The present invention relates to compounds of the general formula wherein R² is -(CH₂)n-aryl or -(CH₂)m-heteroaeryl, wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyl substituted by halogen, lower alkoxy, lower alkyl, cyano, nitro, -O-lower alkyl substituted by halogen or morpholino; R² is -(CH₂)n-aryl or -(CH₂)m-heteroaeryl, wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of lower alkyl, lower alkoxy, halogen or -N(lower alkyl)₂; R₄ is hydrogen or lower alkyl; R₃ is -(CH₂)n-aryl or -(CH₂)m-heteroaeryl, wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen or lower alkoxy, or is lower alkyl, -(CH₂)rcycloalkyl; or R² and R₃ form together with the N-atom a heterocyclic ring; n is 0, 1 or 2; and to pharmaceutically acceptable acid addition salts thereof. It has been found that the compounds of general formula I or their tautomeric forms are good inhibitors of the glycine transporter 1 (GlyT-1), and that they have a good selectivity to glycine transporter 2 (GlyT-2) inhibitors, useful for the treatment of schizophrenia.
The present invention relates to compounds of the general formula

\[
\begin{align*}
\text{R}^1 & \quad \text{is } -(\text{CH}_2)_n\text{-aryl or } -(\text{ClH}_n\text{-heteroaryl}, \text{wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of}\text{ halogen, lower alkyl substituted by halogen, lower alkoxy, lower alkyl, cyano, nitro, -0-lower alkyl substituted by halogen or morpholinyl; } \\
\text{R}^2 & \quad \text{is } -(\text{CH}_2)_n\text{-aryl or } -(\text{ClH}_n\text{-heteroaryl}, \text{wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of lower alkyl, lower alkoxy, halogen or } -\text{N(lower alkyl)}_2; \\
\text{R}^3 & \quad \text{is hydrogen or lower alkyl;} \\
\text{R}^4 & \quad \text{is } -(\text{CH}_2)_n\text{-aryl or } -(\text{ClH}_n\text{-heteroaryl}, \text{wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen or lower alkoxy, or is lower alkyl, } -(\text{ClH}_n\text{-cycloalkyl;} \text{ or}} \\
\text{R}^3 \text{ and } \text{R}^4 & \text{form together with the N-atom a heterocyclic ring;} \\
n & \text{is 0, 1 or 2;} \\
\text{and to pharmaceutically acceptable acid addition salts thereof.}
\end{align*}
\]

If $\text{R}^3$ is hydrogen, the structure of formula I includes also its tautomeric form of formula
wherein

- \( R^1 \) is \(-(CH_2)_n\) -aryl or \(-(CH_2)_n\) -heteroaryl, wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyl substituted by halogen, lower alkoxy, lower alkyl, cyano, nitro, -O-lower alkyl substituted by halogen or morpholinyl;

- \( R^2 \) is \(-(CH_2)_n\) -aryl or \(-(CH_2)_n\) -heteroaryl, wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of lower alkyl, lower alkoxy, halogen or -N(lower alkyl)2;

- \( R^4 \) is \(-(CH_2)_n\) -aryl or \(-(CH_2)_n\) -heteroaryl, wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen or lower alkoxy, or is lower alkyl, \(-(CH_2)_n\) -cycloalkyl; or

\( n \) is 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

The present invention relates to compounds of general formula I or IA, to pharmaceutical compositions containing them and their use in the treatment of neurological and neuropsychiatric disorders. It has surprisingly been found that the compounds of general formula I or IA are good inhibitors of the glycine transporter 1 (GlyT-1), and that they have a good selectivity to glycine transporter 2 (GlyT-2) inhibitors.

Schizophrenia is a progressive and devastating neurological disease characterized by episodic positive symptoms such as delusions, hallucinations, thought disorders and psychosis and persistent negative symptoms such as flattened affect, impaired attention and social withdrawal, and cognitive impairments (Lewis DA and Lieberman JA, Neuron, 28:325-33, 2000). For decades research has focused on the "dopaminergic hyperactivity" hypothesis which has led to therapeutic interventions involving blockade of the dopaminergic system (Vandenbarg RJ and Aubrey KR., Exp. Opin. Ther. Targets, 5(4): 507-518, 2001; Nakazato A and Okuyama S, et al., Exp. Opin. Ther. Patents, 10(1): 75-98, 2000). This pharmacological approach poorly address negative and cognitive symptoms which are the redictors of functional outcome (Sharma T., BrJ. Psychiatry,
A complementary model of schizophrenia was proposed in the mid-1960s based upon the psychotomimetic action caused by the blockade of the glutamate system by compounds like phencyclidine (PCP) and related agents (ketamine) which are non-competitive NMDA receptor antagonists. Interestingly, in healthy volunteers, PCP-induced psychotomimetic action incorporates positive and negative symptoms as well as cognitive dysfunction, thus closely resembling schizophrenia in patients (Javitt DC et al., Biol. Psychiatry, 45: 668-679, 1999). Furthermore, transgenic mice expressing reduced levels of the NMDAR1 subunit display behavioral abnormalities similar to those observed in pharmacologically induced models of schizophrenia, supporting a model in which reduced NMDA receptor activity results in schizophrenia-like behavior (Mohn AR et al., Cell, 98: 427-236, 1999).

Glutamate neurotransmission, in particular NMDA receptor activity, plays a critical role in synaptic plasticity, learning and memory, such that NMDA receptors appear to serve as a graded switch for gating the threshold of synaptic plasticity and memory formation (Wiley, NY; Bliss TV and Collingridge GL, Nature, 361: 31-39, 1993). Transgenic mice overexpressing the NMDA NR2B subunit exhibit enhanced synaptic plasticity and superior ability in learning and memory (Tang JP et al., Natur, 401: 63-69, 1999).

Thus, if a glutamate deficit is implicated in the pathophysiology of schizophrenia, enhancing glutamate transmission, in particular via NMDA receptor activation, would be predicted to produce both anti-psychotic and cognitive enhancing effects.

The amino acid glycine is known to have at least two important functions in the CNS. It acts as an inhibitory amino acid, binding to strychnine-sensitive glycine receptors, and it also influences excitatory activity, acting as an essential co-agonist with glutamate for N-methyl-D-aspartate (NMDA) receptor function. While glutamate is released in an activity-dependent manner from synaptic terminals, glycine is apparently present at a more constant level and seems to modulate/control the receptor for its response to glutamate.

One of the most effective ways to control synaptic concentrations of neurotransmitter is to influence their re-uptake at the synapses. Neurotransmitter transporters act by removing neurotransmitters from the extracellular space, and can control their extracellular lifetime and thereby modulate the magnitude of the synaptic transmission (Gainetdinov RR et al, Trends in Pharm. Sd., 23(8): 367-373, 2002).

Glycine transporters, which form part of the sodium and chloride family of neurotransmitter transporters, play an important role in the termination of post-synaptic glycinergetic actions and maintenance of low extracellular glycine concentration by re-uptake of glycine into presynaptic nerve terminals and surrounding fine glial processes.
Two distinct glycine transporter genes have been cloned (GlyT-1 and GlyT-2) from mammalian brain, which give rise to two transporters with -50% amino acid sequence homology. GlyT-1 presents four isoforms arising from alternative splicing and alternative promoter usage (Ia, Ib, Ic and Id). Only two of these isoforms have been found in rodent brain (GlyT-1a and GlyT-Ib). GlyT-2 also presents some degree of heterogeneity. Two GlyT-2 isoforms (2a and 2b) have been identified in rodent brains. GlyT-1 is known to be located in CNS and in peripheral tissues, whereas GlyT-2 is specific to the CNS. GlyT-1 has a predominantly glial distribution and is found not only in areas corresponding to strychnine sensitive glycine receptors but also outside these areas, where it has been postulated to be involved in modulation of NMDA receptor function (Lopez-Corcuera B et al., Mol. Mem. Biol. 18: 13-20, 2001). Thus, one strategy to enhance NMDA receptor activity is to elevate the glycine concentration in the local microenvironment of synaptic NMDA receptors by inhibition of GlyT-1 transporter (Bergeron R. et al., Proc. Natl. Acad. Sci. USA. 95: 15730-15734, 1998; Chen L. et al., J. Neurophysiol. 89(2): 691-703, 2003).

Glycine transporter inhibitors are suitable for the treatment of neurological and neuropsychiatric disorders. The majority of diseases states implicated are psychoses, schizophrenia (Armer RE and Miller DJ, Exp. Opin. Ther. Patents, 11 (4): 563-572, 2001), psychotic mood disorders such as severe major depressive disorder, mood disorders associated with psychotic disorders such as acute mania or depression, associated with bipolar disorders and mood disorders, associated with schizophrenia, (Pralong ET et al., Prog. Neurobiol, 67: 173-202, 2002), autistic disorders (Carlsson ML., J. Neural Trans., 105: 525-535, 1998), cognitive disorders such as dementias, including age related dementia and senile dementia of the Alzheimer type, memory disorders in a mammal, including a human, attention deficit disorders and pain (Armer RE and Miller DJ, Exp. Opin. Ther. Patents, 11 (4): 563-572, 2001).

Thus, increasing activation of NMDA receptors via GlyT-I inhibition may lead to agents that treat psychosis, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

Objects of the present invention are the compounds of formula I and IA per se, the use of compounds of formula I and IA and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases related to activation of NMDA receptors via Glyt-I inhibition, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I and IA in the control or prevention of illnesses such as psychoses, dysfunction in memory and learning, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.
The preferred indications using the compounds of the present invention are schizophrenia, cognitive impairment and Alzheimer's disease.

Further objects of the invention are all pharmaceutically active salts of compounds of formula I, all racemic mixtures, all their corresponding enantiomers and/or optical isomers and tautomeric forms.

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred alkyl groups are groups with 1 - 4 carbon atoms.

As used herein, the term "cycloalkyl" denotes a saturated ring containing from 3 to 6 carbon atoms.

As used herein, the term "lower alkoxy" denotes a saturated straight- or branched-chain group containing from 1 to 6 carbon atoms as described above, which is connected via an oxygen atom.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "aryl" denotes a monovalent cyclic aromatic hydrocarbon radical consisting of one ring or two fused rings in which at least one ring is aromatic in nature, for example phenyl, benzyl, naphthyl or biphenyl.

