂–N), 4.55 (t, J = 7.2 Hz, 2H, 1–CH₂–CH₂–Ph), 4.95 (br s, 1H, NH/Boc), 7.09 [ddm, J = 6.8 Hz, 2H, Ph–C2(6) –H], 7.22–7.32 [complex signal, 4H, 5-H, Ph–C3(5)–H, Ph–C4–H]; ¹³C NMR (100.6 MHz, CDCl₃) δ 26.2 (CH₂, 4–CH₂–CH₂–N), 28.5 [3CH₃, C(CH₃)₃], 36.9 (CH₂, 1–CH₂–CH₂–Ph), 40.0 (CH₂, 4–CH₂–CH₂–N), 51.6 (CH₂, 1–CH₂–CH₂–Ph), 79.3 [C, C(CH₃)₃], 121.9 (CH, C5), 127.2 (CH), 128.8 (2CH), 128.9 (2CH) (Ph–CH), 137.2 (C, Ph–C1), 145.2 (C, C4), 156.1 (C, NCOO); HRMS (ESI), calcd for (C₁₇H₂₂N₄O₂ + H⁺) 317.1972, found 317.1968.
4.1.5. N-(tert-Butoxycarbonyl)-N-[(1-methyl-1H-1,2,3-triazol-4-yl)methyl]amine 13

It was prepared as described for 9. From iodomethane (0.44 mL, 1.00 g, 7.07 mmol), NaN₃ (502 mg, 7.72 mmol), Na₂CO₃ (2.05 g, 19.3 mmol), ascorbic acid (907 mg, 5.15 mmol), CuSO₄·5H₂O (641 mg, 2.57 mmol), and N-Boc-propargylamine, 7 (1.00 g, 6.44 mmol), compound 13 (938 mg, 69% yield) was obtained as a white solid; R_f 0.87 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05); mp 102–104 ºC; IR (ATR) ν 3379 (N–H), 1679 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.41 [s, 9H, C(CH₃)₃], 4.05 (s, 3H, 1–CH₃), 4.35 (d, J = 6.0 Hz, 2H, 4–CH₂–N), 5.17 (br s, 1H, NH/Boc), 7.48 (s, 1H, 5–H); ¹³C NMR (100.6 MHz, CDCl₃) δ: 28.5 [3CH₃, C(CH₃)₃], 36.2 (CH₂, 4–CH₂–N), 36.7 (CH₃, 1–CH₃), 79.7 [C, C(CH₃)₃], 122.9 (CH, C5), 145.9 (C, C4), 156.0 (C, NCOO); HRMS (ESI), calcd for (C₁₅H₁₉N₂O₂ + H⁺) 213.1346, found 213.1336.

4.1.6. N-(tert-Butoxycarbonyl)-N-[2-(1-phenyl-1H-1,2,3-triazol-4-yl)ethyl]amine 14

It was prepared as described for 9. From phenyl azide (0.5 M solution in tert-butyl methyl ether, 26.2 mL, 13.1 mmol), Na₂CO₃ (3.47 g, 32.7 mmol), ascorbic acid (1.54 g, 8.74 mmol), CuSO₄·5H₂O (1.09 mmol, 4.36 mmol), and N-Boc-3-butynylamine, 8 (2.00 g, 11.8 mmol), compound 14 (1.89 g, 56% yield) was obtained as a yellow solid; R_f 0.90 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05); mp 127–129 ºC; IR (ATR) ν 3297 (N–H), 1712 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.43 [s, 9H, C(CH₃)₃], 3.00 (t, J = 6.8 Hz, 2H, 4–CH₂–CH₂–N), 5.02 (br s, 1H, NH/Boc), 7.43 (tt, J = 7.4 Hz, J’ = 1.2 Hz, 1H, Ph–C4–H), 7.52 [m, 2H, Ph–C3(5)–H], 7.71 [ddd, J = 8.8 Hz, J’ = 2.4 Hz, J” = 1.2 Hz, 2H, Ph–C2(6)–H], 7.81 (s, 1H, 5–H); ¹³C NMR (100.6 MHz, CDCl₃) δ 26.4 (CH₂, 4–CH₂–CH₂–N), 28.5 [3CH₃, C(CH₃)₃], 39.9 (CH₂, 4–CH₂–CH₂–N), 79.4 [C, C(CH₃)₃], 119.8 (CH, Ph–C4), 120.5 (CH, C5), 128.7 (2CH), 129.9 (2CH) [Ph–C2(6), Ph–C3(5)], 137.2 (C, Ph–C1), 146.3 (C, C4), 156.1 (C, NCOO); HRMS (ESI), calcd for (C₁₅H₁₀N₄O₂ + Na⁺) 311.1478, found 311.1476.

4.1.7. N-[(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl]-N-(tert-butoxycarbonyl)amine 15

It was prepared as described for 9. From benzyl bromide (1.04 mL, 1.50 g, 8.74 mmol), NaN₃ (622 mg, 9.57 mmol), Na₂CO₃ (2.53 g, 23.9 mmol), ascorbic acid (1.12 g, 6.36 mmol), CuSO₄·5H₂O (796 mg, 3.19 mmol), and N-Boc-propargylamine, 7 (1.24 g, 7.99 mmol), compound 15 (1.68 g, 68% yield) was obtained as a white solid; R_f 0.62
(CH₂Cl₂ / MeOH / NH₄OH 9.75:0.25:0.05); mp 97–99 ºC; IR (ATR) ν 3400, 3302, 3105, 3059 (N–H), 1684, 1679 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.32 [s, 9H, C(CH₃)₃], 4.27 (d, J = 6.0 Hz, 2H, 4–CH₂–N), 5.06 (br s, 1H, NH[Boc]), 5.40 (s, 2H, 1–CH₂–Ph), 7.26 [m, 2H, Ph–C₂(6)–H], 7.30–7.40 [complex signal, 3H, Ph–C₃(5)–H, Ph–C₄–H], 7.43 (s, 1H, 5-H); ¹³C NMR (100.6 MHz, CDCl₃) δ 28.4 [3CH₃, C(CH₃)₃], 36.2 (CH₂, 4–CH₂–N), 54.2 (CH₂, 1–CH₂–Ph), 79.8 [C, C(CH₃)₃], 121.9 (CH, C₅), 128.2 (2CH), 128.8 (CH), 129.2 (2CH) (Ph–CH), 134.7 (C, Ph–Cl), 146.0 (C, C₄), 155.9 (C, NCOO); HRMS (ESI), calcd for (C₁₃H₂₀N₄O₂ + Na⁺) 311.1478, found 311.1487.

4.1.8. N-(tert-Butoxycarbonyl)-N’-[1(phenethyl-1H-1,2,3-triazol-4-yl)methyl]amine 16

It was prepared as described for 9. From phenethyl bromide (1.11 mL, 1.50 g, 8.13 mmol), NaN₃ (574 mg, 8.83 mmol), Na₂CO₃ (2.34 g, 22.1 mmol), ascorbic acid (1.04 g, 5.91 mmol), CuSO₄·5H₂O (735 mg, 2.94 mmol), and N-Boc-propargylamine, 7 (1.00 g, 6.44 mmol), compound 16 (1.43 g, 73% yield) was obtained as a white solid; Rf 0.57 (CH₂Cl₂ / MeOH / NH₄OH 9.75:0.25:0.05); mp 98–100 ºC; IR (ATR) ν 3410, 3111, 3069, 3054 (N–H), 1684 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.43 [s, 9H, C(CH₃)₃], 3.19 (t, J = 7.2 Hz, 2H, 1–CH₂–CH₂–Ph), 4.34 (d, J = 6.0 Hz, 2H, 4–CH₂–N), 4.56 (t, J = 7.2 Hz, 2H, 1–CH₂–CH₂–Ph), 5.14 (br s, 1H, NH[Boc]), 7.10 [dm, J = 8.4 Hz, 2H, Ph–C₂(6)–H], 7.21–7.32 [complex signal, 4H, 5-H, Ph–C₃(5)–H, Ph–C₄–H]; ¹³C NMR (100.6 MHz, CDCl₃) δ 28.5 [3CH₃, C(CH₃)₃], 36.2 (CH₂, 4–CH₂–N), 36.8 (CH₂, 1–CH₂–CH₂–Ph), 51.7 (CH₂, 1–CH₂–CH₂–Ph), 79.7 [C, C(CH₃)₃], 122.2 (CH, C₅), 127.2 (CH), 128.7 (2CH), 128.9 (2CH) (Ph–CH), 137.0 (C, Ph–Cl), 145.3 (C, C₄), 155.9 (C, NCOO); HRMS (ESI), calcd for (C₁₅H₂₂N₄O₂ + H⁺) 303.1816, found 303.1827.

4.1.9. N-(tert-Butoxycarbonyl)-N’-[1(ethyl-1H-1,2,3-triazol-4-yl)methyl]-N-methylamine 17

A solution of 9 (634 mg, 2.80 mmol) in anhydrous THF (6.5 mL) was cooled to 0 ºC and treated with NaH (60% suspension in mineral oil, 246 mg, 6.15 mmol) and iodomethane (0.19 mL, 433 mg, 3.05 mmol). The reaction mixture was stirred at rt for 3 h, cooled to 0 ºC, diluted dropwise with sat. aq. NH₄Cl (40 mL), and extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried over anhydrous Na₂SO₄
and evaporated under reduced pressure. The resulting residue was washed with pentane (3 × 10 mL) and dried under vacuum, to give 17 (654 mg, 97% yield) as a colorless oil; Rf 0.64 (CHCl₂ / MeOH 9:1); IR (ATR) ν 1688, 1677 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.40 [s, C(CH₃)₃ minor rotamer], 1.42 [s, C(CH₃)₃ major rotamer], 1.50 (t, J = 7.2 Hz, 1–CH₂–CH₃ minor rotamer), 1.51 (t, J = 7.2 Hz, 1–CH₂–CH₃ major rotamer), 2.87 (s, 3H, N–CH₃), 4.39 (q, J = 7.2 Hz, 1–CH₂–CH₃ minor rotamer), 4.40 (q, J = 7.2 Hz, 1–CH₂–CH₃ major rotamer), 4.49 (s, 4–CH₂–N), 7.37 (br s, 5-H minor rotamer), 7.49 (s, 5-H major rotamer); HRMS (ESI), calcd for (C₁₁H₂₀N₄O₂ + H⁺) 241.1659, found 241.1654.

4.1.10. N-(tert-Butoxycarbonyl)-N-[2-(1-ethyl-1H-1,2,3-triazol-4-yl)ethyl]-N-methylamine 18

It was prepared as described for 17. From compound 10 (1.70 g, 7.08 mmol), NaH (60% suspension in mineral oil, 424 mg, 10.6 mmol), and iodomethane (0.48 mL, 1.09 g, 7.71 mmol), stirring at rt for 2 h, compound 18 (1.71 mg, 95% yield) was obtained as a colorless oil; Rf 0.58 (CHCl₂ / MeOH 9:1); IR (ATR) ν 1690 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.41 [s, 9H, C(CH₃)₃], 1.51 (t, J = 7.2 Hz, 3H, 1–CH₂–CH₃), 2.82 (s, 3H, N–CH₃), 2.93 (m, 2H, 4–CH₂–CH₂–N), 3.52 (br t, J = 6.8 Hz, 2H, 4–CH₂–CH₂–N), 4.35 (q, J = 7.2 Hz, 2H, 1–CH₂–CH₃), 7.28 (br s), 7.40 (br s) (5-H); ¹³C NMR (100.6 MHz, CDCl₃) δ 15.6 (CH₃, 1–CH₂–CH₃), 24.3 (CH₂), 24.7 (CH₂) (4–CH₂–CH₂–N), 28.5 [3CH₃, C(CH₃)₃], 34.4 (CH₃, N–CH₃), 45.2 (CH₂, 1–CH₂–CH₃), 48.0 (CH₃), 48.9 (CH₂) (4–CH₂–CH₂–N), 79.5 [C, C(CH₃)₃], 120.8 (CH, C₅), 145.2 (br C, C₄), 155.8 (br C, NCOO); HRMS (ESI), calcd for (C₁₂H₂₂N₄O₂ + H⁺) 255.1816, found 255.1815.

4.1.11. N-(tert-Butoxycarbonyl)-N-[2-(1-benzyl-1H-1,2,3-triazol-4-yl)ethyl]-N-methylamine 19

It was prepared as described for 17. From compound 11 (3.67 g, 12.1 mmol), NaH (60% suspension in mineral oil, 0.73 g, 18.2 mmol), and iodomethane (0.83 mL, 1.89 g, 13.3 mmol), stirring at rt for 3 h, compound 19 (3.64 g, 95% yield) was obtained as a yellowish oil; Rf 0.60 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05); IR (ATR) ν 1687 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.37 [s, 9H, C(CH₃)₃], 2.78 (s, 3H, N–CH₃), 2.90 (m, 2H, 4–CH₂–CH₂–N), 3.48 (t, J = 6.8 Hz, 2H, 4–CH₂–CH₂–N), 5.45
(s, 2H, 1–CH$_2$-Ph), 7.20–7.37 (complex signal, 6H, 5-H, Ph–CH$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 24.2 (CH$_2$), 24.7 (CH$_2$ (4–CH$_2$–CH$_2$–N), 28.4 [3CH$_3$, C(CH$_3$)$_3$], 34.4 [CH$_3$, N–CH$_3$), 48.0 (CH$_2$), 48.7 (CH$_2$ (4–CH$_2$–CH$_2$–N), 54.1 (CH$_2$, 1–CH$_2$–Ph), 79.5 [C, C(CH$_3$)$_3$], 121.4 (br CH, C5), 128.1 (2CH), 128.7 (CH), 129.1 (2CH) (Ph–CH$_2$), 134.9 (C, Ph–C1), 145.6 (br C, C4), 155.7 (C, NCOO); HRMS (ESI), calcd for (C$_{17}$H$_{24}$NaO$_2$ + H$^+$) 317.1972, found 317.1964.

4.1.12. N-(tert-Butoxycarbonyl)-N-methyl-N-[2-(1-phenethyl-1H-1,2,3-triazol-4-yl)ethyl]amine 20

It was prepared as described for 17. From compound 12 (876 mg, 2.77 mmol), NaH (60% suspension in mineral oil, 167 mg, 4.17 mmol), and iodomethane (0.19 mL, 433 mg, 3.05 mmol), stirring at rt for 1.5 h, compound 20 (738 mg, 81% yield) was obtained as a yellowish oil; $R_f$ 0.57 (CH$_2$Cl$_2$ / MeOH / 50%aq. NH$_4$OH 9.5:0.5:0.05); mp 58–60 °C; IR (ATR) $\nu$ 1686 (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.42 [s, 9H, C(CH$_3$)$_3$], 2.80 (s, 3H, N–CH$_3$), 2.90 (m, 2H, 4–CH$_2$–CH$_2$–N), 3.18 (t, $J$ = 7.2 Hz, 2H, 1–CH$_2$–CH$_2$–Ph), 3.48 (m, 2H, 4–CH$_2$–CH$_2$–N), 4.54 (t, $J$ = 7.2 Hz, 2H, 1–CH$_2$–CH$_2$–Ph), 7.03 (br s), 7.19 (br s) (5-H), 7.10 [dm, $J$ = 8.0 Hz, 2H, Ph–C2(6–H)], 7.21–7.32 (complex signal, 3H, Ph–C3(5–H, Ph–C4–H)]; $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 24.2 (CH$_2$), 24.6 (CH$_2$ (4–CH$_2$–CH$_2$–N), 28.5 (3CH$_3$, C(CH$_3$)$_3$], 34.5 (CH$_3$, N–CH$_3$), 36.9 (CH$_2$, 1–CH$_2$–CH$_2$–Ph), 48.1 (CH$_2$), 48.9 (CH$_2$ (4–CH$_2$–CH$_2$–N), 51.6 (CH$_2$, 1–CH$_2$–CH$_2$–Ph), 79.5 [C, C(CH$_3$)$_3$], 121.8 (CH, C5), 127.1 (CH), 128.7 (2CH), 128.9 (2CH) (Ph–CH), 137.2 (C, Ph–C1), 144.8 (br C, C4), 155.8 (C, NCOO); HRMS (ESI), calcd for (C$_{18}$H$_{26}$NaO$_2$ + H$^+$) 331.2129, found 331.2122.

4.1.13. N-(tert-Butoxycarbonyl)-N-methyl-N-[1-(1-methyl-1H-1,2,3-triazol-4-yl)methyl]amine 21

It was prepared as described for 17. From compound 13 (928 mg, 4.38 mmol), NaH (60% suspension in mineral oil, 263 mg, 6.57 mmol), and iodomethane (0.30 mL, 684 mg, 4.82 mmol), stirring at rt for 1.5 h, compound 21 (945 mg, 95% yield) was obtained as a yellowish oil; $R_f$ 0.31 (CH$_2$Cl$_2$ / MeOH / 50%aq. NH$_4$OH 9.5:0.5:0.05); IR (ATR) $\nu$ 1686 (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.45 [s, 9H, C(CH$_3$)$_3$], 2.89 (s, 3H, N–CH$_3$), 4.07 (s, 3H, 1–CH$_3$), 4.47 (s, 2H, 4–CH$_2$–N), 7.37 (br s), 7.49 (broad s) (5-H);
$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 28.6 [3CH$_3$, C(CH$_3$_)$_3$], 34.2 (br CH$_3$), 34.6 (br CH$_3$) (N–CH$_3$), 36.8 (CH$_3$, 1–CH$_2$), 43.8 (br CH$_2$), 44.5 (br CH$_2$) (4–CH$_2$–N), 79.9 [br C, C(CH$_3$_)$_3$], 122.6 (br CH), 123.5 (br CH) (C5), 145.3 (br C), 145.8 (br C) (C4), 155.3 (br C), 155.9 (br C) (NCOO); HRMS (ESI), calcd for (C$_{10}$H$_{18}$N$_4$O$_2$ + Na$^+$) 249.1322; found 249.1323.

