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**Original article**

# Synthesis and structure–affinity relationships of 1,3,5-alkylsubstituted cyclohexylamines binding at NMDA receptor PCP site

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**Abstract** – A series of 1,3,5-alkylsubstituted cyclohexylamines **2** were synthesized as ligands for the N-methyl-D-aspartate (NMDA) receptor phencyclidine (PCP) binding site. Pure diastereomers with defined configuration of amino group **2**-*ax* and **2**-*eq* were obtained. The optimal size of 1,3,5-substituents was determined for cyclohexylamines **2** with an equatorial amino group in the lowest energy conformation using Hansch analysis. According to the data, the lipophilic part of cyclohexylamines **2** does not discriminate between hydrophobic regions of the PCP binding site but rather recognizes this site as a whole lipophilic pocket. © 2000 Éditions scientifiques et médicales Elsevier SAS

**NMDA receptor / PCP / cyclohexylamines / Hansch analysis**

## 1. Introduction

The antagonism of the NMDA receptor has a potential for a wide range for therapeutic applications in the case of CNS disorders associated with pathological glutamate release from presynaptic neurones [1]. Non-competitive NMDA receptor antagonists are known to bind at a phencyclidine (PCP, *figure 1*) binding site located inside the NMDA receptor cation channel [1, 2]. A number of structurally diverse compounds have been shown to act at the PCP binding site including structural analogues of PCP, dizocilpine (MK-801) (*figure 1*), ketamine, dextromethorphan, etc. [3]. However, it has been recognized that the high affinity NMDA receptor ion channel blockers have undesirable psychotomimetic side effects while moderate affinity agents are clinically tolerated [1, 3]. It has been shown that 1-amino-3,5-substituted adamantane derivatives **1** (*figure 1*) exhibit a moderate affinity for the NMDA receptor [4]. Moreover, two representatives of this class, i.e. 1-aminoadamantane (amantadine) and 1-amino-3,5-dimethyladamantane (memantine) are already used clinically for the treatment of Parkinson's disease and dementia [1].

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However, the number of 1-aminoadamantanes possessing a considerable affinity for the NMDA receptor is limited, therefore only scant information on the structure-affinity relationships is available for such compounds [3]. This prompted us to design and synthesize 1-aminoadamantane **1** structural analogues 1,3,5-substituted cyclohexylamines **2** (*figure 1*). Systematic variation of the substituents from hydrogen to propyl groups would allow the estimation of the dependence of the size of lipophilic globule on the binding affinity.

## 2. Chemistry

The synthesis of 1,3,5-alkylcyclohexylamines **2** (*figure 2*) was performed starting with 2-cyclohexen-1-ones **3a**–**g** summarized in *table I*. Compounds **3a**–**d** are commercially available. The rest of the 2-cyclohexen-1-ones **3e**–**g** were prepared according to the literature procedure [5] as shown in *figure 3*.

2-Cyclohexen-1-ones **3** were then converted to cyclohexanones **4a**–**d** and **f**–**m** (*table II*) by 1,4-conjugate addition of organocuprates prepared in situ from alkylmagnesium halides and copper (I) chloride. In the case of enone **3c** the addition of diethyl- and dipropylmagne-

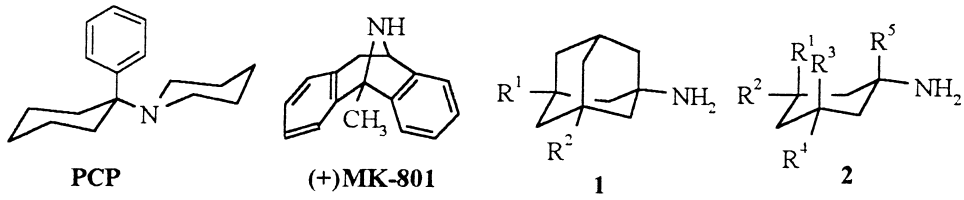


**Figure 1.** Chemical structure of PCP, MK-801, 3,5-substituted amino adamantanes **1** and 1,3,5-substituted cyclohexylamines **2**.

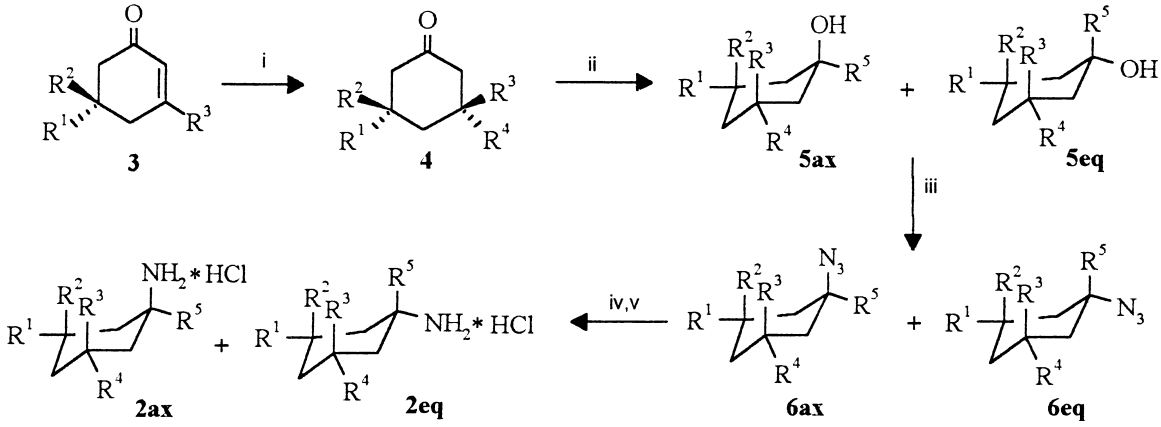


**Figure 2.** The general scheme for the synthesis of 1,3,5-substituted cyclohexylamines **2**. Conditions: i) $R^4{}_2CuMgX$; ii) $R^5MgX$; iii) A: $HN_3$, $TiCl_4$ B: $TMSN_3$, $BF_3{*}Et_2O$; iv) $LiAlH_4$; v) HCl.

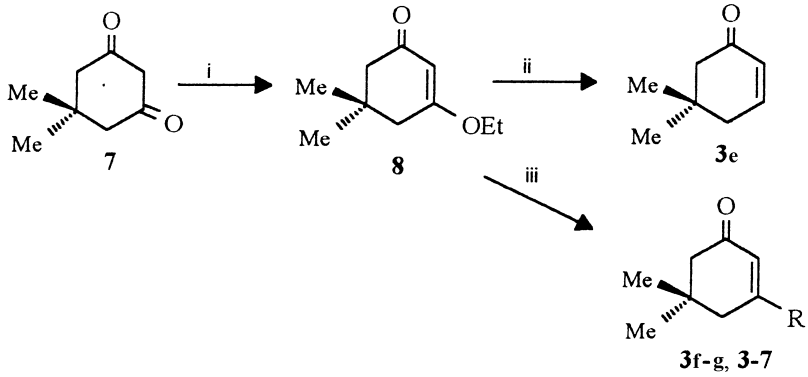


**Figure 3.** The preparation of cyclohexen-2-ones **3**. Conditions: i) EtOH, TsOH; ii) $LiAlH_4$ then 10% $H_2SO_4$; iii) RMgI then 5% $H_2SO_4$.