The term "heteroaryl" denotes a monovalent aromatic carbocyclic radical consisting of one ring or two fused rings, which contains at least one heteroatom, for example pyridyl, pyrazolyl, furanyl or thiophenyl.

The term "alkyl, substituted by halogen" denotes for example the following groups: CF₃, CHF₂, CH₂F, CH₂CF₃, CH₂CHF₂, CH₂CH₂F, CH₂CH₂CF₃, CH₂CH₂CH₂CF₃, CH₂CH₂Cl, CH₂CF₂CF₃, CH₂CF₂CHF₂, CF₂CHFCF₃, (CH₃)₂CF₃, CH(1H₃)CF₃ or CH(CH₂F)CH₂F.

The term "heterocyclic ring" denotes a saturated or partially saturated ring system, wherein an N-atom is in 1-position, for example azepan-1-yl or 3,4-dihydro-isoquinolin-1-yl.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid,
phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

Preferred compounds of the present application are compounds of formula I, wherein $R^1$ is phenyl substituted by halogen, $R^2$ is phenyl and $R^4$ is benzyl, for example

(\textit{Rac})-4-benzylamino-1-(4-chloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one

(\textit{7a}c)-4-benzylamino-1-(3,4-dichloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one or

(-)-4-benzylamino-1-(4-chloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one.

Preferred compounds of the present application are further compounds of formula I, wherein $R^1$ is phenyl substituted by halogen, $R^2$ is phenyl substituted by lower alkyl and $R^4$ is benzyl, for example

(Rac)-4-benzylamino-1-(3,4-dichloro-phenyl)-5-p-tolyl-1,5-dihydro-imidazol-2-one or

(Rac)-4-benzylamino-1-(3,4-dichloro-phenyl)-5-(3,4-dimethyl-phenyl)-1,5-dihydro-imidazol-2-one.

Preferred compounds of the present application are compounds of formula I, wherein $R^1$ and $R^2$ are phenyl substituted by halogen and $R^4$ is benzyl, for example

(Rac)-4-benzylamino-5-(4-chloro-phenyl)-1-(3,4-dichloro-phenyl)-1,5-dihydro-imidazol-2-one

(Rac)-4-benzylamino-1-(3,4-dichloro-phenyl)-5-(4-fluoro-phenyl)-1,5-dihydro-imidazol-2-one or

(Rac)-4-benzylamino-1-(3-chloro-4-fluoro-phenyl)-5-(4-fluoro-phenyl)-1,5-dihydro-imidazol-2-one.

Preferred compounds of the present application are compounds of formula I, wherein $R^1$ is phenyl substituted by halogen, $R^2$ is phenyl substituted by methoxy and $R^4$ is benzyl, for example

(Rac)-4-benzylamino-1-(3,4-dichloro-phenyl)-5-(3-methoxy-phenyl)-1,5-dihydro-imidazol-2-one.

Preferred compounds of the present application are further compounds of formula I, wherein $R^1$ is phenyl substituted by halogen, $R^2$ is phenyl and $R^4$ is benzyl substituted by halogen, for example

Rac-\textit{1-}(3,4-dichloro-phenyl)-4-(4-fluorobenzylamino)-5-phenyl-1,5-dihydro-imidazol-2-one.

Preferred compounds of the present application are further compounds of formula I, wherein $R^1$ is phenyl substituted by halogen, $R^2$ is phenyl and $R^4$ is lower alkyl, for example

Rac-\textit{1-}(3,4-dichloro-phenyl)-4-(3-methyl-butylamino)-5-phenyl-1,5-dihydroimidazol-2-
one or

\((Rac)-1-(3,4\text{-dichloro-phenyl})-4\text{-hexylamino-S-phenyl-1^-dihydro-imidazol-1-one.}\)

Preferred compounds of the present application are further compounds of formula I, wherein \(R^1\) is phenyl substituted by halogen, \(R^2\) is phenyl and \(R^4\) is -CH\(_2\)-cycloalkyl, for example

\((Rac)-4-(\text{cyclohexylmethyl-amino}-1-(3,4\text{-dichloro-phenyl})-5\text{-phenyl-1,5-dihydro-imidazol-2-one.}\)

The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes (a) or (b) described below, which process comprises

a) brominating a compound of formula

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{R}^3 \text{R}^4
\end{array}
\]

followed by reaction with an amine of formula

\[ \text{NHR}^3 \text{R}^4 \]

to a compound of formula

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{N} \text{R}^4
\end{array}
\]

wherein the substituents \(R^1\), \(R^2\), \(R^3\) and \(R^4\) are as defined above, or

b) reacting in one step a primary amine of formula \(R^2\text{NH}_2 (\text{III})\), together with

\[
\begin{array}{c}
\text{R}^3 \text{N} \\
\text{N} \text{C} \text{C}^- \\
\text{V}
\end{array}
\]

called potassium cyanate, an isonitrile of formula (V) and an aldehyde of formula \(R^1\text{C(O)H (IV)}\) to a compound of formula

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4
\end{array}
\]

wherein the substituents \(R^1\), \(R^2\) and \(R^4\) are as defined above, and
if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The compounds of formula I may be prepared in accordance with process variants (a) or (b) and with the following schemes 1 or 2. The starting materials are either commercially available, are otherwise known in the chemical literature, or may be prepared in accordance with methods well known in the art.

Scheme 1

A 4-step-synthesis is shown in scheme 1

1) Reaction of an isocyanate with an amino ketone in the presence of a base to yield the 3-(2-oxo)-urea derivatives.

2) Cyclisation of 3-(2-oxo)-urea derivatives in the presence of concentrated hydrochloric acid leads to the formation of 1,5-substituted-1,3-dihydro-imidazol-2-one derivatives.

3) Bromination of 1,5-substituted-1,3-dihydro-imidazol-2-one derivatives,

4) followed by reaction with primary amines leads to formation of compounds of general structure I.

Step 1: Synthesis of ureas of formula IX

To a suspension of a compound of formula VIII and of a compound of formula VII is added an aqueous solution of sodium carbonate. The reaction mixture is stirred overnight at room temperature affording a precipitate which is filtered off. The precipitate is worked up in conventional manner.

Step 2: Synthesis of 1,3-dihydro-imidazol-2-ones of formula II
Concentrated hydrochloric acid is added to a compound of formula \( I \) to form a suspension at room temperature. The reaction mixture is stirred for one week until the suspension has transformed into a corresponding compound of formula \( II \).

Steps 3 and 4: Bromination and amination of 1,5-diphenyl-1,3-dihydro-imidazol-2-ones

To a solution of a compound of formula \( II \) in dry chloroform in the presence of molecular sieves (4Å), a solution of bromine in chloroform is added dropwise using a syringe. The reaction mixture is stirred at 0°C until completion of bromination is observed by TLC. An amine of formula \( \text{NHR} \text{R}^3 \text{R}^4 \) is then added via a syringe and the reaction is allowed to warm to room temperature and is then heated to about 65°C for 24 hours. The reaction is carried under nitrogen throughout.

Compounds of formula \( I \) can further be prepared by Ugi's reaction (\textit{Liebigs Ann. Chem.}, 1963, 80, 670 or \textit{Chem. Ber.}, 1964, 97, 2276, or \textit{Angew. Chem.}, 1962, 74, 9). This is a one step reaction of primary amines, potassium cyanate, isonitriles and aldehydes or ketones, as shown in scheme 2.

\[
\text{Scheme 2}
\]

A mixture of an aldehyde of formula \( IV \) and a corresponding isocyanide of formula \( V \) in methanol is treated with a solution of potassium cyanate of formula \( VI \) in water. A compound of formula \( III \) and pyridinium hydrochloride is added and the mixture is stirred at room temperature for about 48 hours. The solid form is filtered off and triturated with diethyl ether to give the compound of formula 1-1 or the corresponding tautomere.

Isolation and purification of the compounds

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the preparations and
examples herein below. However, other equivalent separation or isolation procedures could, of course, also be used. Racemic mixtures of chiral compounds of formula I can be separated using chiral HPLC.

**Salts of compounds of formula I**

The compounds of formula I may be basic, for example in cases where the residue R³ contains a basic group such as an aliphatic or aromatic amine moiety. In such cases the compounds of formula I maybe converted to a corresponding acid addition salt.

The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained between 0 °C and 50 °C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

The acid addition salts of the basic compounds of formula I maybe converted to the corresponding free bases by treatment with at least a stoichiometric equivalent of a suitable base such as sodium or potassium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

The compounds of formula I and their pharmacetically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention are good inhibitors of the glycine transporter I (GlyT-I).

The compounds were investigated in accordance with the test given hereinafter.

**Solutions and materials**

**DMEM complete medium:** Nutrient mixture F-12 (Gibco life-technologies), fetal bovine serum (FBS) 5 %, (Gibco life technologies), Penicillin/Streptomycin 1 % (Gibco life technologies), Hygromycin 0.6 mg/ml (Gibco life technologies), Glutamine 1 mM Gibco life technologies)

**Uptake buffer (UB):** 150 mM NaCl, 10 mM Hepes-Tris, pH 7.4, 1 mM CaCl₂, 2.5 mM KCl, 2.5 mM MgSO₄, 10 mM (+) D-glucose.

**Flp-in™-CHO (Invitrogen Cat n° R758-07)** cells stably transfected with mGlyTlb cDNA.
Glycine uptake inhibition assay (niGlyT-Ib)

On day 1 mammalian cells, (Flp-in™-CHO), transfected with mGlyT-Ib cDNA, were plated at the density of 40,000 cells/well in complete F-12 medium, without hygromycin in 96-well culture plates. On day 2, the medium was aspirated and the cells were washed twice with uptake buffer (UB). The cells were then incubated for 20 min at 22°C with either (i) no potential competitor, (ii) 10 mM non-radioactive glycine, (iii) a concentration of a potential inhibitor. A range of concentrations of the potential inhibitor was used to generate data for calculating the concentration of inhibitor resulting in 50% of the effect (e.g. IC_{50}, the concentration of the competitor inhibiting glycine uptake of 50%). A solution was then immediately added containing [^3H]-glycine 60 nM (11-16 Ci/mmol) and 25 μM non-radioactive glycine. The plates were incubated with gentle shaking and the reaction was stopped by aspiration of the mixture and washing (three times) with ice-cold UB. The cells were lysed with scintillation liquid, shaken 3 hours and the radioactivity in the cells was counted using a scintillation counter.