4.1.14. $N$-(tert-Butoxycarbonyl)-$N$-methyl-$N$-[2-(1-phenyl-1H-1,2,3-triazol-4-yl)ethyl]amine 22

It was prepared as described for 17. From compound 14 (1.82 g, 6.32 mmol), NaH (60% supension in mineral oil, 0.76 g, 19.0 mmol), and iodomethane (1.96 mL, 4.47 g, 31.5 mmol), stirring at rt overnight, compound 22 (1.82 g, 95% yield) was obtained as a yellowish oil; $R_f$ 0.86 (CH$_2$Cl$_2$ / MeOH / 50% aq. NH$_4$OH 9:1:0.05); IR (ATR) $\nu$ 1689, 1681 (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.42 [s, 9H, C(CH$_3$_)$_3$], 2.88 (s, 3H, N–CH$_3$), 3.04 (m, 2H, 4–CH$_2$–CH$_2$–N), 3.61 (m, 2H, 4–CH$_2$–CH$_2$–N), 7.43 (m, 1H, Ph–C4–H), 7.51 [m, 2H, Ph–C3(5)–H], 7.71 [dm, $J = 8.8$ Hz, 2H, Ph–C2(6)–H], 7.89 (br s, 1H, 5-H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 24.3 (br CH$_3$), 24.6 (br CH$_2$) (4–CH$_2$–CH$_2$–N), 28.5 [3CH$_3$, C(CH$_3$_)$_3$], 34.4 (CH$_3$, N–CH$_3$), 47.8 (br CH$_2$), 48.7 (br CH$_2$) (4–CH$_2$–CH$_2$–N), 79.6 [C, C(CH$_3$_)$_3$], 119.8 (CH, Ph–C4), 120.5 (CH, C5), 128.6 (2CH), 129.8 (2CH) [Ph–C2(6), Ph–C3(5)], 137.2 (C, Ph–C1), 145.9 (br C, C4), 155.8 (br C, NCOO); HRMS (ESI), calcd for (C$_{18}$H$_{22}$N$_4$O$_2$ + H$^+$) 303.1816, found 303.1809.

4.1.15. $N$-[(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl]-$N$-(tert-butoxycarbonyl)-$N$-methylamine 23

It was prepared as described for 17. From compound 15 (1.60 g, 5.16 mmol), NaH (60% suspension in mineral oil, 670 mg, 16.7 mmol), and iodomethane (1.73 mL, 3.94 g, 27.8 mmol), stirring at rt overnight, compound 23 (1.30 g, 83% yield) was obtained as a brown solid; $R_f$ 0.68 (CH$_2$Cl$_2$ / MeOH / NH$_4$OH 9.75:0.25:0.05); mp 79–81 °C; IR (ATR) $\nu$ 1679 (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.41 [br s, 9H, C(CH$_3$_)$_3$], 2.89 (s, 3H, N–CH$_3$), 4.45 (s, 2H, 4–CH$_2$–N), 5.50 (s, 2H, 1–CH$_2$–Ph), 7.26 [br dd, $J = 8.0$ Hz, $J' = 1.6$ Hz, 2H, Ph–C2(6)–H], 7.34–7.40 [complex signal, 3H, Ph–C3(5)–H, Ph–C4–H], 7.44 (br s, 1H, 5-H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 28.4 [3CH$_3$, C(CH$_3$_)$_3$], 34.5 (CH$_3$, N–CH$_3$), 43.8 (CH$_2$), 44.6 (CH$_2$) (4–CH$_2$–N), 54.2 (CH$_2$, 1–CH$_2$–Ph), 79.8 [C, C(CH$_3$_)$_3$], 121.6 (CH), 122.4 (CH) (C5), 128.1 (2CH), 128.8...
(CH), 129.2 (2CH (Ph–CH), 134.7 (C, Ph–Cl), 145.4 (C), 145.6 (C) (C4), 155.4 (C), 155.8 (C) (NCOO); HRMS (ESI), calcd for (C_{16}H_{22}N_{4}O_{2} + Na^+) 325.1635, found 325.1638.

4.1.16. N-(tert-Butoxycarbonyl)-N-methyl-N-[(1-phenetyl-1H-1,2,3-triazol-4-yl)methyl]amine 24

It was prepared as described for 17. From compound 16 (1.27 g, 4.20 mmol), NaH (60% suspension in mineral oil, 505 mg, 12.6 mmol), and iodomethane (1.31 mL, 2.99 g, 21.0 mmol), stirring at rt overnight, compound 24 (1.07 g, 81% yield) was obtained as a brown oil; \( R_f 0.59 \) (CH2Cl2 / MeOH / NH4OH 9.75:0.25:0.05); IR (ATR) \( \nu 1687 \) (C=O) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl3) \( \delta 1.43 \) [s, 9H, (CH3)3], 2.84 (s, 3H, N–CH3), 3.19 (t, \( J = 7.2 \) Hz, 2H, 1–CH2–CH2–Ph), 4.43 (s, 2H, 4–CH2–N), 4.56 (m, 2H, 1–CH2–CH2–Ph), 7.08 [dm, \( J = 8.4 \) Hz, 2H, Ph–C2(6)–H], 7.20–7.32 [complex signal, 4H, 5-H, Ph–C3(5)–H, Ph–C4–H]; \(^13\)C NMR (100.6 MHz, CDCl3) \( \delta 28.2 \) [CH3, C(CH3)3 minor rotamer], 28.3 [CH3, C(CH3)3 major rotamer], 33.9 (CH3, N–CH3 minor rotamer), 34.2 (CH3, N–CH3 major rotamer), 36.5 (CH2, 1–CH2–CH2–Ph minor rotamer), 36.6 (CH2, 1–CH2–CH2–Ph major rotamer), 43.5 (CH2, 4–CH2–N major rotamer), 44.2 (CH2, 4–CH2–N minor rotamer), 51.4 (CH2, 1–CH2–CH2–Ph minor rotamer), 51.5 (CH2, 1–CH2–CH2–Ph major rotamer), 79.6 [br C, C(CH3)3], 121.9 (CH, C5 minor rotamer), 122.6 (CH, C5 major rotamer), 126.8 (CH, Ph–C4 minor rotamer), 127.0 (CH, Ph–C4 major rotamer), 128.4 (CH), 128.5 (CH), 128.7 (CH) [Ph–C2(6), Ph–C3(5)], 136.8 (C, Ph–C1 minor rotamer), 136.9 (C, Ph–C1 major rotamer), 144.4 (br C, C4), 155.2 (C, NCOO minor rotamer), 155.7 (C, NCOO major rotamer); HRMS (ESI), calcd for (C_{17}H_{24}N_{4}O_{2} + H^+) 317.1972, found 317.1979.

4.1.17. N-[(1-Ethyl-1H-1,2,3-triazol-4-yl)methyl]-N-methylamine 25

To a solution of 17 (411 mg, 1.71 mmol) in CH2Cl2 (6 mL), H3PO4 (85% purity, 2.96 mL, 25.7 mmol) was added. The reaction mixture was stirred at rt for 2 h, cooled to 0 °C, diluted with H2O (15 mL), alkalinized dropwise to pH = 14 with 5 N NaOH, and extracted with CH2Cl2 (2 \times 30 mL). The combined organic extracts were dried over anhydrous Na2SO4 and evaporated under reduced pressure to give amine 25 (205 mg, 86% yield) as a colorless oil; \( R_f 0.07 \) (CH2Cl2 / MeOH / 50% aq. NH4OH 9:1:0.05).
A solution of amine 25 (25 mg, 0.18 mmol) in CH₂Cl₂ (4 mL) was filtered through a PTFE filter (0.2 µm), treated with a HCl / MeOH solution (0.75 N, 0.71 mL, 0.53 mmol), and evaporated under reduced pressure. The resulting residue was washed with pentane (3 × 2 mL) to give, after drying under standard conditions, 25·HCl (28 mg) as a beige sticky solid; IR (ATR) ν 3500–2500 (max at 3386, 3126, 3080, 3028, 2981, 2935, 2756, 2695, 'N–H and C–H) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 1.55 (t, J = 7.2 Hz, 3H, 1–CH₂–CH₃), 2.76 (s, 3H, N–CH₃), 4.35 (s, 2H, 4–CH₂–N), 4.50 (q, J = 7.2 Hz, 2H, 1–CH₂–CH₃), 4.96 (s, 'NH₂), 8.22 (s, 1H, 5-H); ¹³C NMR (100.6 MHz, CD₃OD) δ 15.8 (CH₃, 1–CH₂–CH₃), 33.1 (CH₃, N–CH₃), 44.2 (CH₂, 4–CH₂–N), 46.8 (CH₂, 1–CH₂–CH₃), 126.2 (CH, C5), 139.3 (C, C4); HRMS (ESI), calcd for (C₆H₁₂N₄ + H⁺) 141.1135, found 141.1133.

4.1.18. N-[2-(1-Ethyl-1H-1,2,3-triazol-4-yl)ethyl]-N-methylamine 26
It was prepared as described for 25. From 18 (263 mg, 1.03 mmol) and H₃PO₄ (85% purity, 1.80 mL, 15.6 mmol), and stirring at rt for 4 h, amine 26 (143 mg, 90% yield) was obtained as a colorless oil; Rₜ 0.07 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05). 26·HCl: beige sticky solid, IR (ATR) ν 3500–2400 (max at 3395, 3116, 3064, 2976, 2936, 2752, 2691, 2446, 'N–H and C–H) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 1.54 (t, J = 7.2 Hz, 3H, 1–CH₂–CH₃), 2.76 (s, 3H, N–CH₃), 3.17 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 3.37 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 4.48 (q, J = 7.2 Hz, 2H, 1–CH₂–CH₃), 4.87 (s, 'NH₂), 8.07 (s, 1H, 5-H); ¹³C NMR (100.6 MHz, CD₃OD) δ 15.6 (CH₃, 1–CH₂–CH₃), 22.9 (CH₂, 4–CH₂–CH₂–N), 33.7 (CH₃, N–CH₃), 47.1 (CH₂, 1–CH₂–CH₃), 49.3 (CH₂, 4–CH₂–CH₂–N), 124.6 (CH, C5), 143.3 (C, C4); HRMS (ESI), calcd for (C₇H₁₄N₄ + H⁺) 155.1291, found 155.1297.

4.1.19. N-[2-(1-Benzyl-1H-1,2,3-triazol-4-yl)ethyl]-N-methylamine 27
It was prepared as described for 25. From 19 (1.12 g, 3.54 mmol) and H₃PO₄ (85% purity, 6.08 mL, 52.7 mmol), amine 27 (721 mg, 94% yield) was obtained as a yellow oil; Rₜ 0.23 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05). 27·HCl: beige solid, mp 189–190 °C; IR (ATR) ν 3600–2400 (max at 3554, 3064, 3013, 2927, 2868, 2735, 2685, 2447, C-H, 'N–H and C–H) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 2.75 (s, 3H, N–CH₃), 3.24 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 3.38 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 4.98 (s, 'NH₂), 5.72 (s, 2H, 1–CH₂–Ph), 7.35–7.46
It was prepared as described for 25. From 20 (693 mg, 2.10 mmol) and H₃PO₄ (85% purity, 3.61 mL, 31.3 mmol), amine 28 (472 mg, 98% yield) was obtained as a yellow oil; R₉ 0.26 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05).

28·HCl: beige solid, mp 160–162 °C; IR (ATR) ν 3500–2400 (max at 3413, 3354, 3126, 3092, 2954, 2783, 2703, 2444, "N–H and C–H") cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 2.75 (s, 3H, N–CH₃), 3.25 (t, J = 7.2 Hz, 2H, 1–CH₂–CH₂–Ph), overimposed in part 3.29 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 3.37 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 4.80 (t, J = 7.2 Hz, 2H, 1–CH₂–CH₂–Ph), 4.99 (s, "NHNH₂), 7.18–7.30 (complex signal, 5H, Ph–CH₃), 8.30 (s, 1H, 5–H); ¹³C NMR (100.6 MHz, CD₃OD) δ 22.1 (CH₂, 4–CH₂–CH₂–N), 33.8 (CH₃, N–CH₃), 36.7 (CH₂, 1–CH₂–CH₂–Ph), 48.4 (CH₂, 4–CH₂–CH₂–N), 54.6 (CH₂, 1–CH₂–CH₂–Ph), 127.5 (CH, C₅), 128.2 (CH), 129.8 (4CH) (Ph–CH), 137.9 (C, Ph–C₁), 141.6 (C, C₄); HRMS (ESI), calcd for (C₁₃H₁₈N₄ + H⁺) 231.1604; found 231.1604.

It was prepared as described for 25. From 23 (723 mg, 2.39 mmol) and H₃PO₄ (85% purity, 4.14 mL, 35.9 mmol), amine 29 (420 mg, 87% yield) was obtained as a brown oil; R₉ 0.14 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.75:0.25:0.05).

29·HCl: yellow solid, mp 218–219 °C; IR (ATR) ν 3500–2400 (max at 3126, 3059, 3018, 2981, 2940, 2852, 2770, 2697, "N–H and C–H") cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 2.74 (s, 3H, N–CH₃), 4.33 (s, 2H, 4–CH₂–N), 4.87 (s, "NHNH₂), 5.64 (s, 2H, 1–CH₂–Ph), 7.31–7.40 (complex signal, 5H, Ph–CH₃), 8.19 (s, 1H, 5–H); ¹³C NMR (100.6 MHz, CD₃OD) δ 33.1 (CH₃, N–CH₃), 44.2 (CH₂, 4–CH₂–N), 55.0 (CH₂, 1–CH₂–Ph), 126.5 (CH, C₅), 129.3 (2CH), 129.7 (CH), 130.0 (2CH) (Ph–CH), 136.6
(C, Ph–C1), 139.8 (C, C4); HRMS (ESI), calcd for (C11H14N4 + H+) 203.1291, found 203.1284.

4.1.22. N-Methyl-N-[(1-phenethyl-1H-1,2,3-triazol-4-yl)methyl]amine 30

It was prepared as described for 25. From 24 (983 mg, 3.11 mmol) and H3PO4 (85% purity, 5.37 mL, 46.6 mmol), amine 30 (258 mg, 38% yield) was obtained as a colorless oil; Rf 0.16 (CH2Cl2 / MeOH / 50% aq. NH4OH 9.75:0.25:0.05).

30-HCl: yellow solid, mp 173–175 °C; IR (ATR) ν 3500–2400 (max at 3111, 3069, 3023, 2981, 2925, 2764, 2749, 2692, 2599, 2542, 161 cm−1; 1H NMR (400 MHz, CD3OD) δ 2.67 (s, 3H, N–CH3), 3.24 (t, J = 7.2 Hz, 2H, 1CH2–CH2–Ph), 4.26 (s, 2H, 4–CH2–N), 4.71 (t, J = 7.2 Hz, 2H, 1–CH2–CH2–Ph), 4.87 (s, NH2), 7.15 [dm, J = 8.4 Hz, 2H, Ph–C2(6)–H], 7.16–7.29 [complex signal, 3H, Ph–C3(5)–H, Ph–C4–H], 7.94 (s, 1H, 5-H); 13C NMR (100.6 MHz, CD3OD) δ 32.9 (CH3, N–CH3), 37.3 (CH2, 1–CH2–CH2–Ph), 44.1 (CH2, 4–CH2–N), 52.7 (CH2, 1–CH2–CH2–Ph), 126.8 (CH, C5), 128.0 (CH), 129.7 (2CH), 129.8 (2CH) (Ph–CH), 138.6 (C, Ph–C1), 139.0 (C, C4); HRMS (ESI), calcd for (C12H16N4 + H+) 217.1448, found 217.1443.

4.1.23. N-[(1-Ethyl-1H-1,2,3-triazol-4-yl)methyl]-N-methyl-N-propargylamine 31

A solution of amine 25 (85 mg, 0.61 mmol) in anhydrous acetone (20 mL) was cooled to 0 °C and treated with Cs2CO3 (199 mg, 0.61 mmol) and propargyl bromide (80% solution in toluene, 0.09 mL, 0.61 mmol). The reaction mixture was stirred at rt overnight, then filtered, and evaporated under reduced pressure to give an oily residue (161 mg), which was purified through column chromatography (40–60 µm silica gel, CH2Cl2 / MeOH / 50% aq. NH4OH mixtures, gradient elution). On elution with CH2Cl2 / MeOH / 50% aq. NH4OH 98:2:0.2, propargylamine 31 (97 mg, 89% yield) was isolated as a colorless oil; Rf 0.33 (CH2Cl2 / MeOH / 50% aq. NH4OH 9:1:0:0.05).