**Table I.** Alkylsubstituted 2-cyclohexen-1-ones **3**.

| Compound | $R^1$ | $R^2$ | $R^3$ | Yield[a] (%) |
|---|---|---|---|---|
| **3a** | H | H | H | – |
| **3b** | H | H | Me | – |
| **3c** | H | Me | Me | – |
| **3d** | Me | Me | Me | – |
| **3e** | Me | Me | H | 70 |
| **3f** | Me | Me | Et | 40 |
| **3g** | Me | Me | Pr | 40 |

[a] Commercially available if omitted.

siumcuprates yielded mainly isomers **4g** and **4h** (> 95%, GC) with 3- and 5-methyl groups in *cis* configuration as a result of preferred anti-parallel addition to 5-substituted cyclohexenones [6]. This was confirmed by analysis of the $^1$H-NMR spectra of final amines **2g** and **h** (see below).

Ketones **4** were treated with alkylmagnesium halides providing cyclohexanols **5a**–**m** (*table III*). Noteworthy, 3-monosubstituted cyclohexanones **4a**–**c** afforded the mixtures of both isomers **5a–c**-*ax* and **5a–c**-*eq*, whereas 3,3,5-trisubstituted cyclohexanones **4f**–**j** gave cyclohexanols **5f**–**j**-*ax* as the sole product (-*ax* and -*eq* indicates the axial or equatorial position of heteroatom functionality in the most favourable conformation of diastereomer (*figure 4*)). Such a stereochemical outcome was in agreement with the published examples of nucleophilic additions to 3-methyl- and 3,3,5-tetramethylcyclohexanones [7]. The isomeric mixtures of alcohols **5a–c** were used for the next step, as either isomer yields the same ratio of products [8]. Samples of pure isomers **5a–c**-*ax* and **5a–c**-*eq* were obtained by flash chromatography for characterization purposes only.

**Table II.** Alkylsubstituted cyclohexanones **4**.

| Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield[a] (%) |
|---|---|---|---|---|---|
| **4a** | H | H | H | Me | – |
| **4b** | H | H | H | Et | 63 |
| **4c** | H | H | H | Pr | 79 |
| **4d** | H | H | Me | Me | 78 |
| **4e** | Me | H | H(Me) | Me(H) | 86[b] |
| **4f** | Me | H | Me | Me | 57 |
| **4g** | Me | H | Et | Me | 78 |
| **4h** | Me | H | Pr | Me | 82 |
| **4i** | Me | Me | H | Et | 54 |
| **4j** | Me | Me | H | Pr | 74 |
| **4k** | Me | Me | Me | Me | – |
| **4l** | Me | Me | Et | Et | 84 |
| **4m** | Me | Me | Pr | Pr | 79 |

[a] Commercially available if omitted. [b] Prepared by oxidation of 3,5-dimethylcyclohexanol (*figure 5*).

**Table III.** Alkylsubstituted cyclohexanols **5**.

| Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield[a] (%) |
|---|---|---|---|---|---|---|
| **5a**-*ax*, **5a**-*eq* | H | H | H | Me | Me | 88 |
| **5b**-*ax*, **5b**-*eq* | H | H | H | Et | Me | 93 |
| **5c**-*ax*, **5c**-*eq* | H | H | H | Pr | Me | 93 |
| **5d** | H | H | Me | Me | Me | 78 |
| **5e**-*eq* | Me | H | H | Me | Me | 15 |
| **5f**-*ax* | Me | H | Me | Me | Me | 85 |
| **5g**-*ax* | Me | H | Et | Me | Me | 94 |
| **5h**-*ax* | Me | H | Pr | Me | Me | 88 |
| **5i**-*ax* | Me | Me | H | Et | Me | 84 |
| **5j**-*ax* | Me | Me | H | Pr | Me | 88 |
| **5k** | Me | Me | Me | Me | Me | 93 |
| **5l** | Me | Me | Me | Me | Et | 92 |
| **5m** | Me | Me | Me | Me | Pr | 85 |
| **5n** | Me | Me | Et | Et | Me | 87 |
| **5o** | Me | Me | Pr | Pr | Me | 90 |
| **5p** | H | H | H | H | Me | – |

[a] Commercially available if omitted.

1,*cis*-3,*cis*-5-Trimethylcyclohexanol **5e**-*eq* was prepared by a different route (*figure 5*). Thus, oxidation of a commercially available isomeric mixture of 3,5-dimethylcyclohexanol **9** resulted in a mixture of *cis*- and *trans*-dimethylcyclohexanones **4e**, separation of which has been described [9]. However, we found it more convenient to separate trimethylcyclohexanol with the desired *cis* geometry of 3,5-methyl groups **5e**-*eq* from a mixture of isomeric alcohols by flash chromatography after the Grignard reaction of ketones **4e**.

The azidation of cyclohexanols **5a**–**n** in the presence of a Lewis acid turned out to be the method of choice to introduce the amino functionality. The conversion to azides **6a**–**p** (*table IV*) was performed either by using hydrazoic acid and titanium tetrachloride (method A) [8] or by applying trimethylsilyl azide as a hydrazoic acid equivalent in combination with boron trifluoride etherate (method B) [10]. The latter method avoids the use of poisonous and explosive hydrazoic acid. Isomeric azides **6a–c**-*ax*,-*eq* and **6e**–**j**-*ax*, -*eq* were successfully separated by flash chromatography on silica gel. The reduction of azides **6a**–**p** to the corresponding cyclohexylamines **2a**–**p** (*table V*) provided pure diastereomers **2a**–**c** and **e**–**j**-*ax* and **2a**–**c** and **e**–**j**-*eq*. The conformational analysis of cyclohexylamine salts **2a**–**p** (*figure 4*) was made by a semiquantitative assessment of conformational energies using A and U values [11]. For amine isomers **2a–c**-*ax*, **2e**-*ax* and **2f–j**-*ax* the conformation with the amino group in the axial position was found to be energetically favoured by 3.4 kcal/mol, 8.8 kcal/mol and 5.1 kcal/mol,

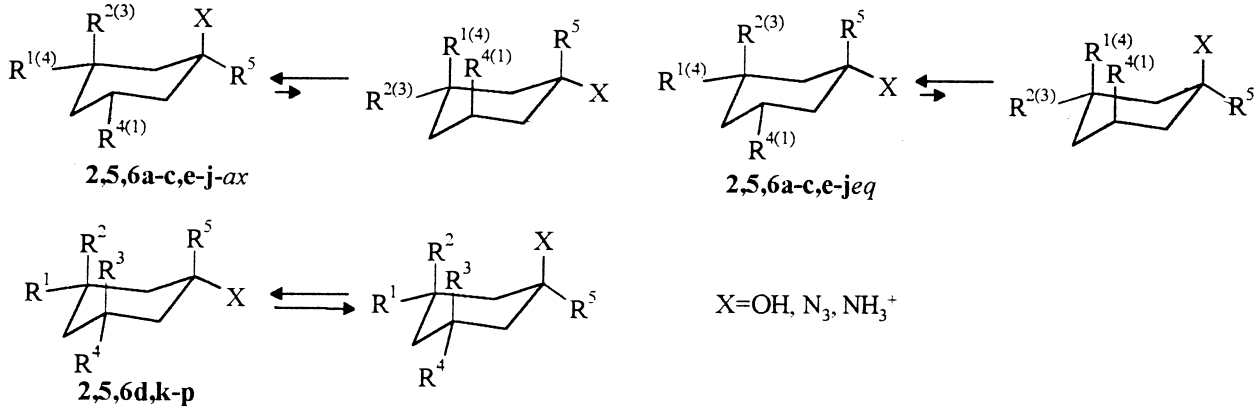


**Figure 4.** Conformational analysis of 1,3,5-substituted cyclohexanols **5**, cyclohexylazides **6** and cyclohexylamines **2**.