The preferred compounds show an IC_{50} (μM) at GlyT-I in the range of 0.007 - 0.1, as shown in the table below.

<table>
<thead>
<tr>
<th>Example</th>
<th>IC_{50} (μM)</th>
<th>Example</th>
<th>IC_{50} (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.062</td>
<td>44</td>
<td>0.058</td>
</tr>
<tr>
<td>13</td>
<td>0.076</td>
<td>50</td>
<td>0.062</td>
</tr>
<tr>
<td>24</td>
<td>0.04</td>
<td>51</td>
<td>0.007</td>
</tr>
<tr>
<td>25</td>
<td>0.057</td>
<td>53</td>
<td>0.082</td>
</tr>
<tr>
<td>28</td>
<td>0.035</td>
<td>57</td>
<td>0.077</td>
</tr>
<tr>
<td>41</td>
<td>0.072</td>
<td>58</td>
<td>0.024</td>
</tr>
<tr>
<td>43</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The compounds of formula I and IA and the pharmaceutically acceptable salts of the compounds of formula I and IA can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragees, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected
rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and IA can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragees and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are however usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I and IA or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I and IA and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of schizophrenia, cognitive impairment and Alzheimer's disease.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1 000 mg per day of a compound of general formula I or IA or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.
Tablet Formulation (Wet Granulation)

<table>
<thead>
<tr>
<th>Item</th>
<th>Ingredients</th>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 mg</td>
</tr>
<tr>
<td>1</td>
<td>Compound of formula I or IA</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Lactose Anhydrous DTG</td>
<td>125</td>
</tr>
<tr>
<td>3</td>
<td>Sta-Rx 1500</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Microcrystalline Cellulose</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>Magnesium Stearate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>167</td>
</tr>
</tbody>
</table>

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

<table>
<thead>
<tr>
<th>Item</th>
<th>Ingredients</th>
<th>mg/capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 mg</td>
</tr>
<tr>
<td>1</td>
<td>Compound of formula I or IA</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Hydrous Lactose</td>
<td>159</td>
</tr>
<tr>
<td>3</td>
<td>Corn Starch</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>Talc</td>
<td>10</td>
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<td>Magnesium Stearate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total</td>
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</tr>
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Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.
The following examples illustrate the invention but are not intended to limit its scope. The following abbreviations were used in the examples:

Example 1

4-Benzylamino-1-(2,4-difluoro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one

A mixture of 2.32 mmol benzaldehyde and 2.32 mmol benzylisocyanide in 1 ml methanol was treated with a solution of 2.32 mmol potassium cyanate in 0.5 ml water. 2.32 mmol of 2,4-difluoroaniline and 2.32 mmol of pyridinium hydrochloride was added and the mixture stirred at room temperature for 48 hours. The solid formed was filtered off and tritutrated with diethyl ether to give 103 mg of the title compound as a slightly brown solid. Yield = 12%. MS (m/e): 378.5 (100%; M+H+), 400.1 (46%; M+Na).

Example 2

rac-4-Benzylamino-1,5-diphenyl-1,5-dihydro-imidazol-2-one

The title compound can be prepared in a similar way as example 1 from benzaldehyde, benzylisocyanide, and aniline. MS (m/e): 340.3 (M-H).

Example 3

rac-4-Benzylamino-5-phenyl-1-p-tolyl-1,5-dihydro-imidazol-2-one

The title compound can be prepared in a similar way as example 1 from benzaldehyde, benzylisocyanide, and 4-methylaniline. MS (m/e): 354.3 (M-H).

Example 4

rac-4-Benzylamino-5-phenethyl-l-phenyl-l,5-dihydro-imidazol-2-one
The title compound can be prepared in a similar way as example 1 from 3-phenylproprioaldehyde, benzylisocyanide, and aniline. MS (m/e): 368.3 (M-H).

Example 5

rac-4-Benzylamino-l-(3,4-dichloro-phenyl)-5-phenethyl-l,5-dihydro-imidazol-2-one

The title compound can be prepared in a similar way as example 1 from 3-phenylproprioaldehyde, benzylisocyanide, and 3,4-dichloroaniline. MS (m/e): 436.1 (M-H).

Example 6

rac-l-Benzyl-4-benzylamino-5-phenethyl-l,5-dihydro-imidazol-2-one

The title compound can be prepared in a similar way as example 1 from 3-phenylproprioaldehyde, benzylisocyanide, and benzylamine. MS (m/e): 384 (M+H+) .

Example 7

4-Benzylamino-5-phenyl-l-(4-trifluoromethyl-phenyl)-l,5-dihydro-imidazol-2-one

Prepared in analogy to example 1 from benzaldehyde, benzylisocyanide, potassium cyanate, 4-aminobenzotrifluoride and pyridinium hydrochloride as a light brown solid. Yield = 51%. MS (m/e): 410.3 (100%; M+H+), 432.3 (21%; M+Na).
Example 8

\((R\alpha\alpha\alpha)-4\text{-benzylamino}-1\text{-} (4\text{-methoxy-phenyl})\text{-}5\text{-phenyl}\text{-}1,5\text{-dihydro-imidazol-2-one}\)

Similarly to compound \(1,/?\text{-anisidine, benzaldehyde and benzylisocyanide afforded the title compound}\) as a black solid (130 mg, 41%). \(\delta_H\) NMR (CDCl\(_3\), 300 MHz) 7.38-7.18 (1OH, m, H arom), 6.76 (4H, d, J = 9.1 Hz, H arom), 5.51 (IH, s, C\(_5\)H), 5.20 (IH, br signal, NH), 4.72 (IH, dd, J = 14.9, 6.1 Hz, CH\(_A\)H\(_B\)Ph), 4.54 (IH, dd, J = 14.7, 5.3 Hz, CH\(_A\)H\(_B\)Ph), 3.71 (3H, s, OCH\(_3\)); m/z (EI) 372.1 (100 %, M+H\(^+\)).

Example 9

\((R\alpha\alpha\alpha)-4\text{-benzylamino}-1\text{-} (4\text{-methoxy-phenyl})\text{-}5\text{-phenyl}\text{-}1,5\text{-dihydro-imidazol-2-one hydrochloride}\)

20 mg of \((/?\alpha\alpha\alpha\text{-clc})\text{-4-benzylamino-1}\text{-} (4\text{-methoxy-phenyl})\text{-}5\text{-phenyl}\text{-}1,5\text{-dihydro-imidazol-2-one}\) was stirred for 2 hours at room temperature in a solution of 3N HCl in methanol. Evaporation of the solvent gave the title compound, m/z (EI) 372.2 (100 %, M+H\(^+\)).

Example 10

\((R\alpha\alpha\alpha)-4\text{-benzylamino}-1\text{-} (4\text{-chloro-phenyl})\text{-}5\text{-phenyl}\text{-}1,5\text{-dihydro-imidazol-2-one}\)

The numbers in the formula are aimed for characterizing NMR-spectra.
To a solution of benzaldehyde (1 equiv., 0.85 mmol, 94 µL) and benzylisocyanide (1 equiv., 0.85 mmol, 92 µL) in methanol (0.6 mL) was added KOCN (1 equiv., 0.85 mmol, 68 mg) in H₂O (0.3 mL) followed by 4-chloroaniline (1 equiv., 0.85 mmol, 98 mg) and pyridinium hydrochloride (1 equiv., 0.85 mmol). The reaction was stirred at room temperature for 3 days and the precipitate filtered. Work-up and purification afforded (rac)-4-benzylamino-1-(4-chloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one (117 mg, 37 %) as an amber solid. δH NMR (CDCl₃, 300 MHz) 7.45-7.10 (14H, m, H arom), 5.54 (IH, s, C₅H), 5.35 (IH, br signal, NH), 4.71 (IH, dd, J = 14.5, 5.6 Hz, CH₆H₄Ph), 4.52 (IH, dd, J = 14.5, 4.1 Hz, CH₆H₄Ph); m/z (EI) 378.3 (37 %), 377.3 (26), 376.3 (100, M+H⁺).

Example 11

(Rac)-4-benzylamino-1-(3,4-dimethyl-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to compound 1, 3,4-dimethylaniline, benzaldehyde and benzylisocyanide afforded the title compound as a dark green solid (77 mg, 25 %). δH NMR (CDCl₃, 300 MHz) 7.41-7.26 (9H, m, H arom), 7.17 (2H, dd, J = 7.4, 3.4 Hz, H arom), 7.02 (IH, dd, J = 8.2, 2.3 Hz, H arom), 6.94 (IH, d, J = 8.2 Hz, H arom), 5.54 (IH, s, C₅H), 5.23 (IH, app t, J = 6.5 Hz, NH), 4.71 (IH, dd, J = 14.6, 5.9 Hz, CH₆H₄Ph), 4.53 (IH, dd, J = 14.6, 5.5 Hz, CH₆H₄Ph), 2.16 (3H, s, CH₃), 2.12 (3H, s, CH₃); m/z (EI) 371.2 (31 %), 370.2 (100, M+H⁺).

Example 12

(Rac)-4-benzylamino-1-(4-isopropyl-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to compound 1, 4-isopropylaniline, benzaldehyde and benzylisocyanide afforded the title compound as a light brown solid (50 mg, 15 %). δH NMR (CDCl₃, 300 MHz) 7.39-7.26 (10H, m, H arom), 7.17-7.14 (2H, m, H arom), 7.07-7.05 (2H, app d, J = 9.3 Hz, H arom), 5.56 (IH, s, C₅H), 5.37 (IH, app t, J = 6.2 Hz, NH), 4.68 (IH, dd, J =
14.8, 6.1 Hz, $CH_AH_BPh$), 4.51 (IH, dd, $J = 14.6, 5.5$ Hz, $CH_AH_BPh$), 2.78 (1H, sept, $J = 7.1$ Hz, $CH(CHg)_2$), 1.15 (6H, d, $J = 7.0$ Hz, 2 x $CH_3$); m/z (El) 384.2 (100 %, M+H+).

