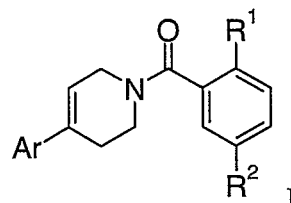


## BENZOYL-TETRAHYDROPYRIDINE AS GLYT-1 INHIBITORS

The present invention relates to compounds of the general formula I



wherein

- 5     $R^1$         is a non aromatic heterocycle or  $OR'$ ;  
        $R'$         is lower alkyl, lower alkyl substituted by halogen or is  $-(CH_2)_n$ -cycloalkyl;  
        $R^2$         is  $NO_2$ ,  $CN$  or  $SO_2R''$ ;  
        $R''$         is lower alkyl;  
        $Ar$         is phenyl, optionally substituted by halogen, cyano, lower alkyl substituted by  
 10        halogen or  $SO_2R''$ ;  
        $n$         is 0, 1 or 2;  
       and to pharmaceutically active acid addition salts.

15        The present invention relates to compounds of general formula I, to processes for preparation of those compounds, to pharmaceutical composition containing them and to their use in the treatment of neurological and neuropsychiatric disorders.

It has surprisingly been found that the compounds of general formula I are good inhibitors of the glycine transporter 1 (GlyT-1), and that they have a good selectivity to glycine transporter 2 (GlyT-2) inhibitors.

20        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*, 2000, 28:325-33). For decades research has focused on the "dopaminergic hyperactivity"  
 25        hypothesis which has led to therapeutic interventions involving blockade of the dopaminergic system (Vandenberg RJ and Aubrey KR., *Exp. Opin. Ther. Targets*, 2001, 5(4): 507-518; Nakazato A and Okuyama S, et al., 2000, *Exp. Opin. Ther. Patents*, 10(1):

75-98). This pharmacological approach poorly address negative and cognitive symptoms which are the best predictors of functional outcome (Sharma T., *Br.J. Psychiatry*, 1999, 174(suppl. 28): 44-51).

A complementary model of schizophrenia was proposed in the mid-1960' 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., 1999, *Biol. Psychiatry*, 45: 668-679 and refs. herein). Furthermore transgenic mice expressing reduced levels of the NMDAR1 subunit displays 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., 1999, *Cell*, 98: 427-236).

Glutamate neurotransmission, in particular NMDA receptor activity, plays a critical role in synaptic plasticity, learning and memory, such as the NMDA receptors appears to serve as a graded switch for gating the threshold of synaptic plasticity and memory formation (Hebb DO, 1949, *The organization of behavior*, Wiley, NY; Bliss TV and Collingridge GL, 1993, *Nature*, 361: 31-39). Transgenic mice overexpressing the NMDA NR2B subunit exhibit enhanced synaptic plasticity and superior ability in learning and memory (Tang JP et al., 1999, *Nature*: 401- 63-69).

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 by removing neurotransmitters from the extracellular space, can control

their extracellular lifetime and thereby modulate the magnitude of the synaptic transmission (Gainetdinov RR et al, 2002, Trends in Pharm. Sci., 23(8): 367-373) .

Glycine transporters, which form part of the sodium and chloride family of neurotransmitter transporters, play an important role in the termination of post-synaptic  
5 glycinergic 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  
10 promoter usage (1a, 1b, 1c and 1d). Only two of these isoforms have been found in rodent brain (GlyT-1a and GlyT-1b). 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  
15 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., 2001, *Mol. Mem. Biol.*, 18: 13-20). 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  
20 (Bergereon R. Et al., 1998, *Proc. Natl. Acad. Sci. USA*, 95: 15730-15734; Chen L et al., 2003, *J. Neurophysiol.*, 89 (2): 691-703).

Glycine transporters 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, 2001, *Exp. Opin. Ther. Patents*, 11 (4): 563-572),  
25 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., 2002, *Prog. Neurobiol.*, 67: 173-202), autistic disorders (Carlsson ML, 1998, *J. Neural Transm.* 105: 525-535), cognitive disorders such as dementias, including age related  
30 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, 2001, *Exp. Opin. Ther. Patents*, 11 (4): 563-572).

Thus, increasing activation of NMDA receptors via GlyT-1 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 per se, the use of  
5 compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases related to activation of NMDA receptors via Glyt-1 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 in  
10 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.

Furthermore, the invention includes all racemic mixtures, all their corresponding  
15 enantiomers and/or optical isomers.

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 7 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.

20 As used herein, the term "cycloalkyl" denotes a saturated carbon ring, containing from 3 to 7 carbon atoms, for example, cyclopropyl, cyclopentyl or cyclohexyl.

As used herein the term "non aromatic heterocycle" denotes a five or six membered heterocyclic ring, containing one or two heteroatoms, selected from the group consisting of O, N or S. Preferred rings are 1-pyrrolidine, 1-piperidine, 1-piperazine or 1-  
25 morpholine.