respectively. For diastereomers **2a–c**-*eq*, **2e**-*eq* and **2f–j**-*eq* the conformation with the amino group in the equatorial position was found to be energetically favoured by 3.9 kcal/mol, 9.2 kcal/mol and 5.6 kcal/mol, respectively. Such an energy difference corresponds to more than 99% of the population of the favoured conformer. Thus, diastereomers **2a–c** and **2e–j** can be regarded as conformationally biased structures with a defined position of the amino group. In the case of symmetrical cyclohexylamines **2d** and **2p** the energy difference was only 0.2–0.3 kcal/mol in favour of the conformer with the equatorial amino group. This means that an *eq*-amino conformer is only slightly preferred. The same could also be true for amines **2k–o**, however, the cut-off value of both chair conformers is exceeded in these cases. Therefore, a population of non-chair conformations could also be expected in those cases. This, however, can be estimated only on the basis of more extensive conformational studies.

The configuration of the amino group in diastereomers of 1,3-disubstituted cyclohexylamines **2a–c** and 1,3,5-trimethylcyclohexylamine **2e** could not be determined unequivocally by $^1$H-NMR spectra due to the small difference of the chemical shifts. To solve this problem $^{13}$C-NMR spectra of the diastereomers **2a**-*ax* and **2a**-*eq* were recorded. The signal assignment was made by correlation with already interpreted spectra of 1,3-dimethylcyclohexanols **5a**-*ax* and **5a**-*eq* [12]. As for cyclohexanols, the 1-methyl group in amine **2a**-*eq* was shifted upfield by 5.8 ppm compared to that in its counterpart **2a**-*ax* due to the shielding δ-effect. Noteworthy, amine **2a**-*ax* had about 0.2 min shorter retention time than **2a**-*eq* in GC analysis. This is a known property of conformationally biased cyclohexanols which stems from the smaller tendency of the axial substituent to form hydrogen bonds [13]. For cyclohexylamine **2a** homologues **2b** and **2c** as well as for **2e**, the isomers with shorter retention times were assigned to be **2b** and **c**-*ax* and **2e**-*ax*.

In the case of 1,3,3,5-tetrasubstituted cyclohexylamines **2e–j**, $^1$H-NMR was used to determine the configuration of substituents. Axial 3-Me group protons in compounds **2e**, **f**, **i** and **j**-*ax* were shifted downfield for ~0.25 ppm compared to the corresponding isomers **2e**, **f**, **i** and **j**-*eq*. Such an effect was attributed to the more pronounced σ-compression effect of the electronegative axial amino

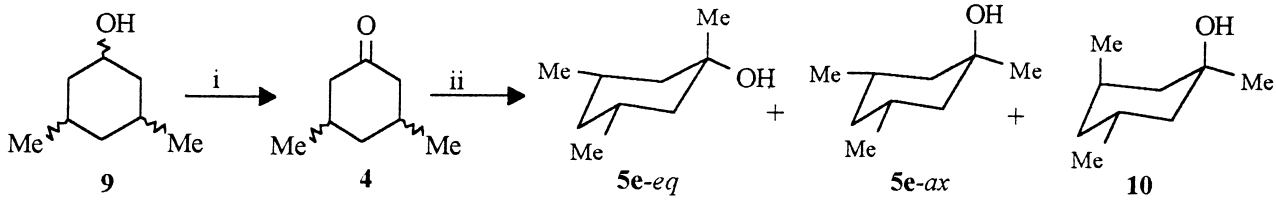


**Figure 5.** The synthesis of 1,3,5-trimethylcyclohexanol **5e**-*eq*. Conditions: i) $H_2SO_4$, $CrO_3$; ii) MeMgX.

**Table IV.** Alkylsubstituted cyclohexyl azides **6**.

| Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Procedure | Yield (%) |
|---|---|---|---|---|---|---|---|
| **6a**-*ax* | H | H | H | Me | Me | B | 24 |
| **6a**-*eq* | | | | | | | 12 |
| **6b**-*ax* | H | H | H | Et | Me | A | 26 |
| **6b**-*eq* | | | | | | | 4 |
| **6c**-*ax* | H | H | H | Pr | Me | A | 24 |
| **6c**-*eq* | | | | | | | 11 |
| **6d** | H | H | Me | Me | Me | A | 65 |
| **6e**-*ax* | Me | H | H | Me | Me | B | 43 |
| **6e**-*eq* | | | | | | | 19 |
| **6f**-*ax* | Me | H | Me | Me | Me | A | 42 |
| **6f**-*eq* | | | | | | | 12 |
| **6g**-*ax* | Me | H | Et | Me | Me | A | 47 |
| **6g**-*eq* | | | | | | | 12 |
| **6h**-*ax* | Me | H | Pr | Me | Me | A | 44 |
| **6h**-*eq* | | | | | | | 9 |
| **6i**-*ax* | Me | Me | H | Et | Me | B | 45 |
| **6i**-*eq* | | | | | | | 12 |
| **6j**-*ax* | Me | Me | H | Pr | Me | A | 54 |
| **6j**-*eq* | | | | | | | 7 |
| **6k** | Me | Me | Me | Me | Me | A | 67 |
| **6l** | Me | Me | Me | Me | Et | A | 39 |
| **6m** | Me | Me | Me | Me | Pr | A | 65 |
| **6n** | Me | Me | Et | Et | Me | A | 66 |
| **6o** | Me | Me | Pr | Pr | Me | A | 61 |
| **6p** | H | H | H | H | Me | A | 27 |

**Table V.** Alkylsubstituted cyclohexylamine hydrochlorides **2**[a].

| Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield (%) |
|---|---|---|---|---|---|---|
| **2a**-*ax* | H | H | H | Me | Me | 63 |
| **2a**-*eq* | | | | | | 48 |
| **2b**-*ax* | H | H | H | Et | Me | 66 |
| **2b**-*eq* | | | | | | 43 |
| **2c**-*ax* | H | H | H | Pr | Me | 80 |
| **2c**-*eq* | | | | | | 81 |
| **2d** | H | H | Me | Me | Me | 73 |
| **2e**-*ax* | Me | H | H | Me | Me | 74 |
| **2e**-*eq* | | | | | | 55 |
| **2f**-*ax* | Me | H | Me | Me | Me | 74 |
| **2f**-*eq* | | | | | | 57 |
| **2g**-*ax* | Me | H | Et | Me | Me | 68 |
| **2g**-*eq* | | | | | | 60 |
| **2h**-*ax* | Me | H | Pr | Me | Me | 57 |
| **2h**-*eq* | | | | | | 36 |
| **2i**-*ax* | Me | Me | H | Et | Me | 69 |
| **2i**-*eq* | | | | | | 44 |
| **2j**-*ax* | Me | Me | H | Pr | Me | 83 |
| **2j**-*eq* | | | | | | 44 |
| **2k** | Me | Me | Me | Me | Me | 82 |
| **2l** | Me | Me | Me | Me | Et | 74 |
| **2m** | Me | Me | Me | Me | Pr | 88 |
| **2n** | Me | Me | Et | Et | Me | 78 |
| **2o** | Me | Me | Pr | Pr | Me | 72 |
| **2p** | H | H | H | H | Me | 69 |