Example 13

$Rac$-4-benzylamino-l-(3,4-dichloro-phenyl)-5-phenyl-l,5-dihydro-imidazol-2-one

Similarly to compound 1, benzaldehyde, benzyliisonitrile, and 3,4,-dichloroaniline, afforded the title compound.

$δ H$ NMR (DMSO, 300 MHz) 8.85 (IH, app t, $J = 6.0$ Hz, NH), 7.92 (IH, d, $J = 2.5$ Hz, H arom), 7.46-7.25 (HH, m, H arom), 7.15 (IH, dd, $J = 7.9, 1.9$ Hz, H arom), 6.17 (IH, s, CH), 4.46 (2H, d, $J = 6.0$ Hz, CH2Ph); m/z (El) 413.2 (14 %), 412.2 (43), 411.1 ...

410.1 (M+H+), M - H 408.1, M+H 410.3

Example 14

$(Rac)$-4-benzylamino-l-(4-chloro-3-trifluoromethyl-phenyl)-5-phenyl-l,5-dihydro-imidazol-2-one

Similarly to compound 1, 5-amino-2-chlorobenzyl-trifluoride, benzaldehyde and benzylisocyanide afforded the title compound as a dark brown solid (26 mg, 7 %). $δ H$ NMR (CDCl$_3$, 300 MHz) 7.77 (IH, d, $J = 2.7$ Hz, H arom), 7.66 (IH, dd, $J = 8.8, 2.6$ Hz, H arom), 7.43-7.35 (3H, m, H arom), 7.34-7.23 (6H, m, H arom), 7.14-7.10 (2H, m, H arom), 5.92 (IH, br signal, NH), 5.60 (IH, s, $C_3H$), 4.65 (IH, dd, $J = 14.9, 5.5$ Hz, $CH_AH_BPh$), 4.45 (IH, dd, $J = 14.7, 4.7$ Hz, $CH_AH_BPh$); m/z (El) 446.2 (26 %), 445.2 (28), 444.3 (100, M+H+).
Example 15

(Rac)-4-benzylamino-l-(4-isopropyl-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to compound 1, 4-isopropylaniline, benzaldehyde and benzylisocyanide afforded the title compound as a light brown solid (50 mg, 15 %). $\delta_H$ NMR (CDCl$_3$, 300 MHz) 7.39-7.26 (1OH, m, H arom), 7.17-7.14 (2H, m, H arom), 7.07-7.05 (2H, app d, $J =$ 9.3 Hz, H arom), 5.56 (IH, s, C$_5$H), 5.37 (IH, app t, $J =$ 6.2 Hz, NH), 4.68 (IH, dd, $J =$ 14.8, 6.1 Hz, CH$_A$H$_B$Ph), 4.51 (IH, dd, $J =$ 14.6, 5.5 Hz, CH$_A$H$_B$Ph), 2.78 (1H, sept, $J =$ 7.1 Hz, CH(CH$_3$)$_2$), 1.15 (6H, d, $J =$ 7.0 Hz, 2 x CH$_3$); m/z (EI) 384.2 (100 %, M+H$^+$).

Example 16

(Rac)-4-benzylamino-l-(4-ethyl-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to compound 1, 4-ethylaniline, benzaldehyde and benzylisocyanide afforded the title compound as a light brown solid (60 mg, 19 %). $\delta_H$, NMR (CDCl$_3$, 300 MHz) 7.26-7.23 (1OH, m, H arom), 7.15-7.12 (2H, m, H arom), 7.02 (2H, d, $J =$ 8.5 Hz, H arom), 5.66 (IH, app t, $J =$ 5.5 Hz, NH), 5.57 (IH, s, C$_5$H), 4.64 (IH, dd, $J =$ 14.9, 6.4 Hz, CH$_A$H$_B$Ph), 4.46 (IH, dd, $J =$ 14.8, 5.5 Hz, CH$_A$H$_B$Ph), 2.51 (2H, q, $J =$ 7.6 Hz, CH$_3$CH$_2$), 1.13 (3H, t, $J =$ 7.6 Hz, CH$_3$CH$_2$); m/z (EI) 370.2 (100 %, M+H$^+$).

Example 17

(Rac)-4-benzylamino-l-(3,5-dichloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one
Similarly to compound 1, 3,5-dichloroaniline, benzaldehyde and benzylisocyanide afforded the title compound as a dark brown oil (16 mg, 5%). δ_H NMR (CDCl_3, 300 MHz) 7.45-7.37 (5H, m, H arom), 7.35-7.25 (5H, m, H arom), 7.14-7.11 (2H, m, H arom), 6.96 (IH, t, J = 1.7 Hz, H arom), 5.65 (IH, br signal, NH), 5.53 (IH, s, C_5H), 4.68 (IH, dd, J = 14.9, 5.6 Hz, CH_4H_BPh), 4.49 (IH, dd, J = 14.9, 5.6 Hz, CH_AH_BPh); m/z (EI) 412.2 (39%), 410.1 (100, M+H+).

Example 18
(Rac)-4-(4-benzylamino-2-oxo-5-phenyl-2,5-dihydro-imidazol-1-yl)-benzonitrile

Similarly to compound 1, 4-aminobenzonitrile, benzaldehyde and benzylisocyanide afforded the title compound as a brown solid (45 mg, 14%). δ_H NMR (CDCl_3, 300 MHz) 7.64 (2H, d, J = 7.9 Hz, H arom), 7.48-7.39 (5H, m, H arom), 7.33-7.26 (5H, m, H arom), 7.16-7.12 (2H, m, H arom), 5.65 (IH, br signal, NH), 5.60 (IH, s, C_5H), 4.70 (IH, dd, J = 14.8, 6.1 Hz, CH_AH_BPh), 4.50 (IH, dd, J = 14.7, 5.5 Hz, CH_AH_BPh); m/z (EI) 337.2 (100%, M+H+).

Example 19
(Rac)-4-benzylamino-5-phenyl-l-(5-trifluoromethyl-pyridin-2-yl)-1,5-dihydro-imidazol-2-one

Similarly to compound 1, 3-amino-6-(trifluoromethyl)pyridine, benzaldehyde and benzylisocyanide afforded the title compound as a black solid (31 mg, 9%). δ_H NMR (CDCl_3, 300 MHz) 8.52 (IH, dd, J = 8.7, 2.4 Hz, H arom), 8.44 (IH, d, J = 2.5 Hz, H arom), 7.56 (IH, d, J = 8.7 Hz, H arom), 7.45-7.24 (8H, m, H arom), 7.15-7.09 (2H, m, H arom), 5.92 (IH, app t, J = 5.3 Hz, NH), 5.67 (IH, s, C_5H), 4.68 (IH, dd, J = 14.8, 6.1 Hz, CH_4HuPh), 4.49 (IH, dd, J = 14.8, 5.5 Hz, CH_AH_BPh); m/z (EI) 411.2 (100%, M+H+).

Example 20
(Rac)-4-benzylamino-l-(4-nitro-phenyl)-5-phenyl-l,5-dihydro-imidazol-2-one
Similarly to compound 1, 4-nitroaniline, benzaldehyde and benzylisocyanide afforded the title compound as a yellow oil (37 mg, 11%). $\delta$H NMR (CDCl$_3$, 300 MHz) 8.09 (IH, ddd, J = 9.1, 3.1, 1.9 Hz, H arom), 7.70 (IH, ddd, J = 9.4, 3.2, 2.2 Hz, H arom), 7.47-7.38 (4H, m, H arom), 7.36-7.14 (8H, m, H arom), 5.62 (IH, s, C$_5$H), 5.51 (IH, br signal, NH), 4.71 (IH, dd, J = 14.8, 5.9 Hz, CH$_4$H$_B$Ph), 4.53 (IH, dd, J = 14.8, 5.5 Hz, CH$_A$H$_B$Ph); m/z (EI) 387.2 (100 %, M+H$^+$).

**Example 21**

(Rac)-4-benzylamino-l-(3,4-dichloro-phenyl)-5-(3-methoxy-phenyl)-1,5-dihydroimidazol-2-one

Similarly to compound 1, 3,4-dichloroaniline, isopropylbenzaldehyde and benzylisocyanide afforded the title compound as a white solid (47 mg, 12%). $\delta$H NMR (CDCl$_3$, 300 MHz) 7.75 (IH, d, J = 2.2 Hz, H arom), 7.31-7.14 (8H, m, H arom), 5.49 (IH, s, C$_5$H), 5.32 (IH, br signal, NH), 4.73 (IH, dd, J = 14.7, 6.1 Hz, CH$_A$H$_B$Ph), 4.53 (IH, dd, J = 14.8, 5.4 Hz, CH$_A$H$_B$Ph), 2.90 (1H, sept, J = 6.7 Hz, CH(CH$_3$)$_2$), 1.27 (6H, d, J = 7.0 Hz, 2 x CH$_3$); m/z (EI) 454.3 (100 %), 453.3 (38), 452.2 (94, M+H$^+$).

**Example 22**

(Rac)-4-benzylamino-l-(3,4-dichloro-phenyl)-5-thiophen-3-yl-1,5-dihydroimidazol-2-one
Similarly to compound 1, 3,4-dichloroaniline, 3-thiophene carboxaldehyde and benzylisocyanide afforded the title compound as light brown solid (18 mg, 5%). $\delta_H$ NMR (DMSO, 300 MHz) 8.87 (IH, app t, $J = 5.6$ Hz, $\text{NHCH}_2\text{Ph}$), 7.94 (IH, d, $J = 2.1$ Hz, H arom), 7.72 (IH, dd, $J = 2.8$, 1.1 Hz, H thiophene), 7.54 (IH, dd, $J = 5.1$, 3.0 Hz, H thiophene), 7.48-7.41 (2H, m, H arom), 7.33-7.18 (5H, m, H arom), 6.95 (IH, dd, $J = 5.1$, 1.3 Hz, H thiophene), 6.27 (IH, s, $\text{C}_5\text{H}$), 4.49 (2H, d, $J = 5.6$ Hz, $\text{CH}_2\text{Ph}$); m/z (EI) 419.2 (17%), 418.2 (61), 417.2 (21), 416.3 (100, M+H$^+$).