31-HCl: beige sticky solid, IR (ATR) ν 3500–2300 (max at 3412, 3205, 3126, 2987, 2941, 2568, 2477, 2381, N–H = C–H, and C–H), 2125 (C≡C) cm−1; 1H NMR (400 MHz, CD3OD) δ 1.56 (t, J = 7.6 Hz, 3H, 1–CH2–CH3), 2.94 (s, 3H, N–CH3), 3.39 (t, J = 2.4 Hz, 1H, propargyl CH), 4.12 (d, J = 2.4 Hz, 2H, propargyl CH2), 4.50 (q, J = 7.6 Hz, 2H, 1–CH2–CH3), 4.54 (s, 2H, 4–CH2–N), 4.87 (s, NH), 8.26 (s, 1H, 5-H); 13C NMR (100.6 MHz, CD3OD) δ 15.7 (CH3, 1–CH2–CH3), 40.3 (CH3, N–CH3), 45.6 (CH2, propargyl CH2), 46.8 (CH2, 1–CH2–CH3), 50.4 (CH2, 4–CH2–N), 73.3 (C,
propargyl C), 81.2 (CH, propargyl CH), 127.4 (CH, C5), 137.8 (C, C4); HRMS (ESI), calcd for (C₈H₄N₄ + H⁺) 179.1291, found 179.1289.

4.1.24. N-[2-(1-Ethyl-1H-1,2,3-triazol-4-yl)ethyl]-N-methyl-N-propargylamine 32

It was prepared as described for 31. From amine 26 (299 mg, 1.94 mmol), Cs₂CO₃ (630 mg, 1.93 mmol), and propargyl bromide (80% solution in toluene, 0.47 mL, 1.95 mmol), and stirring at 0 °C for 2.5 h, propargylamine 32 (220 mg, 59% yield) was obtained as a yellow oil, without the need of chromatographic purification; Rf 0.55 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).

32·HCl: yellow sticky solid, IR (ATR) ν 3500–2300 (max at 3417, 3191, 2937, 2521, 2434, 2359, 1760, =C–H, and C–H), 2124 (C≡C) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 1.53 (t, J = 7.2 Hz, 3H, 1–CH₂–CH₃), 3.05 (s, 3H, N–CH₃), 3.24 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 3.41 (t, J = 2.8 Hz, 1H, propargyl CH), 3.62 (br t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 4.24 (d, J = 2.8 Hz, 2H, propargyl CH₂), 4.46 (q, J = 7.2 Hz, 2H, 1–CH₂–CH₃), 4.86 (s, ²NH), 8.01 (s, 1H, 5-H); ¹³C NMR (100.6 MHz, CD₃OD) δ 15.7 (CH₃, 1–CH₂–CH₃), 21.6 (CH₂, 4–CH₂–CH₂–N), 40.7 (CH₃, N–CH₃), 46.3 (CH₂, propargyl CH₂), 46.8 (CH₂, 1–CH₂–CH₃), 55.4 (CH₂, 4–CH₂–CH₂–N), 72.6 (C, propargyl C), 81.6 (CH, propargyl CH), 124.2 (CH, C5), 143.1 (C, C4); HRMS (ESI), calcd for (C₁₀H₁₆N₄ + H⁺) 193.1448, found 193.1440.

4.1.25. N-[2-(1-Benzyl-1H-1,2,3-triazol-4-yl)ethyl]-N-methyl-N-propargylamine 33

It was prepared as described for 31. From amine 27 (690 mg, 3.19 mmol), Cs₂CO₃ (1.04 g, 3.19 mmol), and propargyl bromide (80% solution in toluene, 0.47 mL, 3.16 mmol), and stirring at rt for 2 h, propargylamine 33 (577 mg, 71 % yield) was obtained as a yellow oil, without the need of chromatographic purification; Rf 0.48 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:5:0.5:0.05).

33·HCl: brown solid, mp 97–99 oC; IR (ATR) ν 3500–2300 (max at 3413, 3194, 2948, 2522, 1760, =C–H, and C–H), 2124 (C≡C) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 3.03 (s, 3H, N–CH₃), 3.31 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 3.39 (t, J = 2.4 Hz, 1H, propargyl CH), 3.62 (m, 2H, 4–CH₂–CH₂–N), 4.23 (d, J = 2.4 Hz, 2H, propargyl CH₂), 5.00 (s, ²NH), 5.68 (s, 2H, 1–CH₂–Ph), 7.33–7.43 (complex signal, 5H, Ph–CH), 8.23 (s, 1H, 5-H); ¹³C NMR (100.6 MHz, CD₃OD) δ 21.2 (CH₂, 4–CH₂–CH₂–N), 40.7 (CH₃, N–CH₃), 46.4 (CH₂, propargyl CH₂), 54.8 (CH₂, 4–CH₂–CH₂–N), 56.1 (CH₂, 2H, 1–CH₂–CH₃), 58.1 (CH₂, 1–CH₂–CH₃), 127.1 (CH, propargyl CH), 150.1 (C, C6), 160.6 (CO, triazol).
1–CH$_2$–Ph), 72.6 (C, propargyl C), 81.7 (CH, propargyl CH), 126.1 (CH, C5), 129.6 (2CH), 130.0 (CH), 130.1 (2CH) (Ph–CH), 135.6 (C, Ph–C1), 142.6 (C, C4); HRMS (ESI), calcd for (C$_{13}$H$_{18}$N$_4$ + H$^+$) 255.1604, found 255.1607.

4.1.26. **N-Methyl-N-[2-(1-phenethyl-1H-1,2,3-triazol-4-yl)ethyl]-N-propargylamine 34**

It was prepared as described for 31. From amine 28 (384 mg, 1.67 mmol), Cs$_2$CO$_3$ (543 mg, 1.67 mmol), and propargyl bromide (80% solution in toluene, 0.25 mL, 1.68 mmol), and stirring at rt for 3 h, an oily residue (451 mg) was obtained and subjected to purification through column chromatography (40–60 µm silica gel, CH$_2$Cl$_2$ / MeOH mixtures, gradient elution). On elution with CH$_2$Cl$_2$ / MeOH 98:2, propargylamine 35 (195 mg, 39% yield) was isolated as a colorless oil; $R_f$ 0.48 (CH$_2$Cl$_2$ / MeOH 9.75:0.25).

34·HCl: brown solid, mp 157–159 °C; IR (ATR) v 3500–2300 (max at 3471, 3369, 3203, 3094, 3059, 3023, 2925, 2842, 2584, 2532, 34 MeOH / 50% aq. NH$_4$OH 9.5:0.5:0.05).

34·HCl: brown solid, mp 157–159 °C; IR (ATR) v 3500–2300 (max at 3471, 3369, 3203, 3094, 3059, 3023, 2925, 2842, 2584, 2532, 34 MeOH / 50% aq. NH$_4$OH 9.5:0.5:0.05).

34·HCl: brown solid, mp 157–159 °C; IR (ATR) v 3500–2300 (max at 3471, 3369, 3203, 3094, 3059, 3023, 2925, 2842, 2584, 2532, 34 MeOH / 50% aq. NH$_4$OH 9.5:0.5:0.05).

34·HCl: brown solid, mp 157–159 °C; IR (ATR) v 3500–2300 (max at 3471, 3369, 3203, 3094, 3059, 3023, 2925, 2842, 2584, 2532, 34 MeOH / 50% aq. NH$_4$OH 9.5:0.5:0.05).

34·HCl: brown solid, mp 157–159 °C; IR (ATR) v 3500–2300 (max at 3471, 3369, 3203, 3094, 3059, 3023, 2925, 2842, 2584, 2532, 34 MeOH / 50% aq. NH$_4$OH 9.5:0.5:0.05).

34·HCl: brown solid, mp 157–159 °C; IR (ATR) v 3500–2300 (max at 3471, 3369, 3203, 3094, 3059, 3023, 2925, 2842, 2584, 2532, 34 MeOH / 50% aq. NH$_4$OH 9.5:0.5:0.05.)
J = 2.8 Hz, 2H, propargyl CH₂), 4.57 (s, 2H, 4–CH₂–N), 4.86 (s, ¹NH), 5.66 (s, 2H, 1–CH₂–Ph), 7.32–7.41 (complex signal, 5H, Ph–CH), 8.27 (s, 1H, 5–H); ¹³C NMR (100.6 MHz, CD₃OD) δ 40.2 (CH₃, N–CH₃), 45.7 (CH₂, propargyl CH₂), 50.3 (CH₂, 4–CH₂–N), 55.1 (CH₂, 1–CH₂–Ph), 72.9 (C, propargyl C), 81.6 (CH, propargyl CH), 128.1 (CH, C5), 129.3 (2CH), 129.7 (CH), 130.1 (2CH) (Ph–CH), 136.5 (C, Ph–C1), 137.9 (C, C4); HRMS (ESI), calcd for (C₁₄H₁₆N₄ + H⁺) 241.1448, found 241.1444.

4.1.28. N-Methyl-N-[(1-phenethyl-1H-1,2,3-triazol-4-yl)methyl]-N-propargylamine 36

It was prepared as described for 31. From amine 30 (258 mg, 1.19 mmol), Cs₂CO₃ (199 mg, 0.61 mmol), and propargyl bromide (80% solution in toluene, 0.17 mL, 1.14 mmol), and stirring at rt for 3 h, an oily residue (204 mg) was obtained and subjected to purification through column chromatography (40–60 μm silica gel, CH₂Cl₂ / EtOAc mixtures, gradient elution). On elution with CH₂Cl₂ / EtOAc 0:100, propargylamine 36 (63 mg, 22% yield) was isolated as a colorless oil; Rf 0.26 (EtOAc).

36·HCl: beige sticky solid, IR (ATR) ν 3500–2300 (max at 3400, 3271, 3209, 3023, 2945, 2501, ¹N–H, =C–H, and C–H), 2124 (C≡C) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 2.88 (s, 3H, N–CH₃), 3.25 (t, J = 7.2 Hz, 2H, 1–CH₂–CH₂–Ph), 3.42 (t, J = 2.4 Hz, 1H, propargyl CH), 4.02 (br s, 2H, propargyl CH₂), 4.51 (s, 2H, 4–CH₂–N), 4.73 (t, J = 7.2 Hz, 2H, 1–CH₂–CH₂–Ph), 4.90 (s, ¹NH), 7.14 [dm, J = 8.4 Hz, 2H, Ph–C2(6)–H], 7.17–7.29 [complex signal, 3H, Ph–C3(5)–H, Ph–C4–H], 8.02 (s, 1H, 5–H); ¹³C NMR (100.6 MHz, CD₃OD) δ 37.3 (CH₂, 1–CH₂–CH₂–Ph), 40.1 (CH₃, N–CH₃), 45.5 (CH₂, propargyl CH₂), 50.2 (CH₂, 4–CH₂–N), 52.8 (CH₂, 1–CH₂–CH₂–Ph), 72.8 (C, propargyl C), 81.7 (CH, propargyl CH), 128.0 (CH), 128.4 (CH) (C5, Ph–C4), 129.7 (2CH), 129.9 (2CH) (Ph–C2(6), Ph–C3(5)), 137.0 (C, Ph–C1), 138.6 (C, C4); HRMS (ESI), calcd for (C₁₃H₁₄N₄ + H⁺) 255.1604, found 255.1601.

4.1.29. N-(tert-Butoxycarbonyl)-N-[(1-ethyl-5-methyl-1H-1,2,3-triazol-4-yl)methyl]-N-methylamine 37

A solution of 17 (420 mg, 1.75 mmol) in anhydrous THF (30 mL) was cooled to −78 °C and then treated with n-BuLi (2.5 M solution in hexanes, 1.05 mL, 2.62 mmol) and iodomethane (0.43 mL, 980 mg, 6.91 mmol). The reaction mixture was stirred at −78 °C for 1 h, then warmed to rt and stirred an additional 2 h. The resulting solution was diluted with H₂O (20 mL) and extracted with CH₂Cl₂ (2 × 40 mL). The combined
organic extracts were dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The resulting residue was washed with pentane (3 x 10 mL) and dried under vacuum, to give compound 37 (427 mg, 96% yield) as a colorless oil; Rf 0.57 (CH₂Cl₂ / MeOH 9:1); IR (ATR) ν 1686 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.46 [s, 9H, C(CH₃)₃], superimposed in part 1.47 (t, J = 7.6 Hz, 3H, 1–CH₂–CH₃), 2.31 (s, 3H, 5–CH₃), 2.85 (s, 3H, N–CH₃), 4.26 (q, J = 7.6 Hz, 2H, 1–CH₂–CH₃), 4.48 (s, 2H, 4–CH₂–N); ¹³C NMR (100.6 MHz, CDCl₃) δ 7.8 (CH₃, 5–CH₃), 15.2 (CH₃, 1–CH₂–CH₃), 28.5 [3CH₃, C(CH₃)₃], 34.0 (CH₃, N–CH₃), 42.7 (CH₂, 4–CH₂–N), 43.1 (CH₂, 1–CH₂–CH₃), 79.8 [C, C(CH₃)₃], 130.5 (C, C₅), 142.0 (C, C₄), 156.0 (C, NCOO); HRMS (ESI), calcd for (C₁₂H₂₂N₄O₂ + H⁺) 255.1816, found 255.1811.

4.1.30. N-(tert-Butoxycarbonyl)-N-[2-(1-ethyl-5-methyl-1H-1,2,3-triazol-4-yl)ethyl]-N-methylamine 38

It was prepared as described for 37. From 18 (942 mg, 3.71 mmol), n-BuLi (2.5 M solution in hexanes, 2.97 mL, 7.42 mmol) and iodomethane (0.92 mL, 2.10 g, 14.8 mmol), compound 38 (895 mg, 90% yield) was obtained as a colorless oil; Rf 0.57 (CH₂Cl₂ / MeOH 9:1); IR (ATR) ν 1685 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.40 [s, 9H, C(CH₃)₃], 1.44 (t, J = 7.6 Hz, 3H, 1–CH₂–CH₃), 2.20 (s, 3H, 5–CH₃), 2.77 (s, 3H, N–CH₃), 2.82 (m, 2H, 4–CH₂–CH₂–N), 3.43 (t, J = 7.2 Hz, 4–CH₂–CH₂–N), 4.23 (q, J = 7.6 Hz, 2H, 1–CH₂–CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 7.7 (CH₃, 5–CH₃), 15.3 (CH₃, 1–CH₂–CH₃), 23.7 (br CH₂), 24.1 (br CH₂) (4–CH₂–CH₂–N), 28.5 [3CH₃, C(CH₃)₃], 34.7 (br CH₃), 35.0 (br CH₃) (N–CH₃), 43.0 (CH₂, 1–CH₂–CH₃), 48.7 (br CH₂), 49.2 (br CH₂) (4–CH₂–CH₂–N), 79.4 [C, C(CH₃)₃], 129.2 (br C), 129.4 (br C) (C₅), 142.2 (C, C₄), 155.7 (C, NCOO); HRMS (ESI), calcd for (C₁₃H₂₄N₄O₂ + H⁺) 269.1972, found 269.1974.

4.1.31. N-(tert-Butoxycarbonyl)-N-methyl-N-[2-[5-methyl-1-(α-methyl)benzyl-1H-1,2,3-triazol-4-yl]ethyl]amine 39

It was prepared as described for 37. From 19 (356 mg, 1.13 mmol), n-BuLi (2.5 M solution in hexanes, 0.90 mL, 2.25 mmol) and iodomethane (0.28 mL, 638 mg, 4.50 mmol), compound 39 (306 mg, 79% yield) was obtained as a yellowish oil; IR (ATR) ν 1686, 1681 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.41 [s, 9H, C(CH₃)₃], 2.019 [d, J = 7.2 Hz, 3H, 1–CH(CH₃)–Ph], 2.023 (s, 3H, 5–CH₃), 2.76 (s, 3H, N–CH₃), 2.81 (m,
2H, 4–CH₂–CH₂–N), 3.47 (m, 2H, 4–CH₂–CH₂–N), 5.49 [q, J = 7.2 Hz, 1H, 1–CH(CH₃)–Ph], 7.14 [br d, J = 7.2 Hz, Ph–C2(6)–H], 7.24–7.34 [complex signal, 3H, Ph–C3(5)–H, Ph–C4–H]; HRMS (ESI), caleed for \((\text{C}_{19}\text{H}_{38}\text{N}_{2}\text{O}_{2} + \text{H}^+)\) 345.2285, found 345.2285.

4.1.32. N-(tert-Butoxycarbonyl)-N-\{(5-butyl-1-methyl-1H-1,2,3-triazol-4-yl)methyl\}-N-methylamine 40

It was prepared as described for 37. From 21 (945 mg, 4.18 mmol), n-BuLi (2.5 M solution in hexanes, 3.36 mL, 8.40 mmol) and 1-bromobutane (1.81 mL, 2.31 g, 16.9 mmol), compound 40 (1.14 g, 97% yield) was obtained as a yellowish oil; \(R_f\) 0.87 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:0.5:0.05); IR (ATR) \(v\) 1689 (C=O) cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 0.92 (t, \(J = 7.2\) Hz, 3H, 5–CH₂–CH₂–CH₂–CH₃), 1.35 (tq, \(J = J' = 7.2\) Hz, 2H, 5–CH₂–CH₂–CH₂–CH₃), superimposed 1.40–1.52 (2H, 5–CH₂–CH₂–CH₂–CH₃), 1.44 [s, 9H, C(CH₃)₃], 2.69 (m, 2H, 5–CH₂–CH₂–CH₂–CH₃), 2.81 (s, 3H, N–CH₃), 3.93 (s, 3H, 1–CH₃), 4.49 (s, 2H, 4–CH₂–N); HRMS (ESI), caleed for \((\text{C}_{14}\text{H}_{26}\text{N}_{4}\text{O}_{2} + \text{H}^+)\) 283.2129; found 283.2123.