[a] $R^n$ = H if omitted.

group of **2e**, **f**, **2i** and **j**-*ax* compared to the axial 1-methyl group of isomers **2e**, **f**, **i** and **j**-*eq* (for similar effects in cyclohexanols see ref. [14, 15]). The σ-compression effect of the axial amino group was not observed for the 3-methyl groups of compounds **2g** and **h**-*ax*. This confirmed *cis* configuration of 3- and 5-methyl groups (both equatorial) in cyclohexylamines **2g** and **h**. 1-Methyl group signals in amines **2e–j**-*ax* were shifted upfield by 0.03–0.16 ppm compared to the signals in isomers **2e–j**-*eq*. This again could be explained by the deshielding σ-compression effect of the axial 3-substituent on the axial 1-methyl group in isomers **2e–j**-*eq*. It is necessary to note that isomers **2e–j**-*ax* had shorter retention times compared to **2e–j**-*eq* in GC analysis with a difference of ~0.5 min.

## 3. Pharmacology

The NMDA receptor PCP binding site affinities of cyclohexylamines **2** were determined by radioligand ([$^3$H]MK-801) displacement studies on rat cortical membrane preparations and are listed in *table VI*. A full description of the affinity determination procedure and

**Table VI.** Ki, log (1/Ki), and log (P) values for alkylsubstituted cyclohexylamine hydrochlorides **2**.

| Compound | Ki (μM) | log (1/Ki) | log (P) | Compound | Ki (μM) |
|---|---|---|---|---|---|
| **2a**-*eq* | 65.29 | –1.82 | 2.43 | **2a**-*ax* | 52.6 |
| **2b**-*eq* | 49.10 | –1.69 | 2.96 | **2b**-*ax* | 49.28 |
| **2c**-*eq* | 49.18 | –1.69 | 3.49 | **2c**-*ax* | 70.95 |
| **2d** | 32.20 | –1.57 | 2.97 | | |
| **2e**-*eq* | 19.21 | –1.28 | 2.92 | **2e**-*ax* | 30.0 |
| **2f**-*eq* | 4.66 | –0.67 | 3.46 | **2f**-*ax* | 7.74 |
| **2g**-*eq* | 15.14 | –1.18 | 3.99 | **2g**-*ax* | 13.32 |
| **2h**-*eq* | 57.76 | –1.76 | 4.52 | **2h**-*ax* | 24.02 |
| **2i**-*eq* | 2.88 | –0.46 | 3.99 | **2i**-*ax* | 5.18 |
| **2j**-*eq* | 13.40 | –1.13 | 4.52 | **2j**-*ax* | 15.01 |
| **2k** | 1.47 | –0.17 | 4.00 | | |
| **2l** | 2.28 | –0.36 | 4.53 | | |
| **2m** | 8.09 | –0.91 | 5.06 | | |
| **2n** | 3.16 | –0.50 | 5.06 | | |
| **2o** | 16.48 | –1.22 | 6.13 | | |
| **2p** | 144.33 | –2.16 | 1.94 | | |

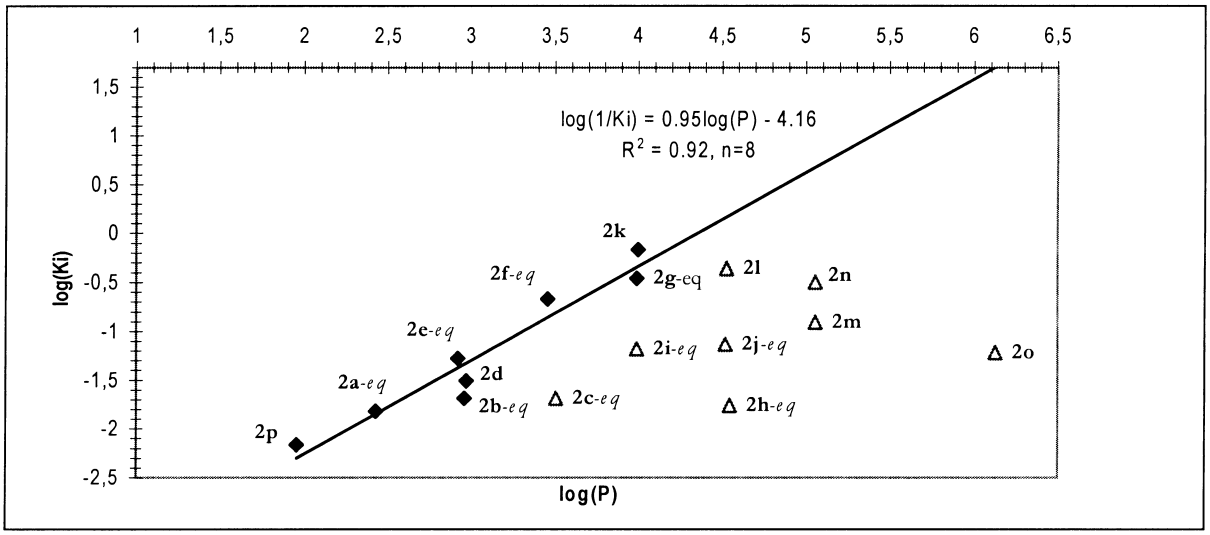


**Figure 6.** Hansch analysis of cyclohexylamines **2a–c**, **e–j**-*eq* and **2d**, **k–p**. Squares indicate the compounds for which the linear relationship log $(1/K_i)$ = a log (P) + c takes place.

more extensive studies on the biological activity of cyclohexylamines **2** were reported separately [16].

## 4. Results and discussion

QSAR analysis has already been carried out for a number of the NMDA receptor PCP site ligands [3]. These studies revealed that this binding site is a size-restricted pocket and both aromatic and amino groups are necessary for the high affinity binding [3, 17]. The importance of hydrophobic effect in binding of ligands has also been reported [18].

In the pharmacophore model developed by molecular modelling, two hydrophobic regions were recognized [3]. One of them requires an aromatic ring for high affinity binding and corresponds to the phenyl ring of the PCP molecule or the aromatic ring of MK-801. The other, common lipophilic size restricted area, corresponds to the cyclohexyl ring of PCP or second aromatic ring of MK-801.

Cyclohexylamine **2** homologues differ in their lipophilicity and steric requirements. Hansch analysis [19] was therefore chosen for SAR evaluation of cyclohexyl amines with an equatorial amino group (in the lowest energy conformation) **2a–c** and **e–j**-*eq* and **2d** and **2k–p**, as they might be regarded as aminoadamantane **1** structural analogues. Equation (1) expresses affinity as a function of log P (describing a hydrophobic effect) and a steric descriptor S. The strength of reinforced ionic binding between the receptor active centre and protonated amino group was assumed to be equal for these compounds. Log P values (*table VI*) for this homologue series were calculated from fragmental constants [20] using software ACD/Log P 1.0.

$$\log ( 1/\mathrm{Ki} ) = a \log ( P ) + b \log ( S ) + c \qquad (1)$$

*Figure 6* shows that for cyclohexylamines **2a**, **b** and **e–g**-*eq* and **2d**, **k** and **p**, affinity expressed as log (1/Ki) is a linear function of lipophilicity (log P). This indicates that steric factor (S) is negligible in these cases, i.e. these compounds fit properly in the PCP binding site. In the case of more bulky compounds such as **2c** and **h–j**-*eq* and **2l–o**, the steric factor becomes more important resulting in an obvious decline from linearity. A nearly perfect linear relationship observed for cyclohexylamines **2d**, **k** and **p** along with **2a**, **b** and **e–g**-*eq* was somewhat surprising, because only slight preference for the conformation with an equatorial amino group was expected for them. The possible reason could be that a conformer with an axial amino group also binds with the receptor. Very similar affinities of conformationally biased cyclohexylamine isomers **2**-*ax* and **2**-*eq* implies that (*table VI*).