Example 23

($R_{ac}$)-4-benzylamino-l-(3,4-difluoro-phenyl)-5-phenyl-l,5-dihydro-imidazol-2-one

Similarly to compound 1, 3,4-difluoroaniline, benzaldehyde and benzylisocyanide afforded the title compound as an off-white solid (68 mg, 21%). $\delta_H$ NMR (CDCl$_3$, 300 MHz) 7.50 (IH, ddd, $J = 20.5$, 7.0, 2.5 Hz, H arom), 7.44-7.35 (3H, m, H arom), 7.33-7.11 (7H, m, H arom), 6.96 (IH, dd, $J = 8.9$, 8.7 Hz, H arom), 6.75 (IH, dd, $J = 9.0$, 8.5 Hz, H arom), 5.51 (IH, s, $\text{C}_5\text{H}$), 5.47 (IH, app t, $J = 5.1$ Hz, NH), 4.69 (IH, dd, $J = 14.7$, 6.0 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 4.51 (IH, dd, $J = 14.7$, 5.4 Hz, CH$_\text{A}\text{H}_\text{B}\text{Ph}$); m/z (EI) 378.3 (100 %, M+H$^+$).

Example 24

($R_{flc}$)-4-benzylamino-l-(3,4-dichloro-phenyl)-5-p-tolyl-l,5-dihydro-imidazol-2-one
Similarly to compound 1, 3,4-dichloroaniline, tolylaldehyde and benzylisocyanide afforded the title compound as a white solid (9 mg, 3%). δ_H NMR (CDCl₃, 300 MHz) 7.72 (IH, d, J = 2.3 Hz, H arom), 7.30-7.15 (HH, m, H arom), 5.45 (IH, s, C₅H), 5.37 (IH, br signal, NH), 4.72 (IH, dd, J = 14.8, 6.2 Hz, CH₃CH₃Ph), 4.51 (IH, dd, J = 14.5, 5.2 Hz, CH₂H₂Ph), 2.33 (3H, s, CH₃); m/z (EI) 427.2 (16%), 426.1 (52), 425.1 (22), 424.2 (100, M+H⁺).

Example 25

(Rac)-4-benzylamino-1-(3,4-dichloro-phenyl)-5-(3,4-dimethyl-phenyl)-1,5-dihydro-imidazol-2-one

Similarly to compound 1, 3,4-dichloroaniline, 3,4-dimethylbenzaldehyde and benzylisocyanide afforded the title compound. (EI) 418.3 (M+H⁺).

Example 26

(Rac)-4-benzylamino-1-(3,4-dichloro-phenyl)-5-(4-isopropyl-phenyl)-1,5-dihydro-imidazol-2-one

Similarly to compound 1, 3,4-dichloroaniline, m-anisaldehyde and benzylisocyanide afforded the title compound as a white solid (100 mg, 27%). δ_H NMR (DMSO, 300 MHz) 8.81 (IH, br signal, NH), 7.91 (IH, d, J = 2.3 Hz, H arom), 7.47-7.38 (2H, m, 2H, arom), 7.32-7.17 (7H, m, H arom), 6.94 (2H, d, J = 8.7 Hz, H arom), 6.10 (IH, s, C₅H), 4.72 (IH, dd, J = 14.8, 6.2 Hz, CH₃CH₃Ph), 4.51 (IH, dd, J = 14.5, 5.2 Hz, CH₂H₂Ph), 2.33 (3H, s, CH₃); m/z (EI) 427.2 (16%), 426.1 (52), 425.1 (22), 424.2 (100, M+H⁺).
Example 27

(Rac)-4-benzylamino-5-(4-chloro-phenyl)-1-(4-ethyl-phenyl)-1,5-dihydro-imidazol-2-one

Similarly to compound 1, 3,4-dichloroaniline, ethylbenzaldehyde and benzylisocyanide afforded the title compound as a white solid (53 mg, 14%). δH NMR (CDCl3, 300 MHz) 7.73 (IH, br s, H arom), 7.30-7.05 (HH, m, H arom), 5.49 (IH, s, C5H), 5.30 (IH, br signal, NH), 4.73 (IH, dd, J = 14.2, 5.1 Hz, CHACH3Ph), 4.52 (IH, dd, J = 14.5, 5.2 Hz, CHAβPh), 2.64 (2H, q, J = 7.4 Hz, CH2CH3), 1.22 (3H, t, J = 7.6 Hz, CH2CH3); m/z (EI) 440.2 (100%), 439.3 (30), 438.3 (60, M+H+).

Example 28

(Rac)-4-benzylamino-5-(4-chloro-phenyl)-1-(3,4-dichloro-phenyl)-1,5-dihydro-imidazol-2-one

Similarly to compound 1, 3,4-dichloroaniline, 4-chlorobenzaldehyde and benzylisocyanide afforded the title compound as an off-white solid (16 mg, 4%). δH NMR (CDCl3, 300 MHz) 7.68 (IH, s, H arom), 7.18-7.14 (HH, m, H arom), 5.50 (IH, s, C5H), 5.29 (IH, br signal, NH), 4.74 (IH, dd, J = 14.3, 5.9 Hz, CHAβPh), 4.53 (IH, dd, J = 14.3, 5.8 Hz, CHAβPh); m/z (EI) 446.1 (86%), 445.2 (28), 444.2 (100, M+H+).

Example 29

rac-4-Benzylamino-1-(3-chloro-4-fluoro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one
Similarly to example 1, reaction of benzaldehyde, benzyl isonitrile, and 3-chloro-4-fluoroaniline afforded the title compound. (EI) (M+H) 394.1

Example 30

Rac-4-Benzylamino-1-(3-fluoro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to example 1, reaction of benzaldehyde, benzyl isonitrile, and 3-fluoroaniline afforded the title compound. (EI) (M+H) 360.0

Example 31

Rac-4-Benzylamino-1-(6-methoxy-pyridin-3-yl)-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to example 1, reaction of benzaldehyde, benzyl isonitrile, and 5-amino-2-methoxypyridine afforded the title compound. (EI) (M+H) 373.3

Example 32

Rac-4-Benzylamino-1-(3-fluoro-4-methyl-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one
Similarly to example 1, reaction of benzaldehyde, benzyl isonitrile, and 3-fluoro-4-methylaniline afforded the title compound. (EI) (M+H) 374.4

Example 33

rac4-Benzylamino-l-(3,5-difluoro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to example 1, reaction of benzaldehyde, benzyl isonitrile, and 3,5-difluoroaniline afforded the title compound. (EI) (M+H) 378.5

Example 34

rac-4-Benzylamino-l-(6-chloro-pyridin-3-yl)-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to example 1, reaction of benzaldehyde, benzyl isonitrile and 5-amino-2-chloropyridine afforded the title compound. (EI) (M-H) 375.3
Example 35

rac-4-Benzylamino-5-phenyl-l-(4-trifluoromethoxy-phenyl)-l,5-dihydro-imidazol-2-one

Similarly to example 1, reaction of benzaldehyde, benzyl isonitrile, and 4-(trifluoromethoxy) aniline afforded the title compound. (EI) (M+H) 426.1

Example 36

rac-4-Benzylamino-5-phenyl-l-(3-trifluoromethyl-phenyl)-l,5-dihydro-imidazol-2-one

Similarly to example 1, reaction of benzaldehyde, benzyl isonitrile and 3-aminobenzotrifluoride afforded the title compound. (EI) (M+H) 410.4.

Example 37

(Rac)-4-benzylamino-l-(3,4-dichloro-phenyl)-5-(2 H-pyrazol-3-yl)-l,5-dihydroimidazol-2-one

Similarly to compound 1, 3,4-dichloroaniline, 2H-pyrazole-3-carbaldehyde and benzylisocyanide afforded the title compound as an off-white solid (17 mg, 4%). \( \delta_H \)
Example 38

(Rac)-4-benzylamino-l-(3,4-dichloro-phenyl)-5-pyridin-3-yl-l,5-dihydro-imidazol-2-one

Similarly to compound 1, 3,4-dichloroaniline, 3-pyridine carboxaldehyde and benzylisocyanide afforded the title compound as an amber solid (36 mg, 10%). \( \delta_H \) NMR (DMSO, 300 MHz) 9.03 (IH, br signal, NH), 8.71 (IH, d, \( J = 1.9 \) Hz, H arom), 8.54 (IH, dd, \( J = 4.8 \), 1.3 Hz, H arom), 7.94 (IH, d, \( J = 2.3 \) Hz, H arom), 7.66 (IH, d, \( J = 7.9 \) H arom), 7.48-7.17 (8H, m, H arom), 6.28 (IH, s, C_5H), 4.48 (2H, s, CH_2Ph); m/z (EI) 413.2 (86 %), 411.1 (100, M+H^+).

Example 39

(Rac)-4-benzylamino-l-(3,4-dichloro-phenyl)-5-pyridin-4-yl-l,5-dihydro-imidazol-2-one

Similarly to compound 1, 3,4-dichloroaniline, 4-pyridine carboxaldehyde and benzylisocyanide afforded the title compound as a light yellow solid (21 mg, 6%). \( \delta_H \) NMR (DMSO, 300 MHz) 9.01 (IH, br signal, NH), 8.59 (2H, d, \( J = 5.2 \) Hz, H arom), 7.48-7.15 (9H, m, H arom), 6.26 (IH, s, C_5H), 4.47 (2H, s, CH_2Ph); m/z (EI) 414.3 (22 %), 413.2 (85), 412.2 (23), 411.2 (100, M+H^+).