4.1.33. N-(tert-Butoxycarbonyl)-N-methyl-N-\{(2-ethyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethyl\}amine 41

It was prepared as described for 37. From 22 (542 mg, 1.79 mmol), n-BuLi (2.5 M solution in hexanes, 1.43 mL, 3.57 mmol) and bromoethane (0.53 mL, 774 mg, 7.10 mmol), compound 41 (578 mg, 98% yield) was obtained as a yellowish oil; \(R_f\) 0.86 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05); IR (ATR) \(v\) 1688, 1683 (C=O) cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 1.05 (t, \(J = 7.6\) Hz, 3H, 5–CH₂–CH₃), 1.45 [s, 9H, C(CH₃)₃], 2.70 (m, 2H, 5–CH₂–CH₃), 2.88 (s, 3H, N–CH₃), 2.93 (m, 2H, 4–CH₂–CH₂–N), 3.58 (t, \(J = 7.6\) Hz, 2H, 4–CH₂–CH₂–N), 7.42 [ddm, \(J = 8.0\) Hz, \(J' = 2.4\) Hz, 2H, Ph–C2(6)–H], 7.48–7.57 [complex signal, 3H, Ph–C3(5)–H, Ph–C4–H]; HRMS (ESI), caleed for \((\text{C}_{18}\text{H}_{36}\text{N}_{4}\text{O}_{2} + \text{H}^+)\) 331.2129; found 331.2128.

4.1.34. N-(tert-Butoxycarbonyl)-N-methyl-N-\{(1-phenyl-5-propyl-1H-1,2,3-triazol-4-yl)ethyl\}amine 42

It was prepared as described for 37. From 22 (577 mg, 1.91 mmol), n-BuLi (2.5 M solution in hexanes, 1.53 mL, 3.82 mmol) and 1-bromopropane (0.69 mL, 934 mg, 7.60
mmol), compound 42 (634 mg, 96% yield) was obtained as an orange oil; \( R_f \) 0.84 (CH\(_2\)Cl\(_2\) / MeOH / 50% aq. NH\(_4\)OH 9:1:0.05); IR (ATR) \( \nu \) 1692, 1682 (C=O) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.82 (t, \( J = 7.6 \) Hz, 3H, 5–CH\(_2\)–CH\(_2\)–CH\(_3\)), superimposed in part 1.42 (tt, \( J = J' = 7.6 \) Hz, 2H, 5–CH\(_2\)–CH\(_2\)–CH\(_2\)–CH\(_3\)), 1.46 [s, 9H, C(CH\(_3\))\(_3\)], 2.63 (m, 2H, 5–CH\(_2\)–CH\(_2\)–CH\(_3\)), 2.88 (s, 3H, N–CH\(_3\)), 2.93 (m, 2H, 4–CH\(_2\)–CH\(_2\)–N), 3.59 (t, \( J = 7.2 \) Hz, 2H, 4–CH\(_2\)–CH\(_2\)–N), 7.41 [ddm, \( J = 8.0 \) Hz, \( J' = 2.4 \) Hz, 2H, Ph–C(2)(6)–H], 7.48–7.56 [complex signal, 3H, Ph–C(3)(5)–H, Ph–C(4)–H]; HRMS (ESI), calcd for \((\text{C}_{19}\text{H}_{28}\text{N}_{4}\text{O}_{2} + \text{H}^+)\) 354.2285, found 354.2286.

4.1.35. \( N\)-(tert-Butoxycarbonyl)-N-methyl-\( N\)-[2-(5-butyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethyl]amine 43

It was prepared as described for 37. From 22 (590 mg, 1.95 mmol), n-BuLi (2.5 M solution in hexanes, 1.56 mL, 3.90 mmol) and 1-bromobutane (0.84 mL, 1.07 g, 7.82 mmol), an oily residue (678 mg) was obtained. After column chromatography purification of the residue (40–60 \( \mu \)m silica gel, CH\(_2\)Cl\(_2\) / 50% aq. NH\(_4\)OH 100:0.2), compound 43 (300 mg, 43% yield) was isolated as a yellow oil; \( R_f \) 0.82 (CH\(_2\)Cl\(_2\) / MeOH / 50% aq. NH\(_4\)OH 9:1:0.05); IR (ATR) \( \nu \) 1692 (C=O) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.82 (t, \( J = 7.2 \) Hz, 3H, 5–CH\(_2\)–CH\(_2\)–CH\(_2\)–CH\(_3\)), 1.21 (tq, \( J = J' = 7.2 \) Hz, 2H, 5–CH\(_2\)–CH\(_2\)–CH\(_2\)–CH\(_3\)), 1.35 (m, 2H, 5–CH\(_2\)–CH\(_2\)–CH\(_2\)–CH\(_3\)), 1.45 [s, 9H, C(CH\(_3\))\(_3\)], 2.65 (m, 2H, 5–CH\(_2\)–CH\(_2\)–CH\(_2\)–CH\(_3\)), 2.87 (s, 3H, N–CH\(_3\)), 2.91 (m, 2H, 4–CH\(_2\)–CH\(_2\)–N), 3.59 (t, \( J = 7.6 \) Hz, 2H, 4–CH\(_2\)–CH\(_2\)–N), 7.41 [ddm, \( J = 8.0 \) Hz, \( J' = 2.4 \) Hz, 2H, Ph–C(2)(6)–H], 7.47–7.56 [complex signal, 3H, Ph–C(3)(5)–H, Ph–C(4)–H]; HRMS (ESI), calcd for \((\text{C}_{20}\text{H}_{30}\text{N}_{4}\text{O}_{2} + \text{H}^+)\) 359.2442, found 359.2438.

4.1.36. \( N\)-[1-Ethyl-5-methyl-1H-1,2,3-triazol-4-yl)methyl]-N-methylamine 44

It was prepared as described for 25. From 37 (370 mg, 1.46 mmol) and H\(_3\)PO\(_4\) (85% purity, 2.52 mL, 21.9 mmol), and stirring at rt for 4 h, amine 44 (205 mg, 91% yield) was obtained as a colorless oil; \( R_f \) 0.11 (CH\(_2\)Cl\(_2\) / MeOH / 50% aq. NH\(_4\)OH 9:1:0.05). 44·HCl: beige sticky solid, IR (ATR) \( \nu \) 3500–2400 (max at 3390, 2925, 2868, 2837, 2757, 2697, 2546, 2440, \(^{13}\)N–H and C–H) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CD\(_3\)OD) \( \delta \) 1.48 (t, \( J = 7.2 \) Hz, 3H, 1–CH\(_2\)–CH\(_3\)), 2.41 (s, 3H, 5–CH\(_3\)), 2.76 (s, 3H, N–CH\(_3\)), 4.28 (s, 2H, 4–CH\(_2\)–N), 4.38 (q, \( J = 7.2 \) Hz, 2H, 1–CH\(_2\)–CH\(_3\)), 4.87 (s, \(^{13}\)NH\(_2\)); \(^{13}\)C NMR (100.6 MHz, CD\(_3\)OD) \( \delta \) 7.7 (CH\(_3\), 5–CH\(_3\)), 15.2 (CH\(_3\), 1–CH\(_2\)–CH\(_3\)), 33.1 (CH\(_3\), N–CH\(_3\)), 43.6
(CH₂), 44.4 (CH₂) (1–CH₂–CH₃, 4–CH₂–N), 134.7 (C, C₅), 136.8 (C, C₄); HRMS (ESI), calea for (C₇H₁₄N₄ + H⁺) 155.1291, found 155.1288.

4.1.37. N-[2-(1-Ethyl-5-methyl-1H-1,2,3-triazol-4-yl)ethyl]-N-methylamine 45
It was prepared as described for 25. From 38 (890 mg, 3.32 mmol) and H₃PO₄ (85% purity, 5.70 mL, 49.4 mmol), and stirring at rt for 1.5 h, amine 45 (495 mg, 89% yield) was obtained as a colorless oil; Rf 0.10 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).
45·HCl: beige sticky solid, IR (ATR) ν 3500–2300 (max at 3374, 2981, 2937, 2746, 2692, 2449, 2359, 1N–H and C–H st) cm⁻¹; ¹H NMR (400 MHz, CD₂OD) δ 1.49 (t, J = 7.2 Hz, 3H, 1–CH₂–CH₃), 2.38 (s, 3H, 5–CH₃), 2.76 (s, 3H, N–CH₃), 3.09 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 3.34 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 4.40 (q, J = 7.2 Hz, 2H, 1–CH₂–CH₃), 4.86 (s, ¹NH₂); ¹³C NMR (100.6 MHz, CD₂OD) δ 7.6 (CH₃, 5–CH₃), 15.0 (CH₃, 1–CH₂–CH₃), 22.2 (CH₂, 4–CH₂–CH₂–N), 33.7 (CH₃, N–CH₃), 44.9 (CH₂, 1–CH₂–CH₃), 49.0 (4–CH₂–CH₂–N), 133.4 (C, C₅), 140.1 (C, C₄); HRMS (ESI), calea for (C₈H₁₆N₄ + H⁺) 169.1448, found 169.1452.

4.1.38. N-Methyl-N-{2-[5-methyl-1-(α-methyl)benzyl-1H-1,2,3-triazol-4-yl]ethyl}amine 46
It was prepared as described for 25. From 39 (306 mg, 0.89 mmol) and H₃PO₄ (85% purity, 1.60 mL, 13.9 mmol), amine 46 (215 mg, quantitative yield) was obtained as a yellow oil; Rf 0.33 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).
46·HCl: yellow sticky solid, IR (ATR) ν 3400–2400 (max at 3373, 2950, 2709, 2434, 1N–H and C–H) cm⁻¹; ¹H NMR (400 MHz, CD₂OD) δ 2.01 [d, J = 7.2 Hz, 3H, 1–CH(CH₃)–Ph], 2.30 (s, 3H, 5–CH₃), 2.76 (s, 3H, N–CH₃), 3.19 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 3.36 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 4.94 (s, ¹NH₂), 5.93 (q, J = 7.2 Hz, 1H, 1–CH(CH₃)–Ph), 7.30 [dm, J = 8.4 Hz, 2H, Ph–C₂(6–H)], 7.36–7.42 [complex signal, 3H, Ph–C₃(5–H), Ph–C₄(4–H)]; ¹³C NMR (100.6 MHz, CD₂OD) δ 8.2 (CH₃, 5–CH₃), 21.7 [CH₃, 1–CH(CH₃)–Ph], 21.9 (CH₂, 4–CH₂–CH₂–N), 33.7 (CH₃, N–CH₃), 53.8 (CH₂, 4–CH₂–CH₂–N), 61.5 [CH, 1–CH(CH₃)–Ph], 127.5 (2CH), 129.7 (CH), 130.2 (2CH) (Ph–CH), 135.6 (C, Ph–C₁), 139.3 (C, C₅), 140.5 (C, C₄); HRMS (ESI), calea for (C₁₄H₂₀N₄ + H⁺) 245.1761, found 245.1762.

4.1.39. N-[(5-Butyl-1-methyl-1H-1,2,3-triazol-4-yl)methyl]-N-methylamine 47
It was prepared as described for 25. From 40 (954 mg, 3.38 mmol) and H₃PO₄ (85% purity, 5.84 mL, 50.7 mmol), amine 47 (620 mg, quantitative yield) was obtained as a yellow oil; Rf 0.06 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05).

47·HCl: beige sticky solid, IR (ATR) ν 3400–2500 (max at 3372, 2957, 2930, 2863, 2711, 7.2 N–H and C–H) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 0.97 (t, J = 7.2 Hz, 3H, 5–CH₂–CH₂–CH₂–CH₃), 1.42 (tq, J = J’ = 7.2 Hz, 2H, 5–CH₂–CH₂–CH₂–CH₃), 2.79 (s, 3H, N–CH₃), 2.87 (t, J = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₂–CH₃), 4.05 (s, 3H, 1–CH₃), 4.31 (s, 2H, 4–CH₂–N), 5.06 (s, ¹NH₃); ¹³C NMR (100.6 MHz, CD₃OD) δ 14.0 (CH₃, 5–CH₂–CH₂–CH₂–CH₃), 22.9 (CH₂), 23.4 (CH₂) (5–CH₂–CH₂–CH₂–CH₃), 31.6 (CH₂, 5–CH₂–CH₂–CH₂–CH₃), 33.3 (CH₃, N–CH₃), 35.5 (CH₃, 1–CH₃) HRMS (ESI), calcd for (C₉H₁₈N₄ + H⁺) 183.1604, found 183.1599.

4.1.40. N-Methyl-N-[2-(5-ethyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethyl]amine 48

It was prepared as described for 25. From 41 (517 mg, 1.57 mmol) and H₃PO₄ (85% purity, 2.68 mL, 23.2 mmol), and stirring at rt for 3 h, an orange oil (435 mg) was obtained and purified through column chromatography (40–60 µm silica gel, CH₂Cl₂ / MeOH / 50% aq. NH₄OH mixtures, gradient elution). On elution with CH₂Cl₂ / MeOH / 50% aq. NH₄OH 98:2:0.2 to 96:4:0.2, amine 48 (322 mg, 89% yield) was obtained as a yellowish oil; Rf 0.51 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).

48·HCl: yellow sticky solid, IR (ATR) ν 3400–2300 (max at 3380, 2964, 2930, 2873, 2741, 2434, 2351, 7.2 N–H and C–H) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 1.05 (t, J = 7.6 Hz, 3H, 5–CH₂–CH₃), superimposed in part 2.80 (q, J = 7.6 Hz, 2H, 5–CH₂–CH₃), 2.81 (s, 3H, N–CH₃), 3.20 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 3.45 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 4.89 (s, ¹NH₂), 7.53 [ddm, J = 7.6 Hz, J’ = 2.0 Hz, 2H, Ph–C(6)–H], 7.62–7.67 [complex signal, 3H, Ph–C(3,5)–H, Ph–C(4–6)–H]; ¹³C NMR (100.6 MHz, CD₃OD) δ 13.4 (CH₃, 5–CH₂–CH₃), 16.9 (CH₂, 5–CH₂–CH₃), 22.5 (CH₂, 4–CH₂–CH₂–N), 33.9 (CH₃, N–CH₃), 49.3 (CH₂, 4–CH₂–CH₂–N), 126.8 (2CH), 130.9 (2CH), 131.4 (CH) (Ph–CH), 137.5 (C, Ph–Cl), 139.1 (C, C₅), 140.5 (C, C₄); HRMS (ESI), calcd for (C₁₃H₁₈N₄ + H⁺) 231.1604; found 231.1607.

4.1.41. N-Methyl-N-[2-(1-phenyl-5-propyl-1H-1,2,3-triazol-4-yl)ethyl]amine 49
It was prepared as described for 25. From 42 (573 mg, 1.66 mmol) and H₃PO₄ (85% purity, 2.85 mL, 24.7 mmol), and stirring at rt for 3 h, an orange oil (564 mg) was obtained and purified through column chromatography (40–60 μm silica gel, CH₂Cl₂ / MeOH / 50% aq. NH₄OH mixtures, gradient elution). On elution with CH₂Cl₂ / MeOH / 50% aq. NH₄OH 99:1:0.2 to 95:5:0.2, amine 49 (270 mg, 67% yield) was obtained as a yellowish oil; Rf 0.52 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).

49·HCl: yellow sticky solid, IR (ATR) ν 3400–2400 (max at 3350, 2960, 2935, 2863, 2721, 2430, 1 5-N–H and C–H) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 0.81 (t, J = 7.6 Hz, 3H, 5–CH₂–CH₂–CH₃), 1.42 (tq, J = J’ = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₃), 2.74 (t, J = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₃), 2.80 (s, 3H, N–CH₃), 3.16 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 3.43 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 4.85 (s, ³¹NH₂), 7.48–7.65 (complex signal, 5H, Ph–CH); ¹³C NMR (100.6 MHz, CD₃OD) δ 13.9 (CH₃, 5–CH₂–CH₂–CH₃), 22.6 (CH₂, 4–CH₂–CH₂–N), 22.9 (CH₂, 5–CH₂–CH₂–CH₃), 25.2 (CH₂, 5–CH₂–CH₂–CH₃), 33.8 (CH₃, N–CH₃), 49.4 (CH₂, 4–CH₂–CH₂–N) 126.8 (2CH), 130.9 (2CH), 131.3 (CH) (Ph–CH), 137.4 (C, Ph–C1), 137.7 (C, C5), 141.3 (C, C4); HRMS (ESI), caled for (C₁₄H₂₀N₄+H⁺) 245.1761, found 245.1761.

4.1.42. N-Methyl-N-[2-(5-butyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethyl]amine 50

It was prepared as described for 25. From 43 (265 mg, 0.74 mmol) and H₃PO₄ (85% purity, 1.27 mL, 11.0 mmol), and stirring at rt for 3 h, amine 50 (175 mg, 92% yield) was obtained as a yellowish oil; Rf 0.54 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).