Cyclohexylamines **2a–c** and **e–j**-*eq* and **2d** and **k–p** were superimposed with one of the most potent PCP site ligands (+)-MK-801 (*figure 7a*). Notably, the amines **2a**, **b** and **e–g**-*eq* and **2d**, **k** and **p** showed a perfect fit in the receptor site (determined by Hansch analysis) and also a perfect fit into the cavity between aromatic rings of

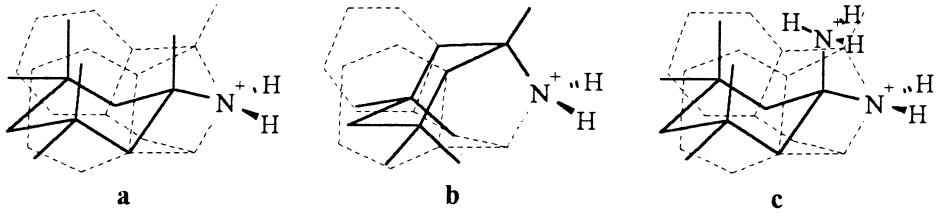


**Figure 7.** Schematic representation of superimposition of 1,3,5 substituted cyclohexylamines **2** with (+)MK-801 (dotted bonds).

MK-801. Moreover, amines **2c** and **h–j**-*eq* and **2l**–**o** with the axial 1,3-substituents larger than methyl or equatorial 3,5-substituents larger than ethyl group markedly exceed MK-801 dimensions and, consequently display a relatively lower affinity for the NMDA receptor.

Aminoadamantanes **1** have been suggested to occupy the region corresponding to the cyclohexyl ring of PCP or one of the aromatic rings of MK-801 [3]. Their moderate affinity has been explained by their large steric bulk not sufficiently tolerated in this region. The present investigation based on more rich information about SAR gives evidence that aminocyclohexanes **2**, and hence aminoadamantanes **1** do not discriminate between hydrophobic regions of PCP binding site but rather recognize this site as a whole lipophilic pocket. The medium affinity of sterically tolerated cyclohexylamines **2** and aminoadamantanes **1** is obviously due to the lack of an aromatic system as a pharmacophore element necessary for high affinity binding.

The similar binding of cylohexylamines with an axial amino group **2**-*ax* and diastereomers with an equatorial amino group **2**-*eq* can be explained in several ways. The superimposition of aminocyclohexanes **2**-*ax* with MK-801 taking the nitrogen atom as a common point also gave a good fit of the 3,5-substituted cyclohexyl globule with MK-801 (*figure 7b*). The lipophilic part of **2**-*ax* markedly exceeds the MK-801 dimensions when axial substituents are larger than methyl and equatorial substituents are larger than ethyl, i.e. the steric requirements of **2**-*ax* binding are similar to **2**-*eq* (*figure 7a*).

It cannot be excluded that the axial amino group in **2**-*ax* may bind to another ionic site point of the PCP binding site. When cyclohexylamine **2**-*ax* is superimposed with MK-801 the same way as **2**-*eq*, the axial amino group of **2**-*ax* is situated next to MK-801 5-methyl substituent (*figure 7c*). Recent SAR studies have revealed that an additional site point might be located in the proximity of the MK-801 5-methyl group [18].

In summary, we have developed a new class of the medium affinity NMDA receptor ion channel blockers based on a cyclohexylamine structure and established their structure–affinity relationships which could promote a rational design of the new PCP binding site ligands.

## 5. Experimental protocols

### *5.1. Chemistry*

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Microanalyses were performed on a Karlo Erba Instruments EA1108 and the results where within ± 0.4% of the calculated values. NMR spectra were recorded on a Brucker WH 90 and Brucker WM 360 spectrometers. Column chromatography was performed on Kieselgel 63–100 μm. TLC analyses were performed on Kieselgel 60 $F_{254}$ plates (Merck). Eluent: hexane/ethyl acetate, visualization agent: iodine vapours. Purity of the final products were determined by GC analysis (MN-OV-1 (Fused Silica), 25 m × 0.53 mm, $d_f$ = 1.0 μ, 50–270 °C (10° C/min)) and were found to be more than 99%.

#### *5.1.1. Cyclohexenones* **3**

##### *5.1.1.1. 5,5-Dimethyl-3-propyl-2-cyclohexen-1-one* **3g**

A solution of 3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one **8** [21] (5.04 g, 30 mmol) in ether was added dropwise to a stirred solution of propylmagnesium iodide prepared from 90 mg of magnesium and 90 mmol of 1-iodopropane in 60 mL of ether. After being stirred for 1 h at ambient temperature the reaction mixture was treated with 5% $H_2SO_4$ solution. The organic phase was separated, washed with brine, dried over $MgSO_4$ and evaporated to give a crude oil which was separated on a silica gel column, eluting with a hexane/ethyl acetate mixture. Cyclohexenone (**3g**) was obtained as a colourless oil (2.0 g, 70%). $^1$H-NMR ($CDCl_3$, TMS) δ: 0.92 (3H, t, *J* = 7 Hz); 1.03 (6H, s); 1.3–1.75 (2H, m); 2.16 (2H, t, *J* = 7 Hz); 2.17 (2H, d, *J* = 1.5 Hz); 2.21 (2H, s) and 5.87 ppm (1H, t, *J* = 1.5 Hz).

**Table VII.** $^1$H-NMR spectra of cyclohexanones **4**.

| Compound | $^1$H-NMR ($CDCl_3$, TMS) δ, ppm |
|---|---|
| **4g** | 0.79 (3H, t, 7 Hz); 0.96 (3H, s); 1.06 (3H, d, 7 Hz), 1.22 (2H, m); 1.5–2.4 (5H, m) |
| **4h** | 0.86 (3H, t, 6 Hz); 0.98 (3H, s); 1.01 (3H, d, 5 Hz), 1.05–1.35 (4H, m); 1.55–2.05 (4H, m); 2.11 (2H, s); 2.34 (1H, m) |
| **4i** | 0.88 (3H, s); 0.90 (3H, t, 7 Hz); 1.06 (3H, s); 1.15–1.45 (2H, m); 2.13 (2H, s); 1.45–2.45 (5H, m) |
| **4j** | 0.87 (6H, m); 1.15 (3H, s); 1.15–1.45 (4H, m); 2.13 (2H, s); 1.45–2.45 (5H, m) |
| **4l** | 0.78 (6H, t, 7 Hz); 1.04 (6H, s); 1.37 (2H, q, 7 Hz); 1.52 (2H, s); 2.16 (4H, s) |
| **4m** | 0.87 (6H, m); 1.03 (6H, s); 1.25 (8H, m); 1.53 (2H, s); 2.16 (4H, s) |

Cyclohexenones **3a–3d** were purchased form Aldrich. Cyclohexenones **3e** and **3f** were prepared as described [5, 22].