Example 40

(Rac)-4-benzylamino-l-(3,4-dichloro-phenyl)-5-furan-2-yl-l,5-dihydro-imidazol-2-one
Similarly to compound 1, 3,4-dichloroaniline, 2-furaldehyde and benzylisocyanide afforded the title compound as an amber solid (22 mg, 7%). $\delta$H NMR (DMSO, 300 MHz) 9.04 (IH, app t, $J = 5.6$ Hz, NH), 7.91 (IH, d, $J = 1.1$ Hz, H arom), 7.65 (IH, d, $J = 1.0$ Hz, H arom), 7.50 (2H, s, H arom), 7.35-7.22 (5H, m, H arom), 7.21 (2H, s, H arom), 6.75 (IH, d, $J = 3.2$ Hz, H furane), 6.46 (IH, dd, $J = 3.2$, 1.9 Hz, H furane), 6.38 (IH, s, C$_5$H), 5.45 (IH, dd, $J = 15.7$, 6.4 Hz, $CH_4H_BPh$), 4.49 (IH, dd, $J = 15.3$, 6.0 Hz, $CH_AH_BPh$); m/z (EI) 403.3 (15%), 402.3 (74), 401.1 (29), 400.1 (100, M+H$^+$).

Example 41

(Rac)-4-benzylamino-l-(3,4-dichloro-phenyl)-5-(3-methoxy-phenyl)-1,5-dihydro-imidazol-2-one

Similarly to compound 1, 3,4-dichloroaniline, p-anisaldehyde and benzylisocyanide afforded the title compound as a white solid (52 mg, 14%). $\delta$H NMR (CDCl$_3$, 300 MHz) 7.75 (IH, d, $J = 2.3$ Hz, H arom), 7.36-7.16 (8H, m, H arom), 6.92-6.87 (2H, m, H arom), 6.75 (IH, s, H arom), 5.47 (IH, s, C$_5$H), 5.36 (IH, app t, $J = 4.4$ Hz, NH), 4.72 (IH, dd, $J = 14.8$, 5.9 Hz, $CH_AH_BPh$), 4.53 (IH, dd, $J = 14.9$, 5.6 Hz, $CH_AH_BPh$), 3.76 (3H, s, OCH$_3$); m/z (EI) 442.3 (56%), 441.3 (19), 440.2 (100, M+H$^+$).

Example 42

(Rac)-4-benzylamino-l-(3,4-dichloro-phenyl)-5-(4-dimethylamino-phenyl)-1,5-dihydro-imidazol-2-one
Similarly to compound 1, 3,4-dichloroaniline, 4-(dimethylamino)benzaldehyde and benzylisocyanide afforded the title compound as a gold solid (36 mg, 9%). δ_H NMR (DMSO, 300 MHz) 8.82 (IH, app t, J = 5.6 Hz, NH), 7.90 (IH, d, J = 1.7 Hz, H arom), 7.46-7.38 (2H, m, H arom), 7.31-7.11 (7H, m, H arom), 6.68 (2H, d, J = 8.5 Hz, H arom), 6.00 (IH, s, C₅H), 4.46 (2H, d, J = 5.7 Hz, CH₂Ph), 2.86 (6H, s, N(CH₃)₂); m/z (EI) 456.4 (19%), 455.3 (74), 454.3 (29), 453.3 (100, M+H⁺).

Example 43

(Rqc)-4-benzylamino-1-(3,4-dichloro-phenyl)-5-(4-fluoro-phenyl)-1,5-dihydro-imidazol-2-one

Similarly to compound 1, 3,4-dichloroaniline, 4-fluorobenzaldehyde and benzylisocyanide afforded the title compound as a white solid (72 mg, 20%). δ_H NMR (DMSO, 300 MHz) 8.89 (IH, app t, J = 5.8 Hz, NH), 7.92 (IH, d, J = 2.3 Hz, H arom), 7.47-7.38 (4H, m, H arom), 7.30-7.16 (7H, m, H arom); 6.21 (IH, s, C₅H), 4.47 (2H, d, J = 5.6 Hz, CH₂Ph); m/z (EI) 431.2 (16%), 430.3 (59), 429.3 (23), 428.3 (100, M+H⁺).

Example 44

Rqc-4-Benzylamino-1-(3-chloro-4-fluoro-phenyl)-5-(4-fluoro-phenyl)-1,5-dihydro-imidazol-2-one
Similarly to example 1, reaction 4-fluorobenzaldehyde and 3-chloro-4-fluorobenzylamine and Benzyl isonitrile afforded the title compound. (EI) (M-H) 375.3; H NMR (DMSO, 300 MHz) 8.84 (IH, app t, J = 5.8 Hz, NH), 7.84 (IH, dd, J = 6.6, 2.1 Hz, H arom), 7.43-7.36 (4H, m, H arom), 7.32-7.16 (7H, m, H arom), 6.19 (IH, s, CH), 4.47 (2H, d, J = 5.7 Hz, CH2Ph; m/z (EI) 412.2 (M+H+).

Example 45

(Rac)-4-benzylamino-l-(3,4-dichloro-phenyl)-5-thiophen-2-yl-l,5-dihydroimidazol-2-one

Similarly to compound 1, 3,4-dichloroaniline, 2-thiophene carboxaldehyde and benzylisocyanide afforded the title compound as a brown solid (7 mg, 2%). δH NMR (DMSO, 300 MHz) 9.00 (IH, app t, J = 5.9 Hz, NHCH2Ph), 7.90 (IH, d, J = 2.1 Hz, H arom), 7.53 (IH, d, J = 5.1 Hz, H thiophene), 7.50-7.47 (2H, m, H arom), 7.03 (IH, dd, J = 5.0, 3.5 Hz, H thiophene), 6.57 (IH, s, C5H), 4.51 (IH, d, J = 5.4Hz, CHA CHβPh), 4.49 (IH, dd, J = 5.5 Hz, CHA HβPh); m/z (EI) 419.1 (18 %), 418.2 (63), 417.2 (21), 416.2 (100, M+H+).

Example 46

Rac-4-Benzylamino-l-(4-fluoro-phenyl)-5-phenyl-l,5-dihydro-imidazol-2-one

Similarly to example 1, reaction of benzaldehyde, benzyl isonitrile and 4-fluoroaniline afforded the title compound. (EI) (M+H) 360.4.

Example 47

rac-4-Benzylamino-l-(4-morpholin-4-yl-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one
Similarly to example 1, reaction of benzaldehyde, benzyl isonitrile and 4-morpholinoaniline afforded the title compound. (EI) (M+H) 427.5.

**Example 48**

rac-l-(3,4-Dichloro-phenyl)-4-[2-(3,4-dimethoxy-phenyl)-ethylamino]-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to example 1, reaction of benzaldehyde, 4-(2-isocyano-ethyl)-l,2-dimethoxybenzene and 4-dichloroaniline afforded the title compound. (EI) (M+H) 484.5.

**Example 49 and Example 50**

(+)-4-Benzylamino-l-(4-chloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one and (-)-4-Benzylamino-l-(4-chloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one

Achiral chromatography of example 10 on Chiralpak AD eluting with heptane-isopropanole 4:1, chiral separated both enantiomers (Example 49 and 50). Mass spectra of Example 49 showed mass peak of 376.4 (M+H) and that of Example 50 showed 376.5 (M+H).
Example 5.1

Rac-l-(3,4-dichloro-phenyl)-4-(4-fluorobenzylamino)-5-phenyl-1,5-dihydro-imidazo-
2-one

Step 1: l-(3,4-Dichloro-phenyl)-5-phenyl-1,3-dihydro-imidazo-
2-one

250 nL of concentrated HCl were added I-(3,4-dichloro-phenyl)-3-(2-oxo-2-phenyl-
ethyl)urea (1 equiv., 56 mmol, 18.0 g) at room temperature. The reaction mixture was
stirred for one week until starting material disappeared giving a white foam which was
filtered off. This foam was purified by recrystallisation in ethanol affording I-(3,4-
dichloro-phenyl)-5-phenyl-1,3-dihydro-imidazo-
2-one (14.4 g, 85 %) as a white solid. Rf
0.2 (tt-heptane/ethyl acetate 2:1). $\delta_H$ NMR (DMSO, 300 MHz) 10.68 (IH, br s, NH), 7.62
(IH, d, J = 8.6 Hz, H arom), 7.53 (IH, d, J = 2.4 Hz, H arom), 7.32-7.20 (3H, m, H
arom), 7.09-7.06 (2H, m, H arom), 7.03 (IH, dd, J = 8.6, 2.5 Hz, H arom), 6.89 (IH, s,
=CH); m/z (El) 309.2 (21 %), 307.2 (97), 306.1 (24), 305.1 (100, M+H+).

Step 2: Rac-l-(3,4-dichloro-phenyl)-4-(4-fluorobenzylamino)-5-phenyl-
1,5-dihydro-
imidazol-2-one

To a stirred solution of l-(3,4-dichloro-phenyl)-5-phenyl-1,3-dihydro-imidazo-
2-one (1
equiv., 0.33 mmol, 100 mg) in chloroform (5 mL) was added dropwise Br2 (1.1 equiv.,
0.36 mmol, 19 µL) in chloroform (2 mL) at 0°C under nitrogen. After 10 min, 4-
fluorobenzylamine (10 equiv., 3.28 mmol, 372 µL) was added in situ at 0°C. The reaction
mixture was allowed to warm up to room temperature and heated at reflux overnight.
After evaporation of solvent, the residue was purified by column chromatography (SiO2,
n-heptane/ethyl acetate: 0-100%) affording the title compound as a white solid (32 mg,
23 %). $\delta_H$ NMR (DMSO, 300 MHz) 8.83 (IH, br, s, NH), 7.91 (IH, d, J = 2.4 Hz, H
arom), 7.46-7.08 (HH, m, H arom), 6.16 (IH, s, C$_2$H), 4.44 (2H, s, CH$_2$Ph); m/z (EI) 431.0 (12 %), 430.0 (74), 429.1 (26), 428.0 (100, M+H$^+$).