50·HCl: yellow oil, IR (ATR) ν 3400–2400 (max at 3389, 2954, 2919, 2868, 2755, 2444, ¹N–H and C–H) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 0.80 (t, J = 7.6 Hz, 3H, 5–CH₂–CH₂–CH₂–CH₃), 1.22 (tq, J = J’ = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₂–CH₃), 1.38 (tt, J = J’ = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₂–CH₃), 2.77 (t, J = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₂–CH₃), 2.81 (s, 3H, N–CH₃), 3.15 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 3.44 (t, J = 7.2 Hz, 2H, 4–CH₂–CH₂–N), 4.85 (s, ³¹NH₂), 7.51 [dm, J = 8.0 Hz, 2H, Ph–C2(6)–H], 7.61–7.66 [complex signal, 3H, Ph–C3(5)–H, Ph–C4–H]; ¹³C NMR (100.6 MHz, CD₃OD) δ 13.8 (CH₃, 5–CH₂–CH₂–CH₂–CH₃), 22.6 (CH₂, 4–CH₂–CH₂–N), 23.0 (CH₂), 23.2 (CH₂) (5–CH₂–CH₂–CH₂–CH₃), 31.6 (CH₂, 5–CH₂–CH₂–CH₂–CH₃), 33.8 (CH₃, N–CH₃), 49.4 (CH₂, 4–CH₂–CH₂–N), 126.8
(2CH), 130.9 (2CH), 131.3 (CH) (Ph–CH), 137.5 (C, Ph–C1), 137.7 (C, C5), 141.2 (C, C4); HRMS (ESI), calcd for (C13H22N4 + H+) 259.1917, found 259.1922.

4.1.43. N-[(1-Ethyl-5-methyl-1H-1,2,3-triazol-4-yl)methyl]-N-methyl-N-propargylamine 51

It was prepared as described for 31. From amine 44 (128 mg, 0.83 mmol), Cs₂CO₃ (270 mg, 0.83 mmol), and propargyl bromide (80% solution in toluene, 0.12 mL, 0.81 mmol), and stirring at 0 °C for 2 h, propargylamine 51 (96 mg, 62% yield) was obtained as a yellow oil, without the need of chromatographic purification; Rf 0.34 (CH₂Cl₂/MeOH/50% aq. NH₄OH 9:1:0.05).

51·HCl: yellow sticky solid, IR (ATR) ν 3500–2300 (max at 3386, 3197, 2938, 2496, 2352, NH, C–H, and C–H), 2123 (C≡C) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 1.50 (t, J = 7.2 Hz, 3H, 1–CH₂C₃H₃), 2.45 (s, 3H, 5–CH₃), 3.00 (s, 3H, N–CH₃), 3.44 (t, J = 2.4 Hz, 1H, propargyl CH), 4.17 (d, J = 2.4 Hz, 2H, propargyl CH₂), 4.39 (q, J = 7.2 Hz, 2H, 1–CH₂C₃H₃), 4.52 (s, 2H, 4–CH₂–N), 4.84 (s, NH); ¹³C NMR (100.6 MHz, CD₃OD) δ 8.0 (CH₃, 5–CH₃), 15.2 (CH₃, 1–CH₂–CH₃), 40.3 (CH₃, N–CH₃), 44.5 (CH₂, 1–CH₂–CH₃), 45.6 (CH₂, propargyl CH₂), 49.8 (CH₂, 4–CH₂–N), 73.1 (C, propargyl C), 81.5 (CH, propargyl CH), 135.1 (C, C5), 136.3 (C, C4); HRMS (ESI), calcd for (C₁₀H₁₆N₄ + H⁺) 193.1448, found 193.1450.

Note: From amine 44 (117 mg, 0.76 mmol), Cs₂CO₃ (362 mg, 1.11 mmol), and propargyl bromide (80% solution in toluene, 0.16 mL, 1.08 mmol), and stirring at rt overnight, an oily residue was obtained and purified through column chromatography (40–60 µm silica gel, CH₂Cl₂/MeOH/50% aq. NH₄OH mixtures, gradient elution). On elution with CH₂Cl₂/MeOH/50% aq. NH₄OH 99:1:0.2 to 98:2:0.2, propargylamine 51 (15 mg, 10% yield) was isolated as a colorless oil. On elution with CH₂Cl₂/MeOH/50% aq. NH₄OH 98:2:0.2, slightly impure N-[(1-ethyl-5-methyl-1H-1,2,3-triazol-4-yl)methyl]-N-methyl-N,N-dipropargylammonium bromide (223 mg) was isolated as a brown oil; Rf 0.04 (CH₂Cl₂/MeOH/50% aq. NH₄OH 9:1:0.05).

A solution of the dipropargylated byproduct (223 mg) in CH₂Cl₂ (20 mL) was filtered through a PTFE filter (0.2 µm) and evaporated under reduced pressure. The resulting residue was washed with pentane (3 × 2 mL) to give, after drying under standard conditions, the analytical sample of the dipropargylated byproduct (213 mg) as a brownish oil; IR (ATR) ν 3207 (≡C–H), 2124 (C≡C st) cm⁻¹; ¹H NMR (400 MHz,
CDCl₃ δ 1.53 (t, J = 7.6 Hz, 3H, 1–CH₂–CH₃), 2.73 (s, 3H, 5–CH₃), 2.85 (t, J = 2.4 Hz, 2H, 2 propargyl CH), 3.42 (s, 3H, N–CH₃), 4.34 (q, J = 7.6 Hz, 2H, 1–CH₂–CH₃), 4.83 (dd, J = 16.0 Hz, J′ = 2.4 Hz, 2H), 4.91 (dd, J = 16.0 Hz, J′ = 2.4 Hz, 2H) (2 propargyl CH₂), 5.34 (s, 2H, 4–CH₂–N); ¹³C NMR (100.6 MHz, CDCl₃) δ 8.8 (CH₃, 5–CH₃), 14.8 (CH₃, 1–CH₂–CH₃), 43.6 (CH₂, 1–CH₂–CH₃), 47.2 (CH₃, N–CH₃), 51.8 (2CH₂, 2 propargyl CH₂), 55.7 (CH₂, 4–CH₂–N), 70.9 (2C, 2 propargyl C), 82.2 (2CH, 2 propargyl CH), 132.5 (C, C5), 136.5 (C, C4); HRMS (ESI), calcd for (C₁₃H₁₉N₄ + H⁺) 231.1604, found 231.1613.

4.1.44. N-[2-(1-Ethyl-5-methyl-1H-1,2,3-triazol-4-yl)ethyl]–N-methyl-N-propargylamine 52

It was prepared as described for 31. From amine 45 (490 mg, 2.91 mmol), Cs₂CO₃ (952 mg, 2.92 mmol), and propargyl bromide (80% solution in toluene, 0.43 mL, 2.89 mmol), and stirring at 0 ºC for 2.5 h, propargylamine 52 (319 mg, 54% yield) was obtained as a yellow oil, without the need of chromatographic purification; Rf 0.59 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).

52·HCl: yellow sticky solid, IR (ATR) ν 3500–2300 (max at 3406, 3181, 2981, 2932, 2583, 2518, 2461, 2408, 2366, ´N–H, =C–H, and C–H), 2123 (C≡C) cm⁻¹; ¹H NMR (400 MHz, CD₂OD) δ 1.56 (t, J = 7.2 Hz, 3H, 1–CH₂–CH₃), 2.50 (s, 3H, 5–CH₃), 3.08 (s, 3H, N–CH₃), 3.35 (t, J = 7.6 Hz, 2H, 4–CH₂–CH₂–N), 3.45 (t, J = 2.8 Hz, 1H, propargyl CH), 3.63 (t, J = 7.6 Hz, 2H, 4–CH₂–CH₂–N), 4.28 (d, J = 2.8 Hz, 2H, propargyl CH₂), 4.51 (q, J = 7.2 Hz, 2H, 1–CH₂–CH₃), 4.94 (s, ´NH); ¹³C NMR (100.6 MHz, CD₃OD) δ 8.0 (CH₃, 5–CH₃), 14.4 (CH₃, 1–CH₂–CH₃), 20.0 (CH₂, 4–CH₂–CH₂–N), 40.7 (CH₃, N–CH₃), 46.3 (CH₂, propargyl CH₂), 46.4 (CH₂, 1–CH₂–CH₃), 54.0 (CH₂, 4–CH₂–CH₂–N), 72.5 (C, propargyl C), 81.9 (CH, propargyl CH), 136.3 (C, C5), 137.8 (C, C4); HRMS (ESI), calcd for (C₁₁H₁₈N₄ + H⁺) 207.1604, found 207.1609.

4.1.45. N-Methyl-N-[2-(5-methyl-1-((α-methyl)benzyl-1H-1,2,3-triazol-4-yl)ethyl]–N-propargylamine 53

It was prepared as described for 31. From amine 46 (234 mg, 0.93 mmol), Cs₂CO₃ (0.30 g, 0.92 mmol), and propargyl bromide (80% solution in toluene, 0.10 mL, 0.67 mmol), and stirring at 0 ºC for 30 min and at rt for an additional 3 h, an orange oily residue
(263 mg) was obtained and purified through column chromatography (40–60 μm silica gel, CH₂Cl₂ / MeOH / 50% aq. NH₄OH mixtures, gradient elution). On elution with CH₂Cl₂ / MeOH / 50% aq. NH₄OH 99.97:0.03:0.2, propargylamine 53 (100 mg, 53% yield) was obtained as a yellow oil; R₇ 0.45 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).

53·HCl: beige sticky solid, IR (ATR) ν 3400–2300 (max at 3386, 3209, 2936, 2351, 17N–H, =C–H, and C–H), 2118 (C=O) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 2.01 [d, J = 6.8 Hz, 3H, 1–CH(CH₃)–Ph], 2.26 (s, 2H, 5–CH₂), 3.06 (s, 3H, N–CH₃), 3.22 (t, J = 8.0 Hz, 2H, 4–CH₂–CH₂–N), 3.42 (t, J = 2.4 Hz, 1H, propargyl CH), 3.59 (t, J = 8.0 Hz, 2H, 4–CH₂–CH₂–N), 4.25 (d, J = 2.4 Hz, 2H, propargyl CH₂), 4.89 (s, ¹NH), 5.86 [q, J = 6.8 Hz, 1H, 1–CH(CH₃)–Ph], 7.24–7.40 (complex signal, 5H, Ph–CH); ¹³C NMR (100.6 MHz, CD₃OD) δ 8.1 (CH₃, 5–CH₃), 20.5 (CH₂, 4–CH₂–CH₂–N), 22.0 [CH₃, 1–CH(CH₃)–Ph], 40.7 (CH₃, N–CH₃), 46.3 (CH₂, propargyl CH₂), 54.7 (CH₂, 4–CH₂–CH₂–N), 61.0 [CH, 1–CH(CH₃)–Ph], 72.6 (C, propargyl C), 81.7 (CH, propargyl CH), 127.4 (2CH), 129.6 (CH), 130.2 (2CH) (Ph–CH), 134.5 (C, Ph–C1), 139.6 (C, C5), 141.1 (C, C4); HRMS (ESI), calcd for (C₁₇H₂₂N₄ + H⁺) 283.1917, found 283.1923.

4.1.46. N-{[5-Butyl-1-methyl-1H-1,2,3-triazol-4-yl]methyl}-N-methyl-N-propargylamine 54

It was prepared as described for 31. From amine 47 (529 mg, 2.90 mmol), Cs₂CO₃ (946 mg, 2.90 mmol), and propargyl bromide (80% solution in toluene, 0.44 mL, 2.96 mmol), and stirring at rt for 3.5 h, propargylamine 54 (418 mg, 65% yield) was obtained as a yellow oil, without the need of chromatographic purification; R₇ 0.29 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:5:0:5:0.05).

54·HCl: brown sticky solid, IR (ATR) ν 3500–2400 (max at 3411, 3219, 2955, 2930, 2863, 2491, 17N–H, =C–H, and C–H), 2121 (C=O) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 0.98 (t, J = 7.6 Hz, 3H, 5–CH₂–CH₂–CH₂–CH₃), 1.43 (tq, J = J′ = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₂–CH₃), 1.59 (tt, J = J′ = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₂–CH₃), 2.88 (t, J = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₂–CH₃), 3.03 (s, 3H, N–CH₃), 3.47 (t, J = 2.4 Hz, 1H, propargyl CH), 4.06 (s, 3H, 1–CH₃), 4.22 (d, J = 2.4 Hz, 2H, propargyl CH₂), 4.55 (s, 2H, 4–CH₂–N), 4.92 (s, ¹NH); ¹³C NMR (100.6 MHz, CD₃OD) δ 14.1 (CH₃, 127.4 (2CH), 129.6 (CH), 130.2 (2CH) (Ph–CH), 134.5 (C, Ph–C1), 139.6 (C, C5), 141.1 (C, C4); HRMS (ESI), calcd for (C₁₇H₂₂N₄ + H⁺) 283.1917, found 283.1923.
5--CH2--CH2--CH2--CH3), 23.0 (CH2), 23.4 (CH2) (5--CH2--CH2--CH2--CH3), 31.6 (CH2, 5--CH2--CH2--CH2--CH3), 35.5 (CH3, 1--CH3), 40.5 (CH3, N--CH3), 45.6 (CH2, propargyl CH2), 49.5 (CH2, 4--CH2--N), 73.2 (C, propargyl C), 81.6 (CH, propargyl CH), 134.9 (C, C5), 140.5 (C, C4); HRMS (ESI), calc for (C12H20N4 + H+) 221.1761, found 221.1762.

4.1.47. N-Methyl-N-[2-(5-ethyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethyl]-Npropargylamine 55
It was prepared as described for 31. From amine 48 (260 mg, 1.13 mmol), Cs2CO3 (0.37 g, 1.14 mmol), and propargyl bromide (80% solution in toluene, 0.13 mL, 0.87 mmol), and stirring at 0 ºC for 30 min and at rt for an additional 3 h, an orange oil (333 mg) was obtained and purified through column chromatography (40–60 µm silica gel, CH2Cl2 / MeOH / 50%aq. NH4OH mixtures, gradient elution). On elution with CH2Cl2 / MeOH / 50%aq. NH4OH 99:9:0.1:0.2, propargylamine 55 (222 mg, 95% yield) was obtained as a yellow oil; Rf 0.59 (CH2Cl2 / MeOH / 50%aq. NH4OH 9:1:0.05).

55-HCl: yellow sticky solid, IR (ATR) ν 3400–2300 (max at 3395, 3193, 3059, 2958, 2925, 2573, 2518, 2459, 2397, 753–H, =C–H, and C–H), 2123 (C=C) cm–1; 1H NMR (400 MHz, CD3OD) δ 1.06 (t, J = 7.6 Hz, 3H, 5–CH2–CH3), 2.81 (q, J = 7.6 Hz, 2H, 5–CH2–CH3), 3.11 (s, 3H, N–CH3), 3.27 (t, J = 7.6 Hz, 2H, 4–CH2–CH2–N), 3.45 (t, J = 2.8 Hz, 1H, propargyl CH), 3.70 (m, 2H, 4–CH2–CH2–N), 4.31 (d, J = 2.8 Hz, 2H, propargyl CH2), 4.88 (s, ′NH), 7.53 [ddm, J = J′ = 7.6 Hz, 2H, Ph–C2(6)–H, 7.62–7.67 [complex signal, 3H, Ph–C3(5)–H, Ph–C4–H]; 13C NMR (100.6 MHz, CD3OD) δ 13.4 (CH3, 5–CH2–CH3), 16.9 (CH2, 5–CH2–CH3), 21.1 (CH2, 4–CH2–CH2–N), 40.8 (CH3, N–CH3), 46.3 (CH2, propargyl CH2), 55.3 (CH2, 4–CH2–CH2–N), 72.7 (C, propargyl C), 81.7 (CH, propargyl CH), 126.7 (2CH), 130.9 (2CH), 131.4 (CH) (Ph–CH), 137.6 (C, Ph–C1), 139.1 (C, C5), 140.2 (C, C4); HRMS (ESI), calc for (C16H20N4 + H+) 269.1761; found 269.1766.

4.1.48. N-Methyl-N-[2-(1-phenyl-5-propyl-1H-1,2,3-triazol-4-yl)ethyl]-N-propargylamine 56
It was prepared as described for 31. From amine 49 (168 mg, 0.69 mmol), Cs2CO3 (0.22 g, 0.68 mmol), and propargyl bromide (80% solution in toluene, 0.07 mL, 0.47 mmol), and stirring at 0 ºC for 30 min and at rt for an additional 3 h, an oily residue (278 mg)
was obtained and purified through column chromatography (40–60 μm silica gel, CH₂Cl₂ / MeOH / 50% aq. NH₄OH mixtures, gradient elution). On elution with CH₂Cl₂ / MeOH / 50% aq. NH₄OH 98:2:0.2, propargylamine 56 (117 mg, 88% yield) was obtained as a yellow oil; Rₜ 0.84 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).