*5.1.2. General procedure for cyclohexanones* **4**

Anhydrous copper (I) chloride (7.5 mmol) was added to a cooled solution of alkylmagnesium iodide (15–18 mmol) in ether. The mixture was stirred in an inert atmosphere for 5 min and a solution of 2-cyclohexene-1-one **3** (10 mmol) in ether was added dropwise keeping the temperature below –5 °C. After the addition of ketone was completed, the reaction mixture was stirred for 1 h and carefully neutralised with saturated aqueous $NH_4Cl$ solution. Traditional workup for Grignard reactions gave crude material that was separated on a silica gel column, eluting with a petroleum ether/ethyl acetate mixture. The cyclohexanones **4** were obtained as oils. The yields are listed in *table II*. The $^1$H-NMR spectral data for all new cyclohexanones **4g**–**4j**, **l** and **m** are given in *table VII*.

3-Methylcyclohexanone **4a** and 3,3,5,5-tetramethylcyclohexanone **4k** were available from Aldrich. Known cyclohexanones were prepared according to the general procedure: 3-ethyl- and 3-propylcyclohexanones **4b** and **4c** [23, 24]; 3,3-dimethyl-,3,5-dimethyl- and 3,3,5-trimethylcyclohexanones **4d–4f** [25–27].

*5.1.3. General procedure for cyclohexanols* **5**

An ethereal solution of alkylmagnesium iodide (3–4 equivalents) was added dropwise to a cooled solution of cyclohexanone **2** in ether. The mixture was stirred for 1 h at ambient temperature and carefully destroyed with saturated aqueous ammonium chloride. Traditional workup for Grignard reactions followed by chromatography on a silica gel column eluting with petroleum ether/ethyl acetate provided cyclohexanols **5**. The yields are listed in *table III*. The $^1$H-NMR spectral data for all new cyclohexanols **5b**, **5c**, **5g**–**5i**, **5n** and **5o** are given in *table VIII*.

Methylcyclohexanol **5p** was purchased from Aldrich. Known cyclohexanols were prepared according to the general procedure: 1,3-dimethylcyclohexanols **5a** [12]; 1,3,3-trimethyl- and 1,3,5- trimethylcylohexanols **5d** and **5e**-*ex* [28, 29]; 1,3,3,5-tetramethyl- and 1,3,3,5,5-pentamethylcyclohexanols **5f**-*ax*, **5k** [15].

*5.1.4. General procedures for cyclohexyl azides* **6**

Procedure A:

The alcohol **5** was mixed with 1.7–2 N hydrazoic acid (10–13 equivalents) solution in chloroform and cooled in an ice bath. A solution of $TiCl_4$ (1.2 equivalents) in chloroform was added dropwise while the temperature was maintained below 5 °C. The mixture was stirred at

**Table VIII.** $^1$H-NMR spectra of cyclohexanols **5**.

| Compound | $^1$H-NMR ($CDCl_3$, TMS) δ, ppm |
|---|---|
| **5b**-*ax* | 0.84 (3H, t, 7 Hz); 1.17 (3H, s); 1.0–1.85 (12H, m) |
| **5b**-*eq* | 0.87 (3H, t, 7 Hz); 1.21 (3H, s); 1.0–1.85 (12H, m) |
| **5c**-*ax* | 0.86 (3H, t, 7 Hz); 1.18 (3H, s); 1.0–1.9 (14H, m) |
| **5c**-*eq* | 0.86 (3H, t, 7 Hz); 1.19 (3H, s); 1.0–1.85 (14H, m) |
| **5g**-*ax* | 0.80 (3H, s); 0.81 (3H, t, 7 Hz); 0.86 (3H, d, 6.5 Hz); 1.17 (3H, s); 0.9–2.0 (10H, m) |
| **5h**-*ax* | 0.81 (6H, m); 0.86 (3H, d, 6.5 Hz); 1.17 (3H, s); 0.9–2.0 (12H, m) |
| **5i**-*ax* | 0.87 (6H, m); 1.08 (3H, s); 1.18 (3H, s); 0.95–1.95 (10H, m) |
| **5j**-*ax* | 0.88 (6H, m); 1.09 (3H, s); 1.18 (3H, s); 0.9–1.95 (12H, m) |
| **5m** | 0.89 (9H, m); 1.21 (6H, s); 0.95–1.7 (11H, m) |
| **5n** | 0.78 (6H, t, 7 Hz); 0.89 (3H, s); 1.19 (6H, s); 0.95–1.3 (7H, m); 1.3–2.05 (4H, m) |
| **5o** | 0.86 (6H, t, 6.5 Hz); 0.88 (3H, s); 1.18 (6H, s); 0.9–1.3 (11H, m); 1.3–2.05 (4H, m) |

**Table IX.** $^1$H-NMR spectra of cyclohexyl azides **6**.

| Compound | $^1$H-NMR ($CDCl_3$, TMS) δ, ppm |
|---|---|
| **6a**-*ax* | 0.89 (3H, d, 6.5 Hz); 1.31 (3H, s); 0.95–2.0 (9H, m) |
| **6a**-*eq* | 0.92 (3H, d, 6.5 Hz); 1.28 (3H, s); 1.0–2.0 (9H, m) |
| **6b**-*ax* | 0.88 (3H, t, 7 Hz); 1.29 (3H, s); 0.95–2.0 (11H, m) |
| **6b**-*eq* | 0.88 (3H, t, 6.5 Hz); 1.27 (3H, s); 1.0–2.0 (11H, m) |
| **6c**-*ax* | 0.88 (3H, t, 6.5 Hz); 1.29 (3H, s); 1.0–2.0 (13H, m) |
| **6c**-*eq* | 0.88 (3H, t, 6.5 Hz); 1.27 (3H, s); 1.0–2.0 (13H, m) |
| **6d** | 0.90 (3H, s); 1.08 (3H, s); 1.27 (3H, s); 1.0–1.95 (8H, m) |
| **6e**-*ax* | 0.87 (6H, d, 6 Hz); 1.29 (3H, s); 0.90–2.1 (8H, m) |
| **6e**-*eq* | 0.90 (6H, d, 6 Hz); 1.27 (3H, s); 1.0–1.9 (8H, m) |
| **6f**-*ax* | 0.86 (3H, d, 6 Hz); 0.89 (3H, s); 1.09 (3H, s); 1.27 (3H, s); 0.95–1.9 (7H, m) |
| **6f**-*eq* | 0.92 (3H, d, 6 Hz); 0.94 (3H, s); 0.97 (3H, s); 1.36 (3H, s); 0.95–2.0 (7H, m) |
| **6g**-*ax* | 0.81 (6H, s and m); 0.86 (3H, d, 6 Hz); 1.27 (3H, s); 0.95–1.95 (9H, m) |
| **6g**-*eq* | 0.81 (3H, t, 7 Hz); 0.87 (3H, s); 0.91 (3H, d, 6 Hz); 1.34 (3H, s); 0.95–2.0 (9H, m) |
| **6h**-*ax* | 0.81 (3H, s); 0.84 (3H, d, 6 Hz); 0.87 (3H, m); 1.27 (3H, s); 1.0–2.0 (11H, m) |
| **6h**-*eq* | 0.88 (6H, s and m); 0.91 (3H, d, 6 Hz); 1.34 (3H, s); 1.0–1.95 (11H, m) |
| **6i**-*ax* | 0.91 (3H, t, 7 Hz); 0.92 (3H, s); 1.12 (3H, s); 1.31 (3H, s); 1.0–1.9 (9H, m) |
| **6i**-*eq* | 0.92 (3H, t, 7 Hz); 0.97 and 0.99 (total 6H, s); 1.37 (3H, s); 1.0–1.9 (9H, m) |
| **6j**-*ax* | 0.90 (6H, s and m); 1.10 (3H, s); 1.28 (3H, s); 0.95–1.9 (11H, m) |
| **6j**-*eq* | 0.89 (3H, t, 7 Hz); 0.95 (3H, s); 0.98 (3H, s); 1.37 (3H, s); 1.0–1.9 (11H, m) |
| **6k** | 0.89 (6H, s); 1.18 (6H, s); 1.29 (3H, s); 0.95–1.9 (6H, m) |
| **6l** | 0.89 (6H, s); 0.96 (3H, t, 7 Hz); 1.19 (6H, s); 1.0–1.9 (8H, m) |
| **6m** | 0.89 (6H, s); 0.93 (3H, m); 1.18 (6H, s); 1.0–1.8 (10H, m) |
| **6n** | 0.78 (6H, t, 7 Hz); 0.90 (3H, s); 1.18 (3H, s); 1.31 (3H, s); 0.95–1.95 (10H, m) |
| **6o** | 0.89 (9H, s and m); 1.17 (3H, s); 1.27 (3H, s); 0.95–1.95 (14H, m) |