Example 52

5 $Rac$-l-(3,4-dichloro-phenyl)-4-isobutylamino-5-phenyl-1,5-dihydroimidazol-2-one

Similarly to compound 51, isopropylamine afforded the title compound as a white solid (88 mg, 71 %). $\delta$$_H$ NMR (DMSO, 300 MHz) 8.34 (IH, app t, $J = 5.6$ Hz, NH), 7.92 (IH, d, $J = 2.1$ Hz, H arom), 7.42-7.31 (7H, m, H arom), 6.06 (IH, s, C$_2$H), 3.17-3.08 (IH, m, NH-C$_H$$_2$H$_s$-iPr), 3.03-2.97 (IH, m, NH-CH$_A$H$_2$-iPr), 1.80 (1H, non, $J = 6.7$ Hz, CH(CH$_3$)$_2$), 0.74 (3H, d, $J = 6.6$ Hz, CH$_3$), 0.71 (3H, d, $J = 6.8$ Hz, CH$_3$); m/z (EI) 379.2 (13 %), 378.2 (65), 377.3 (22), 376.3 (100, M+H$^+$).

Example 53

15 $Rac$-l-(3,4-dichloro-phenyl)-4-(3-methyl-butylamino)-5-phenyl-1,5-dihydroimidazol-2-one

Similarly to compound 51, isoamylamine afforded the title compound as a white solid (52 mg, 41 %). $\delta$$_H$ NMR (DMSO, 300 MHz) 8.28 (IH, br signal, NH), 7.91 (IH, d, $J = 2.1$ Hz, H arom), 7.45-7.30 (7H, m, H arom), 6.05 (IH, s, C$_2$H), 3.25 (2H, br t, $J = 6.9$ Hz, NH-C$_H$$_2$), 1.43 (1H, non, $J = 6.0$ Hz, CH(CH$_3$)$_2$), 1.36-1.29 (2H, m, CH$_2$CH(CH$_3$)$_2$), 0.81 (6H, d, $J = 6.4$ Hz, 2 x CH$_3$); m/z (EI) 393.2 (15 %), 392.2 (66), 391.1 (19), 390.2 (100, M+H$^+$).

Example 54

25 ($Rac$)-l-(3,4-dichloro-phenyl)-5-phenyl-4-[(pyridin-4-ylmethyl)-amino]-1,5-dihydroimidazol-2-one
Similarly to compound 51, 4-aminomethyl)pyridine afforded the title compound as an off-white solid (23 mg, 17%). $\delta_H$ NMR (DMSO, 300 MHz) 8.83 (IH, br signal, NH), 8.46 (2H, d, $J = 6.0$ Hz, H pyridine), 7.92 (IH, d, $J = 2.2$ Hz, H arom), 7.47-7.33 (7H, m, H arom), 7.12 (2H, d, $J = 5.9$ Hz, H pyridine), 6.23 (IH, s, C$_5$H), 4.48 (2H, s, CH$_2$Ph); m/z (EI) 413.0 (30 %), 411.0 (52, M+H$^+$), 200.2 (100).

Example 55

rac-l-(3,4-Dichloro-phenyl)-4-(methyl-propyl-amino)-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to compound 51, iV,iV-methylpropylamine afforded the title compound. (EI) 376.3 (M+H$^+$)

Example 56

(Rac)-4-azepan-l-yl-l-(3,4-dichloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to compound 51, hexamethylenimine afforded the title compound as a white solid (65 mg, 49 %). $\delta_H$ NMR (DMSO, 300 MHz) 7.49 (IH, d, $J = 2.4$ Hz, H arom), 7.56-7.28 (7H, m, H arom), 6.47 (IH, s, C$_5$H), 3.78-3.71 (2H, m, CH$_2$), 3.36-3.33 (4H, m, 2 x CH$_2$), 1.56-1.45 (4H, m, 2 x CH$_2$), 1.32-1.13 (2H, m, CH$_2$); m/z (EI) 405.2 (16 %), 404.2 (78), 403.2 (24), 402.1 (100, M+H$^+$), 200.1 (59).
Example 57

(Rac)-1-(3,4-dichloro-phenyl)-4-hexylamino-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to compound 51, hexylamine afforded the title compound as a white solid (57 mg, 49%). $\delta_{H}$ NMR (DMSO, 300 MHz) 8.30 (IH, app t, $J = 5.7$ Hz, NH), 7.92 (IH, d, $J = 2.1$ Hz, H arom), 7.45-7.28 (7H, m, H arom), 6.05 (IH, s, C$_5$H), 3.25 (IH, d, $J = 5.4$ Hz, NH-C$_5$H$_4$Hs), 3.21 (IH, d, $J = 5.4$ Hz, NH-CH$_3$Hs), 1.42 (2H, qt, $J = 6.7$ Hz, NH-CH$_2$-CH$_2$), 1.23-1.07 (6H, m, CH$_2$-CH$_2$-CH$_2$-CH$_3$), 0.81 (3H, t, $J = 6.5$ Hz, CH$_3$); m/z (El) 406.2 (49%), 405.1 (22), 404.2 (100, M+H$^+$), 200.1 (87).

Example 58

(Rac)-4-(cyclohexylmethyl-amino)-1-(3,4-dichloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to compound 51, (aminomethyl)cyclohexane afforded the title compound as an off-white solid (41 mg, 30%). $\delta_{H}$ NMR (DMSO, 300 MHz) 8.31 (IH, app t, $J = 5.6$ Hz, NH), 7.92 (IH, d, $J = 2.3$ Hz, H arom), 7.45-7.31 (7H, m, H arom), 6.06 (IH, s, C$_5$H), 3.14-3.03 (2H, m, NH-CH$_2$-Cy), 1.59-1.44 (6H, m, 3 x CH$_2$), 1.11-1.04 (3H, m, CH + CH$_2$), 0.80-0.60 (2H, m, CH$_2$); m/z (El) 419.1 (16%), 418.1 (64), 417.1 (26), 416.1 (100, M+H$^+$), 200.2 (34).

Example 59

(Rac)-4-butylamino-1-(3,4-dichloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one
Similarly to compound 51, _n_-butylamine afforded the title compound as a white solid (18 mg, 15%). $\delta_H$NMR (DMSO, 300 MHz) 8.30 (IH, app t, $J = 5.5$ Hz, NH), 7.92 (IH, d, $J = 2.1$ Hz, H arom), 7.45-7.29 (7H, m, H arom), 6.05 (IH, s, C$_5$H), 3.26 (IH, d, $J = 6.6$ Hz, NH-C$_{H_4}$Hs), 3.21 (IH, d, $J = 6.8$ Hz, NH-CH$_2$Hs), 1.42 (2H, qt, $J = 7.4$ Hz, NH-CH$_2$), 1.16 (2H, sext, $J = 7.5$ Hz, CH$_2$-CH$_2$CH$_3$), 0.81 (3H, t, $J = 7.4$ Hz, C$_3$H$_3$); m/z (EI) 378.1 (47%), 376.1 (68, M+H$^+$), 200.1 (100).

Example 60

(Rac)-4-(cyclopropylmethyl-amino)-1-(3,4-dichloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one

![Chemical structure]

Similarly to compound 51, aminomethylcyclopropane afforded the title compound as a light brown solid (31 mg, 25%). $\delta_H$NMR (DMSO, 300 MHz) 8.44 (IH, app t, $J = 4.8$ Hz, NH), 7.91 (IH, br s, H arom), 7.45-7.21 (7H, m, H arom), 6.07 (IH, s, C$_5$H), 3.25-3.16 (IH, m, NH-C$_{H_4}$Hs), 3.10-3.01 (IH, m, NH-CH$_2$Hs), 0.97 (1H, br sept, $J = 8.3$ Hz, CH), 0.37 (2H, br d, $J = 7.7$ Hz, CH$_2$), 0.16 (2H, br d, $J = 3.5$ Hz, CH$_2$); m/z (EI) 377.2 (15%), 376.1 (75), 375.1 (16), 373.9 (100, M+H$^+$).

Example 61

rac-l-(3,4-Dichloro-phenyl)-4-dimethylamino-5-phenyl-1,5-dihydro-imidazol-2-one

![Chemical structure]

Similarly to compound 51, iV,iV-dimethylamine afforded the title compound. (EI) 348.2 (M+H$^+$)

Example 62

rac-l-(3,4-Dichloro-phenyl)-4-methylamino-5-phenyl-1,5-dihydro-imidazol-2-one
Similarly to compound 51, \(\text{N}\text{-methylamine}\) afforded the title compound. (EI) 334.0 (M+H+)

**Example 63**

\[\text{rac-4-Cyclobutylamino-1-(3,4-dichloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one}\]

Similarly to compound 51, \(\text{cyclopropylamine}\) afforded the title compound. (EI) 373.9 (M+H+)

**Example 64**

\[\text{rac-1-(3,4-Dichloro-phenyl)-4-(3,4-dihydro-IH-isoquinolin-2-yl)-5-phenyl-1,5-dihydro-imidazol-2-one}\]

Similarly to compound 51, \(\text{1,2,3,4-tetrahydroquinoline}\) afforded the title compound. (EI) 436.0 (M+H+)

**Example 65**

\[\text{rac-4-Cyclopentylamino-1-(3,4-dichloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one}\]
Similarly to compound 51, cyclopentylamine afforded the title compound. (EI) 388.1 (M+H+)

Example 66

*Rac-l-(4-Chloro-phenyl)-4-isobutylamino-5-phenyl-l,5-dihydro-imidazol-2-one*

**Step 1: Synthesis of l-(2-oxo-phenyl-ethyl)urea**

To a suspension of 1-chloro-4-isocyanato-benzene (0.033mol) and 2-oxo-2-phenyl-ethyl-ammonium chloride (0.033mol, 1 eq.) was added an aqueous solution of sodium carbonate ([1.3], 50ml, 0.065 mol, 2eq.). The reaction mixture was stirred overnight at room temperature affording a white precipitate which was filtered off. The precipitate was dissolved in dichloromethane (10mL), dried over Na₂SO₄, and concentrated *in vacuo* affording the solid product. The product was dried under high vacuum at 60°C for 4 hours.

**Step 2: Synthesis of 1,5-Diphenyl-l,3-dihydro-imidazol-2-ones**

10mL of concentrated hydrochloric acid (fuming 37%) was added to 1-(4-chloro-phenyl)-3-(2-oxo-2-phenyl-ethyl)-urea (0.017mol) to form a suspension at room temperature. The reaction mixture was stirred for one week until the suspension had
transformed into a white foam corresponding to the desired product by LC-MS which was filtered off.