56·HCl: orange sticky solid, IR (ATR) ν 3500–2300 (max at 3400, 3197, 2958, 2930, 2873, 2354, 17–H, =C–H, and C–H), 2121 (C≡C) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 0.83 (t, J = 7.6 Hz, 3H, 5–CH₂–CH₂–CH₃), 1.44 (tq, J = J' = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₃), 2.77 (t, J = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₃), 3.11 (s, 3H, N–CH₃), 3.22 (t, J = 7.6 Hz, 2H, 4–CH₂–CH₂–N), 3.45 (d, J = 2.4 Hz, 2H, propargyl CH₂), 4.85 (s, NH), 7.52 (m, 2H), 7.62-7.66 (complex signal, 3H) (Ph–CH); ¹³C NMR (100.6 MHz, CD₃OD) δ 13.9 (CH₃, 5–CH₂–CH₂–CH₃), 21.1 (CH₂, 4–CH₂–CH₂–N), 22.8 (CH₂, 5–CH₂–CH₂–CH₃), 25.2 (CH₂, 5–CH₂–CH₂–CH₃), 40.9 (CH₃, N–CH₃), 46.3 (CH₂, propargyl CH₂), 55.3 (CH₂, 4–CH₂–CH₂–N), 72.7 (C, propargyl C), 81.7 (CH, propargyl CH), 126.8 (2CH), 130.9 (2CH), 131.4 (CH) (Ph–CH), 137.6 (C), 137.7 (C) (C₅, Ph–C₁), 140.7 (C, C₄); HRMS (ESI), calcd for (C₁₇H₂₂N₄ + H⁺) 283.1917, found 283.1923.

4.1.49. N-Methyl-N-[2-(5-butyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethyl]-N-propargylamine 57

It was prepared as described for 31. From amine 50 (157 mg, 0.61 mmol), Cs₂CO₃ (0.22 g, 0.68 mmol), and propargyl bromide (80% solution in toluene, 0.07 mL, 0.47 mmol), and stirring at 0 °C for 30 min and at rt for an additional 3 h, an oily residue (172 mg) was obtained and purified through column chromatography (40–60 μm silica gel, CH₂Cl₂ / MeOH / 50% aq. NH₄OH mixtures, gradient elution). On elution with CH₂Cl₂ / MeOH / 50% aq. NH₄OH 100:0:0.2 to 99:1:0.2, propargylamine 57 (164 mg, 91% yield) was obtained as a yellow oil; Rₜ 0.86 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).

57·HCl: yellow sticky solid, IR (ATR) ν 3500–2300 (max at 3426, 3209, 2962, 2929, 2869, 2352, 17–H, =C–H, and C–H), 2120 (C≡C) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 0.80 (t, J = 7.6 Hz, 3H, 5–CH₂–CH₂–CH₂–CH₃), 1.23 (tq, J = J' = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₂–CH₃), 1.35 (dt, J = J' = 7.6 Hz, 2H, 5–CH₂–CH₂–CH₂–CH₃), 2.78 (t,
\[ J = 7.6 \text{ Hz}, 2\text{H}, 5-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3, 3.11 \ (s, 3\text{H}, \text{N}-\text{CH}_3), 3.22 \ (t, J = 7.6 \text{ Hz}, 2\text{H}, 4-\text{CH}_2-\text{CH}_2-\text{N}), 3.46 \ (t, J = 2.4 \text{ Hz}, 1\text{H}, \text{propargyl CH}), 3.69 \ (m, 2\text{H}, 4-\text{CH}_2-\text{CH}_2-\text{N}), 4.30 \ (d, J = 2.4 \text{ Hz}, 2\text{H}, \text{propargyl CH}_2), 4.85 \ (s, ^1\text{NH}), 7.50 \ (m, 2\text{H}), 7.62-7.66 \ (\text{complex signal, 2H}) \ (\text{Ph}-\text{CH}); ^{13}\text{C} \text{ NMR} (100.6 \text{ MHz}, \text{CD}_3\text{OD}) \delta 13.8 \ (\text{CH}_3, 5-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3), 21.1 \ (\text{CH}_2, 4-\text{CH}_2-\text{CH}_2-\text{N}), 23.1 \ (\text{CH}_2), 23.2 \ (\text{CH}_2) \ (5-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3), 31.6 \ (\text{CH}_2, 5-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3), 40.9 \ (\text{CH}_3, \text{N}-\text{CH}_3), 46.3 \ (\text{CH}_2, \text{propargyl CH}_2), 55.3 \ (\text{CH}_2, 4-\text{CH}_2-\text{CH}_2-\text{N}), 72.7 \ (\text{C}, \text{propargyl C}), 81.7 \ (\text{CH}, \text{propargyl CH}), 126.8 \ (2\text{CH}), 130.9 \ (2\text{CH}), 131.4 \ (\text{CH}) \ (\text{Ph}-\text{CH}), 137.69 \ (\text{C}), 137.72 \ (\text{C}) \ (\text{C}_5, \text{Ph}-\text{C}_1), 140.6 \ (\text{C}, \text{C}_4); \text{HRMS} \ (\text{ESI}), \text{calcd for} \ (\text{C}_{18}\text{H}_{24}\text{N}_4 + \text{H}^+ ) 297.2074, \text{found} 297.2085.

4.1.50. 3-\{3-(\text{Trimethylsilyl})-2-\text{propynyl}\}\text{benzonitrile} \text{61}

A solution of trimethylsilylacetylene (1.59 mL, 1.11 g, 11.3 mmol) in anhydrous THF (22 mL) was cooled to –78 °C, treated dropwise with n-BuLi (2.5 M solution in hexanes, 4.59 mL, 11.5 mmol), and stirred at –78 °C for 30 min. A solution of ZnBr$_2$ (2.59 g, 11.5 mmol) in anhydrous THF (8 mL) was then added and the resulting mixture was warmed to 0 °C. 3-Bromomethylbenzonitrile, \text{58} (1.50 g, 7.65 mmol), and Pd(PPh$_3$)$_2$Cl$_2$ (290 mg, 0.41 mmol) were added and the reaction mixture was stirred at rt overnight. The reaction mixture was cooled to 0 °C, treated with 1 N HCl (20 mL), and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with sat. aq. NaHCO$_3$ (20 mL), dried over anhydrous Na$_2$SO$_4$, and evaporated under reduced pressure to give a residue (2.02 g), which was purified through column chromatography (40–60 µm silica gel, hexane / EtOAc mixtures, gradient elution). On elution with hexane / EtOAc 95:5, compound \text{61} (1.03 g, 63% yield) was isolated as a colorless oil; \text{Rf} 0.73 (hexane / EtOAc 8:2); 2230 (C≡N), 2178 (C≡C) cm$^{-1}$; \text{^1H} \text{NMR} (400 MHz, CDCl$_3$) $\delta$ 0.20 [s, 9H, Si(CH$_3$)$_3$], 3.68 (s, 2H, 1′-H$_2$), 7.42 (dd, $J = J′ = 7.6$ Hz, 1H, 5-H), 7.53 (d, $J = 7.6$ Hz, 1H), 7.57 (d, $J = 7.6$ Hz, 1H) (4-H, 6-H), 7.65 (br s, 1H, 2-H); \text{^{13}C} \text{ NMR} (100.6 MHz, CDCl$_3$) $\delta$ 0.2 [3CH$_3$, Si(CH$_3$)$_3$], 26.0 (CH$_2$, C1′), 88.6 (C, C3′), 102.4 (C, C2′), 112.7 (C, C1), 118.9 (C, CN), 129.4 (CH), 130.6 (CH), 131.6 (CH), 132.5 (CH) (phenylene CH), 138.1 (C, C3); \text{HRMS} \ (\text{ESI}), \text{calcd for} \ (\text{C}_{13}\text{H}_{15}\text{NSi} + \text{H}^+ ) 214.1047, \text{found} 214.1048.

4.1.51. 4-\{3-(\text{Trimethylsilyl})-2-\text{propynyl}\}\text{benzonitrile} \text{62}
It was prepared as described for 61. From trimethylsilylacetylene (1.06 mL, 737 mg, 7.50 mmol), n-BuLi (2.5 M solution in hexanes, 3.06 mL, 7.65 mmol), ZnBr₂ (1.72 g, 7.64 mmol), 4-bromomethylbenzonitrile, 59 (1.00 g, 5.10 mmol), and Pd(PPh₃)₂Cl₂ (183 mg, 0.26 mmol), a residue (1.38 g) was obtained and purified through column chromatography (40–60 µm silica gel, hexane / EtOAc mixtures, gradient elution). On elution with hexane / EtOAc 90:10, compound 62 (900 mg, 83% yield) was isolated as a colorless oil; Rf 0.77 (hexane / EtOAc 8:2); IR (ATR) ν 2230 (C≡N), 2178 (C≡C) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.19 [s, 9H, Si(CH₃)₃], 3.70 (s, 2H, 1'-H₂), 7.46 [dm, J = 8.4 Hz, 2H, 3(5)-H], 7.61 [dm, J = 8.4 Hz, 2H, 2(6)-H]; ¹³C NMR (100.6 MHz, CDCl₃) δ 0.1 [3CH₃, Si(CH₃)₃], 26.5 (CH₂, C1’), 88.6 (C, C3’), 102.3 (C, C2’), 110.8 (C, C1), 119.0 (C, CN), 128.8 [2CH, C3(5)], 132.5 [2CH, C2(6)], 142.1 (C, C4); HRMS (ESI), calcd for (C₁₃H₁₅NSi + H⁺) 214.1047; found 214.1048.

4.1.52. 4-[3-(Trimethylsilyl)-2-propynyl]phenylacetonitrile 63

It was prepared as described for 61. From trimethylsilylacetylene (5.20 mL, 3.61 g, 36.8 mmol), n-BuLi (2.5 M solution in hexanes, 15.0 mL, 37.5 mmol), ZnBr₂ (8.46 g, 37.6 mmol), 4-(bromomethyl)phenylacetonitrile, 60 (5.26 g, 25.0 mmol), and Pd(PPh₃)₂Cl₂ (940 mg, 1.34 mmol), a residue (7.12 g) was obtained and purified through column chromatography (40–60 µm silica gel, hexane / EtOAc mixtures, gradient elution). On elution with hexane / EtOAc 95:5, compound 63 (2.50 g, 4% yield) was isolated as a yellow oil; Rf 0.50 (hexane / EtOAc 8:2); IR (ATR) ν 2344 (C≡N), 2144 (C≡C) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.19 [s, 9H, Si(CH₃)₃], 3.65 (s, 2H, 1'-H₂), 3.73 (s, 2H, 1–CH₂–CN), 7.28 (br d, J = 8.4 Hz, 2H), 7.36 (br d, J = 8.4 Hz, 2H) (Ph–CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 0.03 [3CH₃, Si(CH₃)₃], 23.3 (CH₂, 1–CH₂–CN), 25.8 (CH₂, C1’), 87.3 (C, C3’), 103.6 (C, C2’), 117.8 (C, CN), 128.1 (2CH), 128.6 (2CH) (Ph–CH), 128.2 (C, Ph–C1), 136.5 (C, Ph–C4); HRMS (ESI), calcd for (C₁₄H₁₇NSi + H⁺) 228.1203; found 228.1203.

4.1.53. 3-(2-Propynyl)benzonitrile 64

To a solution of 61 (1.60 g, 7.51 mmol) in CH₂Cl₂ (70 mL), a solution of AgOTf (193 mg, 0.75 mmol) in MeOH / H₂O 11:1 (50 mL) was added. The reaction mixture was stirred at rt for 7 h, treated with an additional amount of AgOTf (386 mg, 1.50 mmol), and stirred at rt overnight. The resulting mixture was diluted with sat. aq. NH₄Cl (50
mL) and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were washed with H₂O (50 mL), dried over anhydrous Na₂SO₄, and evaporated under reduced pressure to give a crude (944 mg), which was purified through column chromatography (40–60 µm silica gel, hexane / EtOAc mixtures, gradient elution). On elution with hexane / EtOAc 95:5, alkyne 64 (690 mg, 65% yield) was isolated as a white solid; Rₜ 0.72 (hexane / EtOAc 8:2), mp 63–65 ºC; IR (ATR) v 3247 (≡C–H), 2231 (C≡N, C≡C) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.26 (t, J = 2.8 Hz, 1H, 3’-H), 3.64 (d, J = 2.8 Hz, 2H, 1’-H₂), 7.43 (dd, J = J’ = 8.0 Hz, 1H, 5-H), 7.54 (dm, J = 8.0 Hz, 1H), 7.58 (dm, J = 8.0 Hz, 1H) (4-H, 6-H), 7.68 (m, 1H, 2-H); ¹³C NMR (100.6 MHz, CDCl₃) δ 24.6 (CH₂, C’), 71.9 (CH, C3’), 80.3 (C, C2’), 112.8 (C, C1), 118.8 (C, CN), 129.4 (CH), 130.7 (CH), 131.5 (CH), 132.5 (CH) (phenylene CH), 137.7 (C, C3); HRMS (ESI), calcd for (C₁₀H₇N + H⁺) 142.0651, found 142.0653.

4.1.54. 4-(2-Propynyl)benzonitrile 65
It was prepared as described for 64. From 62 (642 mg, 3.01 mmol) and AgOTf [(80 mg, 0.31 mmol) × 2], a crude (548 mg) was obtained and purified through column chromatography (40–60 µm silica gel, hexane / EtOAc mixtures, gradient elution). On elution with hexane / EtOAc 80:20, alkyne 65 (346 mg, 81% yield) was isolated as a white solid; Rₜ 0.76 (hexane / EtOAc 8:2), mp 87–89 ºC; IR (ATR) v 3254 (≡C–H), 2230 (C≡N, C≡C) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.25 (t, J = 2.8 Hz, 1H, 3’-H), 3.67 (d, J = 2.8 Hz, 2H, 1’-H₂), 7.48 [dm, J = 8.8 Hz, 2H, 3(5)-H], 7.62 [dm, J = 8.8 Hz, 2H, 2(6)-H]; ¹³C NMR (100.6 MHz, CDCl₃) δ 25.2 (CH₂, C’), 71.9 (CH, C3’), 80.2 (C, C2’), 111.0 (C, C1), 118.9 (C, CN), 128.8 [2CH, C3(5)], 132.5 [2CH, C2(6)], 141.7 (C, C4); HRMS (ESI), calcd for (C₁₀H₇N + H⁺) 142.0651, found 142.0647.

4.1.55. 4-(2-Propynyl)phenylacetonitrile 66
It was prepared as described for 64. From 63 (2.50 g, 11.0 mmol) and AgOTf (280 mg, 1.09 mmol) × 2], a crude (1.79 g) was obtained and purified through column chromatography (40–60 µm silica gel, hexane / EtOAc mixtures, gradient elution). On elution with hexane / EtOAc 95:5, alkyne 66 (1.31 g, 77% yield) was isolated as a white solid; Rₜ 0.41 (hexane / EtOAc 8:2), mp 58–59 ºC; IR (ATR) v 3262 (≡C–H), 2254 (C≡N, C≡C) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.19 (t, J = 2.8 Hz, 1H, 3’-H), 3.57 (br s, 2H, 1’-H₂), 3.69 (s, 2H, 1–CH₂–CN), 7.27 (br d, J = 8.0 Hz, 2H), 7.36 (br d, J =
4.1.58. 3-[(1-Methyl-1H-1,2,3-triazol-4-yl)methyl]benzonitrile 67

It was prepared as described for 9. From iodomethane (0.30 mL, 0.68 g, 4.82 mmol), NaN₃ (342 mg, 5.26 mmol), Na₂CO₃ (1.39 g, 13.1 mmol), ascorbic acid (616 mg, 3.50 mmol), CuSO₄·5H₂O (436 mg, 1.75 mmol), and alkyne 64 (618 mg, 4.38 mmol), compound 67 (823 mg, 95% yield) was obtained as a yellowish solid; Rₚ 0.64 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05); mp 85–87 ºC; IR (ATR) ν 2229 (C≡N) cm⁻¹; 

1H NMR (400 MHz, CDCl₃) δ 4.05 (s, 3H, 1′′-CH₃), 4.09 (br s, 2H, 3–CH₂), 7.25 (s, 1H, 5'-H), 7.39 (dd, J = J' = 8.0 Hz, 1H, 5-H), 7.48–7.53 (complex signal, 3H, 2-H, 4-H, 6-H); 13C NMR (100.6 MHz, CDCl₃) δ 31.7 (CH₃, 3–CH₃), 36.8 (CH₂, 1′–CH₂), 112.7 (C, C1), 118.8 (C, CN), 122.6 (CH, C5'), 129.5 (CH), 130.4 (CH), 132.2 (CH), 133.4 (CH) (phenylene CH), 140.7 (C, C3), 146.1 (C, C4'); HRMS (ESI), calcd for (C₁₁H₁₀N₄ + H⁺) 199.0978, found 199.0980.