room temperature for 24 h and passed down a column of alumina, eluting with chloroform. Evaporation of solvent provided azides **6** which were purified (in the case of diastereomers also separated) by flash chromatography on silica gel, eluting with light petroleum ether.

Procedure B:

Boron trifluoride etherate (12 mmol) was added dropwise to a stirred solution of cyclohexanol **5** (10 mmol) and trimethylsilyl azide (12 mmol) in benzene (20 mL). After being stirred for 24 h at room temperature the mixture was poured into water (50 mL). The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The solution was dried over $MgSO_4$, filtered and concentrated. The crude product was purified (in the case of diastereomers also separated) by flash chromatography on silica gel, eluting with light petroleum ether.

The yields of cyclohexyl azides **6** are listed in *table IV*. The $^1$H-NMR spectral data for cyclohexyl azides **6a**–**6o** are given in *table IX*. 1-Methylcyclohexyl azide **6p** is a known compound [8].

*5.1.5. General procedure for cyclohexylamines* **2**

A solution of cyclohexyl azide **6** in ether was added dropwise to a stirred suspension of lithium aluminum hydride (4 equivalents) in ether, which was cooled in an ice bath. The reaction mixture was stirred at room temperature for 5 h. Residual lithium aluminium hydride was carefully destroyed with water, the aqueous layer separated and was extracted twice with ether. The combined ethereal phases were washed with brine, dried over NaOH, filtered and evaporated. The product obtained was treated with HCl without subsequent characterization. The amine hydrochloride was prepared either by passing of HCl gas through the amine solution in hexane or by addition of a 1 N HCl solution in ether to the amine solution. In both cases the solvent was removed after HCl addition, the residue treated with hexane or acetonitrile and the crystalline product filtered off to give **2** with excellent purity. The yields of cyclohexylamines **2** are listed in *table V*. The $^1$H-NMR spectral data for cyclohexylamines **2a**–**2o** are given in *table X*. 1-Methylcyclohexylamine **2p** is a known compound [30].