**Step 3: Animation of 1,5-Diphenyl-1,3-dihydro-imidazol-2-ones**

To a solution of 1-(4-chloro-phenyl)-5-phenyl-1,3-dihydro-imidazol-2-one (0.37 mmol) in dry chloroform (3 mL) in the presence of molecular sieves (4 Å), a solution of bromine (3 mL, 0.13 M in chloroform) was added dropwise using a syringe. The reaction mixture was stirred at 0°C until completion of bromination was observed by TLC. Isobutylamine (1.8 mmol, 5 eq.) was then added via a syringe and the reaction was allowed to warm to room temperature and was then heated to 65°C for 24 hours. The reaction was carried under nitrogen throughout. The product was concentrated at reduced pressure and purified by column (amine functionalised SiO₂, heptane: ethylacetate = 0-100%).

**Example 67**

1-(3,4-Difluoro-phenyl)-4-isobutylamino-5-phenyl-1,5-dihydro-imidazol-2-one

Similarly to Example 66, the title compound was prepared from 1,2-difluoro-4-isocyanato-benzene.

**m/z** (Cl⁺) 705.2 (22%), 683.5 (35), 364.1 (29), 343.2 (22), 342.2 (100% M+H⁺)

δ_H NMR (DMSO, 300 MHz) = 8.22 (IH, m, pos Rb₁, NH), 7.54-7.52 (2H, d, J = 8.5 Hz, pos Ra₃, H arom), 7.44-7.20 (5H, m, pos Rc, H arom), 7.25-7.22 (2H, d, J = 8.5 Hz, pos Ra₂, H arom), 6.01 (IH, s, pos 5, H alkyl), 3.14-2.99 (2H, m, pos Rb₂, H alkyl), 1.80-1.76 (IH, m, pos Rb₃, H alkyl), 0.75-0.70 (6H, m, pos Rb₄, H alkyl)
Claims

1. Compounds of general formula

\[
\begin{array}{c}
\text{R}_1 \quad \text{N} \quad \text{N} \\
\text{R}_2 \quad \text{H} \\
\text{R}_3 \quad \text{R}_4 \\
\end{array}
\]

wherein

- \( R_1 \) is -(CH\(_2\))\(_n\)-aryl or -(CH\(_2\))\(_n\)-heteroaryl, wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyl substituted by halogen, lower alkoxy, lower alkyl, cyano, nitro, -O-lower alkyl substituted by halogen or morpholinyl;

- \( R_2 \) is -(CH\(_2\))\(_n\)-aryl or -(CH\(_2\))\(_n\)-heteroaryl, wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of lower alkyl, lower alkoxy, halogen or -N(lower alkyl)\(_2\);

- \( R_3 \) is hydrogen or lower alkyl;

- \( R_4 \) is -(CH\(_2\))\(_n\)-aryl or -(CH\(_2\))\(_n\)-heteroaryl, wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen or lower alkoxy, or is lower alkyl, -(CH\(_2\))\(_n\)-cycloalkyl; or

- \( R_3 \) and \( R_4 \) form together with the N-atom a heterocyclic ring;

- \( n \) is 0, 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

2. Compounds of formula IA according to claim 1.

\[
\begin{array}{c}
\text{R}_1 \quad \text{N} \quad \text{NH} \\
\text{R}_2 \quad \text{H} \\
\text{R}_3 \quad \text{R}_4 \\
\end{array}
\]

IA
wherein

- $R_1$ is $-(\text{CH}_2)_n$-aryl or $-(\text{CH}_2)_n$-heteroaryl, wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen, lower alkyl substituted by halogen, lower alkoxy, lower alkyl, cyano, nitro, -O-lower alkyl substituted by halogen or morpholinyl;

- $R_2$ is $-(\text{CH}_2)_n$-aryl or $-(\text{CH}_2)_n$-heteroaryl, wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of lower alkyl, lower alkoxy, halogen or -N(lower alkyl)$_2$;

- $R_4$ is $-(\text{CH}_2)_n$-aryl or $-(\text{CH}_2)_n$-heteroaryl, wherein such groups are unsubstituted or substituted by one or more substituents, selected from the group consisting of halogen or lower alkoxy, or is lower alkyl, $-(\text{CH}_2)_n$-cycloalkyl; or

- $n$ is 0, 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

3. Compounds of formula I, wherein $R_1$ is phenyl substituted by halogen, $R_2$ is phenyl and $R_4$ is benzyl.

4. Compounds of formula I according to claim 3, which compounds are
   
   - $(R_{ac})$-4-benzylamino-1-(4-chloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one
   
   - $(7t\omega c)$-4-benzylamino-1-(3,4-dichloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one or
   
   - $(-)$-4-benzylamino-1-(4-chloro-phenyl)-5-phenyl-1,5-dihydro-imidazol-2-one.

5. Compounds of formula I, wherein $R_1$ is phenyl substituted by halogen, $R_2$ is phenyl substituted by lower alkyl and $R_4$ is benzyl.

6. Compounds of formula I according to claim 5, which compounds are
   
   - $(R_{ac})$-4-benzylamino-1-(3,4-dichloro-phenyl)-5-p-tolyl-1,5-dihydro-imidazol-2-one or
   
   - $(R_{ac})$-4-benzylamino-1-(3,4-dichloro-phenyl)-5-(3,4-dimethyl-phenyl)-1,5-dihydro-imidazol-2-one.

7. Compounds of formula I, wherein $R_1$ and $R_2$ are phenyl substituted by halogen and $R_4$ is benzyl.
8. Compounds of formula I according to claim 7, which compounds are 
(Rac)-4-benzylamino-5-(4-chloro-phenyl)-l-(3,4-dichloro-phenyl)-1,5-
dihydro-imidazol-2-one  
(Rac)-4-benzylamino-l-(3,4-dichloro-phenyl)-5-(4-fluoro-phenyl)-1,5-
dihydro-imidazol-2-one or  
(Rac)-4-benzylamino-l-(3-chloro-4-fluoro-phenyl)-5-(4-fluoro-phenyl)-1,5-
dihydro-imidazol-2-one.

9. Compounds of formula I, wherein R^1 is phenyl substituted by halogen, R^2 is 
phenyl substituted by methoxy and R^4 is benzyl.

10. Compounds of formula I according to claim 9, wherein the compound is  
(Rac)-4-benzylamino-l-(3,4-dichloro-phenyl)-5-(3-methoxy-phenyl)-1,5-
dihydro-imidazol-2-one.

11. Compounds of formula I, wherein R^1 is phenyl substituted by halogen, R^2 is 
phenyl and R^4 is benzyl substituted by halogen.

12. Compounds of formula I according to claim 11, wherein the compound is  
Rac-l-(3,4-dichloro-phenyl)-4-(fluorobenzylamino)-5-phenyl-1,5-dihydro-
imidazol-2-one.

13. Compounds of formula I, wherein R^1 is phenyl substituted by halogen, R^2 is 
phenyl and R^4 is lower alkyl.

14. Compounds of formula I according to claim 13, wherein the compounds are  
Rac-l-(3,4-dichloro-phenyl)-4-(3-methyl-butylamino)-5-phenyl-1,5-
dihydroimidazol-2-one or  
(Rac)-l-(3,4-dichloro-phenyl)-4-hexylamino-5-phenyl-1,5-dihydro-imidazol-
2-one.

15. Compounds of formula I, wherein R^1 is phenyl substituted by halogen, R^2 is 
phenyl and R^4 is -CH_2-cycloalkyl.

16. Compounds of formula I according to claim 15, wherein the compound is  
(Rac)-4-(cyclohexylmethyl-amino)-l-(3,4-dichloro-phenyl)-5-phenyl-1,5-
dihydro-imidazol-2-one.

17. A process for preparing a compound of formula I as defined in claim 1, which 
process comprises  
a) brominating a compound of formula
followed by reaction with an amine of formula
\[
\text{NHR}^3\text{R}^4
\]
to a compound of formula
\[
\text{R}^1\text{N}^\text{R}^2\text{R}^3\text{R}^4\text{N}^\text{R}^5\text{R}^6\text{R}^7\text{R}^8
\]
wherein the substituents R\(^1\), R\(^2\), R\(^3\) and R\(^4\) are as defined in claim 1, or

b) reacting in one step a primary amine of formula R\(^2\)NH\(_2\) (III), together with potassium cyanate, an isonitrile of formula \(\text{R}^2\text{NNC}^\text{C}^-\text{V}\) and an aldehyde of formula R\(^1\)C(O)H (IV) to a compound of formula
\[
\text{R}^1\text{N}^\text{R}^2\text{R}^3\text{R}^4\text{N}^\text{R}^5\text{R}^6\text{R}^7\text{R}^8
\]
wherein the substituents R\(^1\), R\(^2\) and R\(^4\) are as defined in claim 1, and if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

18. A compound according to claim 1, whenever prepared by a process as claimed in claim 17 or by an equivalent method.

19. A medicament containing one or more compounds as claimed in claim 1 and pharmaceutically acceptable excipients.

20. A medicament according to claim 19 for the treatment of illnesses based on the glycine uptake inhibitor.
21. A medicament according to claim 20, wherein the illnesses are psychoses, pain, dysfunction in memory and learning, schizophrenia, dementia and other diseases in which cognitive processes are impaired, attention deficit disorders or Alzheimer's disease.

22. The use of a compound as claimed in claim 1 for the manufacture of medicaments for the treatment of psychoses, pain, neurodegenerative disfunction in memory and learning, schizophrenia, dementia and other diseases in which cognitive processes are impaired, attention deficit disorders or Alzheimer's disease.

23. The invention as herein before described.
**INTERNATIONAL SEARCH REPORT**

**INTERNATIONAL APPLICATION NO**

PCT/EP2007/051824

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A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D233/92 A61K31/4025 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPG.

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C

See patent family annex

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Date of the actual completion of the international search 29 May 2007

Date of mailing of the international search report 15/06/2007

Name and mailing address of the ISA/ European Patent Office, P B 5818 Patentlaan Z NL- 2280 HV RUSSEL Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016

Authorized officer

Seelmann, Ingo

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