4.1.57. 4-[(1-Methyl-1H-1,2,3-triazol-4-yl)methyl]benzonitrile 68

It was prepared as described for 9. From iodomethane (0.17 mL, 0.38 g, 2.70 mmol), NaN₃ (191 mg, 2.94 mmol), Na₂CO₃ (779 mg, 7.35 mmol), ascorbic acid (350 mg, 1.99 mmol), CuSO₄·5H₂O (250 mg, 1.00 mmol), and alkyne 65 (346 mg, 2.45 mmol), compound 68 (459 mg, 95% yield) was obtained as a white solid; Rₚ 0.63 (CH₂Cl₂ / MeOH / 50% aq. NH₂OH 9.5:0.5:0.05); mp 116–118 ºC; IR (ATR) ν 2227 (C≡N) cm⁻¹;

1H NMR (400 MHz, CDCl₃) δ 4.05 (s, 3H, 1′–CH₃), 4.12 (br s, 2H, 4–CH₂), 7.23 (s, 1H, 5'-H), 7.36 [dm, J = 8.4 Hz, 2H, 3(5)-H], 7.57 [dm, J = 8.4 Hz, 2H, 2(6)-H]; 13C NMR (100.6 MHz, CDCl₃) δ 32.3 (CH₂, 4–CH₂), 36.8 (CH₃, 1′–CH₃), 110.6 (C, C1), 118.9 (C, CN), 122.6 (CH, C5'), 129.6 [2CH, C3(5)], 132.5 [2CH, C2(6)], 144.8 (C, C4), 146.1 (C, C4'); HRMS (ESI), calcd for (C₁₁H₁₀N₄ + H⁺) 199.0978, found 199.0978.

4.1.58. 4-[(1-Methyl-1H-1,2,3-triazol-4-yl)methyl]phenylacetonitrile 69

8.0 Hz, 2H) (Ph–CH); 13C NMR (100.6 MHz, CDCl₃) δ 23.2 (CH₂, 1–CH₂–CN), 24.4 (CH₂, C1'), 70.8 (CH, C3'), 81.4 (C, C2'), 117.8 (C, CN), 128.1 (2CH), 128.6 (2CH) (Ph–CH), 128.3 (C, Ph–C1), 136.1 (C, Ph–C4); HRMS (ESI), calcd for (C₁₁H₁₀N₄ + H⁺) 156.0808, found 156.0808.
It was prepared as described for 9. From iodomethane (0.58 mL, 1.32 g, 9.32 mmol), NaN₃ (660 mg, 10.2 mmol), Na₂CO₃ (2.69 g, 25.4 mmol), ascorbic acid (1.19 g, 6.76 mmol), CuSO₄·5H₂O (840 mg, 3.36 mmol), and alkyne 66 (1.31 g, 8.45 mmol), compound 69 (1.60 g, 89% yield) was obtained as a yellow solid; Rₜ 0.93 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05); mp 86–88 ºC; IR (ATR) ν 2241 (C≡N) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.71 (s, 2H, 1–CH₂–CN), 4.02 (s, 3H, 1'–CH₃), 4.06 (s, 2H, 4–CH₂), 7.21 (s, 1H, 5'-H), 7.23–7.30 (complex signal, 4H, Ph–CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 21.3 (CH₂, 1–CH₂–CN), 31.6 (CH₂, 4–CH₂), 36.4 (CH₃, 1'–CH₃), 117.8 (C, CN), 122.3 (CH, C₅'), 128.0 (C, Ph–C1), 128.1 (2CH), 129.2 (2CH) (Ph–CH), 139.0 (C, Ph–C₄), 147.1 (C, C₄'); HRMS (ESI), calcd for (C₁₂H₁₂N₄ + H⁺) 213.1135, found 213.1135.

4.1.59. 3-{[1-Methyl-1H-1,2,3-triazol-4-yl]methyl}benzylamine 70
A solution of nitrile 67 (739 mg, 3.73 mmol) in anhydrous THF (30 mL) was cooled to 0 ºC and treated dropwise with LiAlH₄ (4 M solution in Et₂O, 2.98 mL, 11.9 mmol). The reaction mixture was stirred under reflux for 2 h, cooled to 0 ºC, treated portionwise with 1 N NaOH (100 mL), diluted with H₂O (100 mL), and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford amine 70 (368 mg, 49% yield) as a yellow oil; Rₜ 0.28 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05).

70-HCl: yellowish solid, mp 119–121 ºC; IR (ATR) ν 3400–2300 (max at 3303, 3077, 2908, 2870, 2356, 2322, 17N–H and C–H) cm⁻¹; ¹H NMR (400 MHz, CD₂OD) δ 4.14 (s, 2H, 3–CH₂), 4.296 (s, 3H, 1'–CH₃), 4.302 (s, 2H, 1–CH₂–N), 4.95 (s, 1NH₃), 7.38–7.52 (complex signal, 4H, phenylene CH), 8.39 (s, 1H, 5'-H); ¹³C NMR (100.6 MHz, CD₂OD) δ 30.2 (CH₂, 3–CH₂), 39.8 (CH₃, 1’–CH₃), 44.1 (CH₂, 1–CH₂–N), 129.1 (CH), 129.2 (CH), 130.7 (2CH), 131.0 (CH) (phenylene CH, C₅'), 135.3 (C), 138.2 (C) (C1, C3), 144.9 (C, C₄'); HRMS (ESI), calcd for (C₁₁H₁₄N₄ + H⁺) 203.1291, found 203.1297.

4.1.60. 4-{[1-Methyl-1H-1,2,3-triazol-4-yl]methyl}benzylamine 71
It was prepared as described for 70. From nitrile 68 (310 mg, 1.56 mmol) and LiAlH₄ (4 M solution in Et₂O, 1.18 mL, 4.72 mmol), amine 71 (254 mg, 81% yield) was obtained as a yellow oil; Rₜ 0.27 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05).
The resulting residue was washed with pentane at rt for 3 h and evaporated under reduced pressure. The reaction mixture was stirred at rt for 3 h and evaporated under reduced pressure. The resulting residue was washed with pentane at rt for 3 h and evaporated under reduced pressure.

4.1.61. 4-[(1-Methyl-1H-1,2,3-triazol-4-yl)methyl]phenethylamine 72

A suspension of nitrile 69 (1.60 g, 7.54 mmol) and Raney-Ni (2.02 g, wet) in 7 N methanolic NH₃ (32 mL) was hydrogenated by bubbling H₂ overnight. The resulting mixture was filtered and the cake was washed with MeOH (2 × 15 mL). The combined filtrates were concentrated under reduced pressure to afford amine 72 (1.70 g, quantitative yield) as an oily residue; R_f 0.17 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05).

72·HCl: yellowish solid, mp 158–160 ºC; IR (ATR) ν 3400–2500 (max at 3390, 3331, 3254, 2994, 2970, 2727, 2627, 2573, ᵃN–H and C–H) cm⁻¹; ᵃH NMR (400 MHz, CD₃OD) δ 2.93 (t, J = 7.6 Hz, 2H, 1–CH₂–CH₂–N), 3.15 (t, J = 7.6 Hz, 2H, 1–CH₂–CH₂–N), 4.04 (s, 2H, 4–CH₂), 4.07 (s, 3H, 1′–CH₃), 4.86 (s, ᵃNH₃), 7.18–7.27 (complex signal, 4H, Ph–CH₂), 7.73 (s, 1H, 5′-H); ᵃC NMR (100.6 MHz, CD₃OD) δ 31.9 (CH₂, 4–CH₂), 34.1 (CH₂, 1–CH₂–CH₂–N), 37.2 (CH₃, 1′–CH₃), 42.0 (CH₂, 1–CH₂–CH₂–N), 125.0 (CH, C₅′), 130.1 (2CH), 130.3 (2CH) (Ph–CH₂), 136.1 (C, Ph–C1), 139.3 (C, Ph–C4), 148.1 (C, C₄′); HRMS (ESI), calcd for (C₁₂H₁₆N₄ + H⁺) 217.1448, found 217.1450.

4.1.62. N-(tert-Butoxycarbonyl)-3-[(1-methyl-1H-1,2,3-triazol-4-yl)methyl]benzylamine 73

To a solution of 70 (352 mg, 1.74 mmol) in anhydrous THF (6 mL), a solution of di-tert-butyl dicarbonate (380 mg, 1.74 mmol) in anhydrous THF (2 mL) was added at 0 ºC. The reaction mixture was stirred at rt for 3 h and evaporated under reduced pressure. The resulting residue was washed with pentane (3 × 10 mL) and dried under vacuum, to afford 73 (520 mg, quantitative yield) as a yellow oil; R_f 0.85 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05); IR (ATR) ν 3341 (N–H), 1697 (C=O) cm⁻¹; ᵃH NMR (400
MHZ, CDCl$_3$) $\delta$ 1.55 [s, 9H, C(CH$_3$)$_3$], 4.12 (s, 3H, 1'-CH$_3$), 4.16 (s, 2H, 3–CH$_2$), 4.38 (d, $J$ = 5.6 Hz, 2H, 1–CH$_2$–N), 4.97 (br s, 1H, NHBoc), 7.22–7.27 (complex signal, 3H), 7.33–7.38 (overlapped signal, 2H) (phenylene CH, 5'-H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 28.5 [3CH$_3$, C(CH$_3$)$_3$], 32.3 (CH$_2$, 3–CH$_2$), 36.7 (CH$_3$, 1’–CH$_3$), 44.7 (CH$_2$, 1–CH$_2$–N), 79.6 [C, C(CH$_3$)$_3$], 122.6 (CH, C5’), 125.7 (CH), 127.8 (2CH), 129.0 (CH) (phenylene CH), 139.4 (C), 139.6 (C) (C1, C3), 147.8 (C, C4’), 156.0 (C, NCOO); HRMS (ESI) calcd for (C$_{16}$H$_{22}$N$_4$O$_2$ + H) $^+$ 303.1816, found 303.1812.

4.1.63. N-(tert-Butoxycarbonyl)-4-[(1-methyl-1H-1,2,3-triazol-4-yl)methyl]benzylamine 74

It was prepared as described for 73. From 71 (90 mg, 0.45 mmol) and di-tert-butyl dicarbonate (98 mg, 0.45 mmol), 74 (133 mg, quantitative yield) was obtained as a beige solid; $R_f$ 0.78 (CH$_2$Cl$_2$ / MeOH / 50% aq. NH$_4$OH 9.5:0.5:0.05).

The analytical sample of 74 was obtained by filtration of a dichloromethane solution through a PTFE filter (0.2 µm), evaporation of the filtrate under reduced pressure and washing of the resulting solid with pentane (3 × 2 mL); IR (ATR) $\nu$ 3382 (N–H), 1690 (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.44 [s, 9H, C(CH$_3$)$_3$], 4.00 (s, 3H, 1'–CH$_3$), 4.04 (s, 2H, 4–CH$_2$), 4.26 (d, $J$ = 5.6 Hz, 2H, 1–CH$_2$–N), 4.86 (br s, 1H, NHBoc), 7.13 (s, 1H, 5'-H), 7.20 (complex signal, 4H, phenylene CH); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 28.5 [3CH$_3$, C(CH$_3$)$_3$], 32.0 (CH$_2$, 4–CH$_2$), 36.7 (CH$_3$, 1’–CH$_3$), 44.4 (CH$_2$, 1–CH$_2$–N), 79.6 [C, C(CH$_3$)$_3$], 122.5 (CH, C5’), 127.8 (2CH), 129.0 (2CH) (phenylene CH), 137.3 (C), 138.3 (C) (C1, C4), 148.0 (C, C4’), 156.0 (C, NCOO); HRMS (ESI) calcd for (C$_{16}$H$_{22}$N$_4$O$_2$ + H) $^+$ 303.1816, found 303.1817.

4.1.64. N-(tert-Butoxycarbonyl)-4-[(1-methyl-1H-1,2,3-triazol-4-yl)methyl]phenethyamine 75

It was prepared as described for 73. From 72 (1.65 g, 7.63 mmol) and di-tert-butyl dicarbonate (1.67 g, 7.65 mmol), 75 (2.34 g, quantitative yield) was obtained as a solid; $R_f$ 0.91 (CH$_2$Cl$_2$ / MeOH / 50% aq. NH$_4$OH 9.5:0.5:0.05); mp 92–94 °C; IR (ATR) $\nu$ 3358 (N–H), 1677 (C=O) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.42 [s, 9H, C(CH$_3$)$_3$], 2.76 (t, $J$ = 6.8 Hz, 2H, 1–CH$_2$–CH$_2$–N), 3.35 (dt, $J$ = $J'$ = 6.8 Hz, 2H, 1–CH$_2$–CH$_2$–N), 4.02 (s, 3H, 1’–CH$_3$), 4.05 (s, 2H, 4–CH$_2$), 4.54 (br s, 1H, NHBoc), 7.12 (br d, $J$ = 8.0 Hz, 2H), 7.19 (br d, $J$ = 8.0 Hz, 2H) (Ph–CH$_2$), 7.16 (s, 1H, 5’-H); $^{13}$C NMR (100.6
MH, CDCl3) δ 28.4 [3CH3, C(CH3)3], 31.8 (CH2, 4–CH2), 35.8 (CH2, 1–CH2–CH2–N), 36.5 (CH3, 1′–CH3), 41.8 (CH2, 1–CH2–CH2–N), 79.2 [C, C(CH3)3], 122.3 (CH, C5′), 128.9 (2CH), 129.0 (2CH) (Ph–CH), 137.16 (C), 137.23 (C) (Ph–C1, Ph–C4), 147.9 (C, C4′), 155.8 (C, NCOO); HRMS (ESI), calcd for (C17H24N4O2 + H+) 317.1972, found 317.1982.

4.1.65. N-(tert-Butoxycarbonyl)-N-methyl-3-[(1-methyl-1H-1,2,3-triazol-4-yl)methyl]benzylamine 76

It was prepared as described for 17. From compound 73 (480 mg, 1.59 mmol), NaH (60% suspension in mineral oil, 96 mg, 2.40 mmol), and iodomethane (0.11 mL, 251 mg, 1.77 mmol), stirring at 60 ºC for 2 h, treating again with NaH (60% suspension in mineral oil, 96 mg, 2.40 mmol), and iodomethane (0.11 mL, 251 mg, 1.77 mmol) and stirring at 60 ºC for an additional 2 h, compound 76 (422 mg, 84% yield) was obtained as an orange oil; Rf 0.85 (CH2Cl2 / MeOH / 50% aq. NH4OH 9.5:0.5:0.05); IR (ATR) ν 1686 (C=O) cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 1.48 [br s, 9H, C(CH3)3], 2.82 (br s, 3H, N–CH3), 4.04 (s, 3H, 1′–CH3), 4.08 (s, 2H, 3–CH2), 4.40 (br s, 2H, 1–CH2–N), 7.08–7.19 (complex signal), 7.25–7.30 (complex signal) (5H, phenylene CH, 5′-H); 13C NMR (100.6 MHz, CDCl3) δ 28.6 [3CH3, C(CH3)3], 32.3 (CH2, 3–CH2), 34.1 (CH3, N–CH3), 36.7 (CH3, 1′–CH3), 52.0 (br CH2), 52.7 (br CH2) (1–CH2–N), 79.8 [C, C(CH3)], 122.5 (CH, C5′), 125.6 (br CH), 125.8 (br CH), 127.7 (CH), 127.8 (br CH), 128.9 (CH) (phenylene CH), 138.6 (C), 139.5 (C) (C1, C3), 147.9 (br C, C4′), 156.4 (br C, NCOO); HRMS (ESI), calcd for (C17H23N4O2 + H+) 317.1972, found 317.1970.

4.1.66. N-(tert-Butoxycarbonyl)-N-methyl-4-[(1-methyl-1H-1,2,3-triazol-4-yl)methyl]benzylamine 77

It was prepared as described for 17. From compound 74 (140 mg, 0.46 mmol), NaH (60% suspension in mineral oil, 28 mg, 0.70 mmol), and iodomethane (0.03 mL, 68 mg, 0.48 mmol), stirring at 60 ºC for 2 h, treating again with NaH (60% suspension in mineral oil, 28 mg, 0.70 mmol), and iodomethane (0.03 mL, 68 mg, 0.48 mmol) and stirring at 60 ºC for an additional 2 h, compound 77 (120 mg, 83% yield) was obtained as a brown oil; Rf 0.56 (CH2Cl2 / MeOH / 50% aq. NH4OH 9.5:0.5:0.05); IR (ATR) ν 1686 (C=O) cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 1.46 [br s, 9H, C(CH3)3], 2.79 (br s, 3H, N–CH3), 4.01 (s, 3H, 1′–CH3), 4.05 (s, 2H, 4–CH2), 4.37 (br s, 2H, 1–CH2–N),
7.14 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H) (phenylene CH), 7.20 (s, 1H, 5'-H); 
13C NMR (100.6 MHz, CDCl3) δ 28.6 [3CH3, C(CH3)3], 32.0 (CH2, 4–CH2), 34.0 (CH3, N–CH3), 36.7 (CH3, 1'-CH3), 51.7 (br CH2), 52.4 (br CH2) (1–CH2–N), 79.8 [C, C(CH3)3], 122.5 (CH, C5'), 127.8 (br CH), 128.0 (br CH), 128.9 (CH), 129.0 (CH) (phenylene CH), 136.4 (C), 138.2 (C (C1, C4), 148.0 (C, C4'); 155.9 (br C, NCOO); HRMS (ESI), calcd for (C17H24N4O2 + H+) 317.1972, found 317.1965.

4.1.67. N-Methyl-3-[(1-methyl-1H-1,2,3-triazol-4-yl)methyl]benzylamine 79

It was prepared as described for 25. From 76 (384 mg, 1.21 mmol) and H3PO4 (85% purity, 2.15 mL, 18.6 mmol), amine 79 (242 mg, quantitative yield) was obtained as an orange oil; *Rf* 0.30 (CH2Cl2 / MeOH / 50% aq. NH4OH 9.5:0:5:0.05).