**Table X.** $^{1}$H-NMR spectra of cyclohexylamines **2***.

| Compound | M.p. (°C) | $^{1}$H-NMR ($CDCl_3$, TMS) δ, ppm |
|---|---|---|
| **2a**-*ax* | > 250 (subl.) | 0.89 (3H, d, 6.5 Hz); 0.7–1.0 (2H, m); 1.2–1.35 (1H, m) 1.45 (3H, s); 1.6–2.1 (6H, m); 8.3 (3H, br s) |
| **2a**-*eq* | 200–202 | 0.91 (3H, d, 6.4 Hz); 0.85–1.0 (1H, m); 1.47 (3H, s); 1.15–1.75 (6H, m); 1.94 (2H, m); 8.3 (3H, br s) |
| **2b**-*ax* | > 250 (subl.) | 0.88 (3H, t, 7.5 Hz); 0.7–1.0 (2H, m); 1.1–1.35 (3H, m); 1.46 (3H, s); 1.6–1.9 (4H, m); 2.0–2.15 (2H, m); 8.35 (3H, br s) |
| **2b**-*eq* | 179–181 | 0.87 (3H, t, 7 Hz); 1.45 (3H, s); 0.8–2.0 (11H, m); 8.3 (3H, br s) |
| **2c**-*ax* | > 250 (subl.) | 0.87 (3H, t, 7.3 Hz); 0.7–1.0 (2H, m); 1.05–1.4 (5H, m); 1.45 (3H, s); 1.55–1.7 (1H, m); 1.75–1.95 (3H, m); 2.0–2.1 (2H, m); 8.3 (3H, br s) |
| **2c**-*eq* | 181–182 | 0.85 (3H, t, 7.1 Hz); 0.8–0.9 (1H, m); 1.47 (3H, s); 1.15–1.5 (7H, m); 1.6–1.8 (3H, m); 1.9–2.0 (2H, m); 8.3 (3H, br s) |
| **2d** | 230–231 | 0.96 (3H, s); 1.06 (3H, s); 1.15–1.40 (2H, m); 1.50 (3H, s); 1.5–1.85 (6H, m); 8.25 (3H, br s) |
| **2e**-*ax* | > 280 | 0.4–0.6 (1H, m); 0.90 (6H, d, 6.5 Hz); 0.8–1.1 (2H, m); 1.44 (3H, s); 1.6–2.15 (5H, m); 8.3 (3H, br s) |
| **2e**-*eq* | 237–238 | 0.45–0.75 (1H, m); 0.90 (6H, d, 5 Hz); 1.47 (3H, s); 1.2–1.7 (6H, m); 1.94 (2H, d, 11.5); 8.3 (3H, br s) |
| **2f**-*ax* | > 240 | 0.72 (1H, t, 12.5 Hz); 0.90 and 0.91 (total 6H, d, 6.5 Hz and s); 0.85–1.0 (1H, m); 1.16 (1H d, 14.8 Hz); 1.23 (3H, s); 1.45 (3H, s); 1.4–1.55 (1H, m); 1.85–2.0 (2H, m); 2.1 (1H, m); 8.2 (3H, br s) |
| **2f**-*eq* | > 240 | 0.96, 1.0 and 1.04 (total 9H, d, 6 Hz, s and s); 0.9–1.1 (1H, m); 1.37 (1H, t, 12 Hz); 1.44 (1H, d, 13 Hz); 1.61 (3H, s); 1.6–1.95 (3H, m); 2.02 (1H, d, 12 Hz) 8.25 (3H, br s) |
| **2g**-*ax* | 250–253 | 0.67 (1H, t, 13 Hz); 0.84 (3H, s); 0.85–0.95 (m, 6H); 1.07 (1H, d, 15.5 Hz); 1.48 (3H, s); 1.5–1.8 (4H, m); 1.9–2.1 (3H, m); 8.15 (3H, br s) |
| **2g**-*eq* | 228–231 | 0.83 (3H, t, 7.5 Hz); 0.88 (3H, s); 0.91 (3H, d, 6.5 Hz); 0.8–0.95 (1H, m); 1.55 (3H, s); 1.15–1.80 (6H, m); 1.9–2.0 (2H, m); 8.3 (3H, br s) |
| **2h**-*ax* | 167–168 | 0.61 (1H, t, 13 Hz); 0.86 (3H, s); 0.89 (3H, d, 6 Hz); 0.85–1.0 (1H, m); 1.00 (3H, t, 7 Hz); 1.13 (1H, d, 15.5 Hz); 1.51 (3H, s); 1.15–1.75 (5H, m); 1.89 (1H, m); 1.95 (1H, d, 15.5 Hz); 2.11 (1H, d, 14.5 Hz); 8.2 (3H, br s) |
| **2h**-*eq* | 237–238 | 0.8–0.95 (10H, m); 1.54 (3H, s); 1.1–1.8 (8H, m); 1.97 (2H, d, 13 Hz); 8.3 (3H, br s) |
| **2i**-*ax* | 255–257 | 0.72 (1H, t, 13 Hz); 0.91 (3H, t, 7.5 Hz); 0.92 (3H, s); 0.8–0.95 (1H, m); 1.23 (3H, s); 1.1–1.3 (3H, m); 1.46 (3H, s); 1.51 (1H, d, 13 Hz); 1.85–2.0 (2H, m); 2.03 (1H, d, 15 Hz); 8.3 (3H, br s) |
| **2i**-*eq* | 216–218 | 0.88 (3H, t, 7.5 Hz); 0.8–0.95 (1H, m); 0.96 (3H, s,); 0.98 (3H, s); 1.2–1.35 (3H, m); 1.56 (3H, s); 1.4–1.56 (3H, m); 1.83 (1H, d, 13 Hz); 2.01 (1H, d, 12 Hz); 8.3 (3H, br s) |
| **2j**-*ax* | 218–221 | 0.72 (1H, t, 13 Hz); 0.89 (3H, t, 7 Hz); 0.92 (3H, s); 0.85–0.9 (1H, m); 1.23 (3H, s); 1.45 (3H, s); 1.0–2.1 (9H, m); 8.2 (3H, br s) |
| **2j**-*eq* | 200–203 | 0.86 (3H, t, 7 Hz); 0.8–0.95 (1H, m); 0.95 (3H, s); 0.98 (3H, s); 1.55 (3H, s); 1.1–1.7 (8H, m); 1.83 (1H, d, 13 Hz); 1.99 (1H, d, 12 Hz); 8.3 (3H, br s) |
| **2k** | 235–237 | 1.02 (6H, s) and 1.07 (6H, s); 1.26 (2H, br s); 1.62 (3H, s); 1.71 (4H, br s) |
| **2l** | 215–218 | 1.03 (3H, s) 1.06 (3H, s); 1.09 (3H, t, 7.5 Hz); 1.30 (2H, br s); 1.63 and 1.78 (total 4H, both d, 14 Hz); 1.97 (2H, q, 7 Hz); 8.15 (3H, br s) |
| **2m** | > 280 | 0.93 (3H, t, 7 Hz); 1.01 (6H, s); 1.04 (6H, s); 1.29 (2H, br s); 1.35–2.0 (4H, m); 1.70 (4H, m); 8.2 (3H, br s) |
| **2n** | 99–102 | 0.75–0.85 (6H, m); 1.04 (3H, s); 1.05 (3H, s); 1.19 (1H, d, 14 Hz); 1.25–1.50 (5H, m); 1.60 (3H, s); 1.67 and 1.75 (total 4H, both d, 14 Hz); 8.25 (3H, br s) |
| **2o** | 167–169 | 0.83–0.89 (6H, m); 1.03 (3H, s); 1.05 (3H, s); 1.15–1.45 (10H, m); 1.57 (2H, d, 14.5 Hz); 1.61 (3H, s); 1.77 (2H, d, 14 Hz); 8.2 (3H, br s) |

* 1,*trans*-3-Dimethylcyclohexylamine hydrochloride **2a**-*ax*: $^{13}$C-NMR ($CDCl_3$, 50 MHz) δ: 21.75 (C-5); 23.02 (3-$CH_3$); 27.99 (C-3); 28.67 (1-$CH_3$); 34.72 (C-4); 36.63 (C-6); 45.50 (C-2); 56.20 (C-1); 1,*cis*-3- dimethylcyclohexylamine hydrochloride semihydrate **2a**-*eq*: $^{13}$C-NMR ($CDCl_3$, 50 MHz) δ: 22.9–23.05 (C-5, 3-$CH_3$, 1-$CH_3$); 29.71 (C-3); 34.68 (C-4); 36.87 (C-6); 45.45 (C-2); 56.81 (C-1); 1-methyl, *trans*-3-ethylcyclohexylamine hydrochloride **2b**-*ax*; 1-methyl,*cis*-3-ethylcyclohexylamine hydrochloride **2b**-*eq*; 1-methyl,*trans*-3-propylcyclohexylamine hydrochloride **2c**-*ax*; 1-methyl,*cis*-3-propylcyclohexylamine hydrochloride **2c**-*eq*; 1,3,3-trimethylcyclohexylamine hydrochloride **2d**; 1,*trans*-3, *trans*-5-trimethylcyclohexylamine hydrochloride **2e**-*ax*; 1,*cis*-3, *cis*-5-trimethylcyclohexylamine hydrochloride hydrate **2e**-*eq*; 1,3,3,*trans*-5-tetramethylcyclohexylamine hydrochloride **2f**-*ax*; 1,3,3,*cis*-5-tetramethylcyclohexylamine hydrochloride semihydrate **2f**-*eq*; *cis*-3-ethyl-1,trans-3,trans-5-trimethylcyclohexylamine hydrochloride **2g**-*ax*; *trans*-3-ethyl-1,cis-3,cis-5-trimethylcyclohexylamine hydrochloride **2g**-*eq*; *cis*-3-propyl-1,trans-3,trans-5-trimethylcyclohexylamine hydrochloride **2h**-*ax*; *trans*-3-propyl-1,cis-3,cis-5-trimethylcyclohexylamine hydrochloride **2h**-*eq*; 1,3,3-trimethyl-*trans*-5-ethylcyclohexylamine hydrochloride **2i**-*ax*; 1,3,3-trimethyl-*cis*-5-ethylcyclohexylamine hydrochloride semihydrate **2i**-*eq*; 1,3,3-trimethyl-*trans*-5-propylcyclohexylamine hydrochloride **2j**-*ax*; 1,3,3-trimethyl-*cis*-5-propylcyclohexylamine hydrochloride **2j**-*eq*; 1,3,3,5,5-pentamethylcyclohexylamine hydrochloride **2k**; 1-ethyl-3,3,5,5-tetramethylcyclohexylamine hydrochloride hydrate **2l**; 1-propyl-3,3,5,5-tetramethylcyclohexylamine **2m**; 3,3-diethyl-1,5,5-trimethylcyclohexylamine hydrate **2n**; 3,3-Dipropyl-1,5,5-trimethylcyclohexylamine **2o**.

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