79·HCl: sticky solid, IR (ATR) ν 3400–2400 (max at 3374, 3116, 3074, 2956, 2778, 2699, 2542, 2417, 'N–H and C–H) cm⁻¹; 1H NMR (400 MHz, CD3OD) δ 2.73 (s, 3H, N–CH3), 4.21 (s, 2H, 3–CH2), 4.32 (s, 3H, 1’–CH3), 4.33 (s, 2H, 1–CH2–N), 4.99 (s, 1H, 5'-H); 13C NMR (100.6 MHz, CD3OD) δ 30.0 (CH2, 3–CH2), 33.2 (CH3, N–CH3), 40.0 (CH3, 1’–CH3), 53.3 (CH2, 1–CH2–N), 129.5 (CH), 130.3 (CH), 131.1 (CH), 131.2 (CH), 131.5 (CH) (phenylene CH, C5'), 133.6 (C, C1), 138.0 (C, C3), 144.5 (C, C4'); HRMS (ESI), calcd for (C12H16N4 + H⁺) 217.1448, found 217.1446.

4.1.68. N-Methyl-4-[(1-methyl-1H-1,2,3-triazol-4-yl)methyl]benzylamine 80

It was prepared as described for 25. From 77 (237 mg, 0.75 mmol) and H3PO4 (85% purity, 1.29 mL, 11.2 mmol), amine 80 (156 mg, 96% yield) was obtained as an orange oil; *Rf* 0.24 (CH2Cl2 / MeOH / 50% aq. NH4OH 9.5:0:5:0.05).

80·HCl: sticky solid, IR (ATR) ν 3400–2400 (max at 3339, 3085, 2931, 2744, 2708, 2547, 2415, 'N–H and C–H) cm⁻¹; 1H NMR (400 MHz, CD3OD) δ 2.71 (s, 3H, N–CH3), 4.19 (s, 2H, 4–CH2), 4.23 (s, 3H, 1’– CH3), 4.24 (s, 2H, 1–CH2–N), 4.90 (s, 1H, 5'-H); 13C NMR (100.6 MHz, CD3OD) δ 30.6 (CH2, 4–CH2), 33.1 (CH3, N–CH3), 39.0 (CH3, 1’–CH3), 53.1 (CH2, 1–CH2–N), 127.9 (CH, C5'), 130.7 (2CH), 131.62 (2CH) (phenylene CH), 131.56 (C, C1), 139.7 (C, C4), 145.6 (C, C4'); HRMS (ESI), calcd for (C12H16N4 + H⁺) 217.1448, found 217.1448.
4.1.69. **N-Methyl-4-[(1-methyl-1H-1,2,3-triazol-4-yl)methyl]phenethylamine 81**

To a suspension of LiAlH₄ (118 mg, 3.11 mmol) in dry THF (4 mL), a solution of 75 (165 mg, 0.52 mmol) in dry THF (4 mL) was added dropwise at 0 °C. The reaction mixture was stirred at reflux for 72 h, cooled to 0 °C, diluted with 1 N NaOH (20 mL), and extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford an oily residue (169 mg), which was purified through column chromatography (40–60 μm silica gel, CH₂Cl₂ / MeOH / 50% aq. NH₄OH mixtures, gradient elution). On elution with CH₂Cl₂ / MeOH / 50% aq. NH₄OH 95:5:0.2, amine 81 (53 mg, 44% yield) was isolated as a yellow oil; Rf 0.16 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).

81·HCl: yellowish solid, mp 149–151 °C; IR (ATR) ν 3400–2400 (max at 3395, 3118, 2938, 2771, 2450, N–H and C–H) cm⁻¹; ¹H NMR (400 MHz, CD₂OD) δ 2.71 (s, 3H, N–CH₃), 2.97 (t, J = 7.2 Hz, 2H, 1–CH₂–CH₂–N), 3.23 (t, J = 7.2 Hz, 2H, 1–CH₂–CH₂–N), 4.06 (s, 2H, 4–CH₂), 4.09 (s, 3H, 1'–CH₃), 4.86 (s, NH₂), 7.24 (dm, J = 8.8 Hz, 2H), 7.27 (dm, J = 8.8 Hz, 2H) (Ph–CH), 7.81 (s, 1H, 5'–H); ¹³C NMR (100.6 MHz, CD₂OD) δ 31.7 (CH₂, 4–CH₂), 32.9 (CH₂, 1–CH₂–CH₂–N), 33.7 (CH₃, N–CH₃), 37.5 (CH₂, 1’–CH₃), 51.4 (CH₂, 1–CH₂–CH₂–N), 125.5 (CH, C₅'), 130.1 (2CH), 130.4 (2CH) (Ph–CH), 136.0 (C), 139.0 (C) (Ph–Cl, Ph–C₄), 147.7 (C, C₄'); HRMS (ESI), caled for (C₁₃H₁₈N₄ + H⁺) 231.1604, found 231.1605.

4.1.70. **N-Methyl-N-[3-[(1-methyl-1H-1,2,3-triazol-4-yl)methyl]benzyl]-N-propargylamine 82**

It was prepared as described for 31. From amine 79 (236 mg, 1.09 mmol), Cs₂CO₃ (354 mg, 1.09 mmol), and propargyl bromide (80% solution in toluene, 0.16 mL, 1.08 mmol), and stirring at at 0 °C for 30 min and at rt for an additional 3 h, propargylamine 82 (180 mg, 66% yield) was obtained as a yellow oil, without the need of chromatographic purification; Rf 0.66 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9.5:0.5:0.05).

82·HCl: sticky solid; IR (ATR) ν 3400–2400 (max at 3389, 3191, 3023, 2930, 2491, N–H, ≡C–H, and C–H), 2122 (C≡C) cm⁻¹; ¹H NMR (400 MHz, CD₂OD) δ 2.94 (s, 3H, N–CH₃), 3.47 (t, J = 2.8 Hz, 1H, propargyl CH), 4.08 (br s, 2H, propargyl CH₂), 4.26 (s, 3H, 1'–CH₃), 4.30 (s, 2H, 3–CH₂), 4.47 (br signal, 2H, 1–CH₂–N), 5.04 (s, NH), 7.48–7.56 (complex signal, 3H, 4-H, 5-H, 6-H), 7.61 (br s, 1H, 2-H), 8.33 (s, 1H, 5'–H); ¹³C NMR (100.6 MHz, CD₂OD) δ 30.5 (CH₂, 3–CH₂), 39.3 (CH₃, 1’–CH₃), 40.1
(CH₃, N–CH₃), 45.4 (CH₂, propargyl CH₂), 59.4 (CH₂, 1–CH₂–N), 72.8 (C, propargyl C), 81.9 (CH, propargyl CH), 128.4 (CH, C5’), 131.0 (CH), 131.2 (CH + C), 131.8 (CH), 132.6 (CH) (C1, phenylene CH), 139.2 (C, C3), 145.2 (C, C4’); HRMS (ESI), calcd for (C₁₅H₁₈N₄ + H⁺) 255.1604, found 255.1600.

4.1.71. N-Methyl-N-{4-[(1-methyl-1H-1,2,3-triazol-4-yl)methyl]benzyl}-N-propargylamine 83

It was prepared as described for 31. From amine 80 (131 mg, 0.61 mmol), Cs₂CO₃ (0.20 g, 0.61 mmol), and propargyl bromide (80% solution in toluene, 0.07 mL, 0.47 mmol), and stirring at at 0 °C for 3.5 h, an orange oily residue (122 mg) was obtained and purified through column chromatography (40–60 µm silica gel, CH₂Cl₂ / 50% aq. NH₄OH 100:0.2), to afford propargylamine 83 (48 mg, 40% yield) as a yellow oil; Rf 0.67 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).

83·HCl: mp 156–158 °C; IR (ATR) ν 3400–2400 (max at 3178, 3095, 2923, 2692, 2501, 2418, νN–H, =C–H, and C–H), 1210 (C=C) cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 2.92 (s, 3H, NCH₃), 3.47 (t, J = 2.8 Hz, 1H, propargyl CH), 4.05 (br signal, 2H, propargyl CH₂), 4.19 (s, 3H, 1’CH₃), 4.22 (s, 2H, 4–CH₂), 4.41 (br signal, 2H, 1–CH₂–N), 4.86 (s, νNH), 7.44 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H) (phenylene CH), 8.10 (s, 1H, 5’-H); ¹³C NMR (100.6 MHz, CD₃OD) δ 30.6 (CH₂, 4–CH₂), 39.0 (CH₃, 1’–CH₃), 40.1 (CH₃, N–CH₃), 45.4 (CH₂, propargyl CH₂), 59.3 (CH₂, 1–CH₂–N), 72.8 (C, propargyl C), 81.9 (CH, propargyl CH), 128.0 (CH, C5’), 129.4 (C, C1), 130.9 (2CH), 132.9 (2CH) (phenylene CH), 140.5 (C, C4), 145.5 (C, C4’); HRMS (ESI), calcd for (C₁₅H₁₈N₄ + H⁺) 255.1604, found 255.1599.

4.1.72. N-methyl-N-{4-[(1-methyl-1H-1,2,3-triazol-4-yl)methyl]phenethyl}-N-propargylamine 84

It was prepared as described for 31. From amine 81 (30 mg, 0.13 mmol), Cs₂CO₃ (42 mg, 0.13 mmol), and propargyl bromide (80% solution in toluene, 0.02 mL, 0.13 mmol), and stirring at 0 °C for 30 min and at rt for an additional 3 h, an oily residue (48 mg) was obtained and purified through column chromatography (40–60 µm silica gel, CH₂Cl₂), to afford propargylamine 84 (20 mg, 57% yield) as a yellow oil; Rf 0.55 (CH₂Cl₂ / MeOH / 50% aq. NH₄OH 9:1:0.05).
84-HCl: sticky solid; IR (ATR) ν 3500–2400 (max at 3413, 3358, 3213, 3068, 2944, 2496, ^3N–H, =C–H, and C–H), 2144 (C≡C) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CD\(_2\)OD) δ 3.02 (s, 3H, N–CH\(_3\)), 3.06 (t, \(J = 6.8\) Hz, 2H, 1–CH\(_2–\)CH\(_2–\)N), 3.41 (m, 1H, propargyl CH), 3.48 (br signal, 2H, 1'–CH\(_3\)), 4.09 (s, 2H, propargyl CH\(_2\)), 4.12 (s, 3H, 1'–CH\(_3\)), 4.18 (s, 2H, 4–CH\(_2\)), 4.86 (s, ^3NH), 7.28 (complex signal, 4H, Ph–CH\(_2\)), 7.89 (s, 1H, 5'–H); \(^13\)C NMR (100.6 MHz, CD\(_2\)OD) δ 31.1 (CH\(_2\)), 31.4 (CH\(_2\)), 37.9 (CH\(_3\)), 40.7 (CH\(_3\), N–CH\(_3\)), 46.3 (CH\(_2\), propargyl CH\(_2\)), 57.5 (CH\(_2\)), 72.8 (C, propargyl C), 81.5 (CH, propargyl CH), 126.1 (CH, C5'), 130.3 (2CH), 130.4 (2CH) (Ph–CH\(_2\)), 135.7 (C), 138.7 (C) (Ph–C1, Ph–C4), 147.3 (C, C4'); HRMS (ESI), calcld for (C\(_{16}\)H\(_{20}\)N\(_4\) + H\(^+\)) 269.1761, found 269.1760.

4.2. Biological assays

4.2.1. Inhibition of hrMAO-A and hrMAO-B

The activity of hrMAO-A and hrMAO-B (Sigma-Aldrich, Madrid, Spain) was determined using Amplex UltraRed fluorometric coupled method. For both MAO isoforms, tyramine hydrochloride was used as substrate and enzymatic assays were performed in 96-well black opaque microplates (OptiPlate-96F, PerkinElmer) in a final volume of 200 μL. Serial dilutions of each inhibitor were pre-incubated with either 0.36 U/mL hrMAO A or 0.0675 U/mL hrMAO B for 30 min at 37 ºC. Enzymatic reactions were started upon the addition of 100 μL of a mixture solution containing 1 mM tyramine, 0.04 U/mL horseradish peroxidase (HRP) and 25 mM Amplex UltraRed® reagent in 0.25 mM sodium phosphate (pH 7.4) as final concentrations. The fluorescence production of resorufin was measured for at least 30 min at 530/590 nm in a spectrophotometric plate reader (FluoStar OPTIMA, BM G Labtech). The enzymatic activity in the absence of compound was used to determine 100% enzyme activity. The potential capacity of the compounds to interfere with the fluorescence generated in the reaction was determined by adding the compounds to solutions in the absence of MAO. From dose-response curves, IC\(_{50}\) values were accordingly calculated using the GraphPad ‘PRISM’ software (version 5.0). Data are expressed as mean ± SEM of at least three different experiments performed in duplicate. Clorgyline and R-deprenyl (Sigma-Aldrich) were used as reference compounds.

4.2.2. Reversibility of hrMAO-B inhibition
To study the reversibility of the inhibition of hrMAO-B by compound 33, 100-fold enzyme concentration was inhibited by 200 nM L-deprenyl or 50 nM 33 (10-fold IC$_{50}$ values) for 1 h at 37 °C. Following pre-incubation times, enzyme solution was rapidly diluted (100-fold) in a mix solution containing 1 mM p-tyramine, HRP and Amplex UltraRed® reagent in 50 mM phosphate buffer pH 7.4. Next, hrMAO-B activity was followed at 530/590 nm for 40 min.

4.2.3. Time-dependent inhibition of hrMAO-B
To investigate the time-dependent inhibition of hrMAO-B activity by compound 33, the enzyme was inhibited by 10 μM 33 for at different pre-incubation times (0-360 min). At the end of each pre-incubation, activity was measured as previously described and plotted as percentage of control samples versus pre-incubation time.

4.2.4. Determination of brain permeability: PAMPA-BBB assay
The in vitro permeability ($P_e$) of the novel 1,2,3-triazole-based compounds and fourteen known drugs (Table 2) through lipid extract of porcine brain membrane was determined by using a parallel artificial membrane permeation assay$^{82}$ using a mixture PBS:EtOH 70:30. Assay validation was made by comparison of the experimental $P_e$ values of the known drugs with their reported values, which showed a good correlation: $P_e$ (exp) = 1.003 $P_e$ (lit) – 0.783 ($R^2 = 0.93$). From this equation and the limits established by Di et al. for BBB permeation,$^{82}$ three ranges of permeability were established: compounds of high BBB permeation (CNS+): $P_e$ ($10^{-6}$ cm s$^{-1}$) > 5.18; compounds of low BBB permeation (CNS–): $P_e$ ($10^{-6}$ cm s$^{-1}$) < 2.06; compounds of uncertain BBB permeation (CNS±): and 5.18 > $P_e$ ($10^{-6}$ cm s$^{-1}$) > 2.06.

Table 2. Reported and experimental permeability values ($P_e$ $10^{-6}$ cm s$^{-1}$) of 14 commercial drugs used for the PAMPA-BBB assay validation

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<tr>
<th>Compound</th>
<th>Literature value$^a$</th>
<th>Experimental value$^b$</th>
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56
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<tr>
<th>Compound</th>
<th>IC50</th>
<th>Kd ± SD</th>
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<td>Cimetidine</td>
<td>0.0</td>
<td>0.70 ± 0.03</td>
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<tr>
<td>Lomefloxacin</td>
<td>0.0</td>
<td>0.78 ± 0.04</td>
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<tr>
<td>Norfloxacin</td>
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<td>0.90 ± 0.02</td>
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<td>Ofloxacin</td>
<td>0.8</td>
<td>0.98 ± 0.06</td>
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<tr>
<td>Hydrocortisone</td>
<td>1.9</td>
<td>1.40 ± 0.05</td>
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<tr>
<td>Piroxicam</td>
<td>2.5</td>
<td>1.93 ± 0.11</td>
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<td>Clonidine</td>
<td>5.3</td>
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<td>Corticosterone</td>
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<td>16</td>
<td>28.1 ± 1.6</td>
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* Taken from ref. [82].

Values are expressed as the mean ± SD of three independent experiments.

4.3. Docking studies

The binding mode of selected 1,2,3-triazole derivatives was explored by means of docking calculations carried out with Glide, using an empirical scoring function calibrated on the basis of protein–ligand complexes. Docking was performed using the MAO-B X-ray structure of the complex with inhibitor 6 (PDB entry 4CRT) and deprenyl (PDB entry 2BYB), but no significant differences were found for the best ligand poses. The protocol defined in our previous studies was adopted here. Briefly, the docking volume was defined as the space covered by the binding cavity in MAO-B. Suitable restraints were introduced to keep the amine nitrogen of the proargylamine unit close to the position found for the corresponding atom in deprenyl and rasagiline (PDB entry 2BK4) in order to mimic the orientation after irreversible linkage with the FAD. Each compound was subjected to 100 docking runs. Whereas the protein was kept rigid, Glide accounts for the conformational flexibility of the ligand around rotatable bonds during docking calculations. The output docking modes were analyzed by visual inspection in conjunction with the docking scores.

Acknowledgements
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## Bioorganic and Medicinal Chemistry

**CHECKLIST FOR COMPOUND CHARACTERIZATION**

*only for new/unknown compounds*

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*Compound Characterization Checklist*