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

As used herein the term "lower alkyl, substituted by halogen" denotes an alkyl group as defined above, wherein at least one hydrogen atom is replaced by halogen, for example CF<sub>3</sub>, CHF<sub>2</sub>, CH<sub>2</sub>F, CH<sub>2</sub>CF<sub>3</sub> and the like.

30 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 formula I are those, wherein  $R^1$  is morpholine, for example the followings:

- 5 4-[1-(2-morpholin-4-yl-5-nitro-benzoyl)-1,2,3,6-tetrahydro-pyridin-4-yl] benzonitrile, (5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone or [4-(4-methanesulfonyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

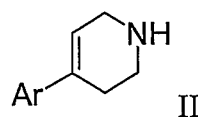
- 10 Further preferred are compounds, wherein  $R^1$  is -O-lower alkyl, substituted by halogen, which compound is [5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone.

- Further preferred are compounds, wherein  $R^1$  is -O-lower alkyl, which compound is  
15 3-[4-(4-chloro-phenyl)-3,6-dihydro-2H-pyridine-1-carbonyl]-4-isopropoxy-benzonitrile.

- Preferred compounds of formula I are further those, wherein  $R^1$  is -O-(CH<sub>2</sub>)<sub>n</sub>-cycloalkyl, for example the following compounds:  
(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-methanesulfonyl-phenyl)-3,6-  
20 dihydro-2H-pyridin-1-yl]-methanone or [4-(4-chloro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone.

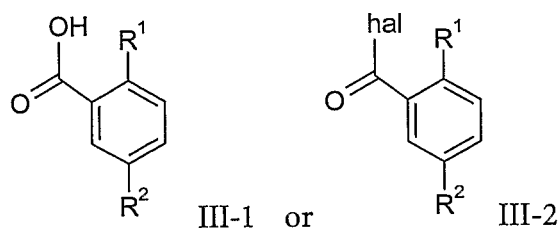
- The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below,  
25 which process comprises

a) reacting a compound of formula



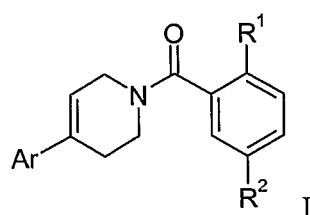
with a compound of formula

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in the presence of an activating agent such as TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate) for compounds of formula III-1,

to a compound of formula



5

wherein hal is a halogen atom, such as chloride and Ar, R<sup>1</sup> and R<sup>2</sup> are as defined above, and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

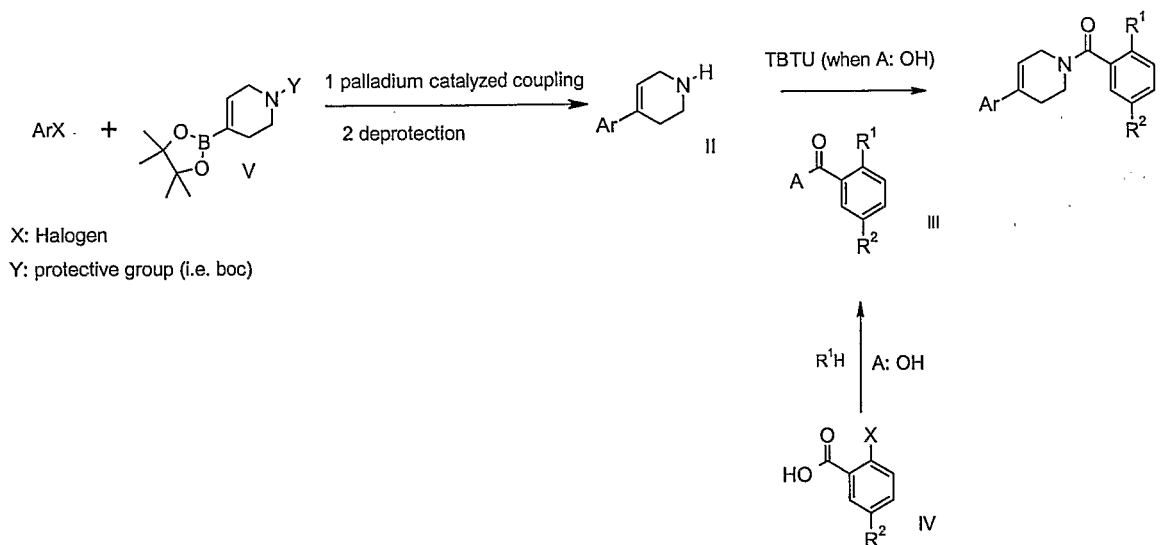
- 10 The compounds of formula I may be prepared in accordance with process variant a) and with the following scheme 1. All starting materials are either commercially available, described in the literature or can be prepared by methods well known in the art. The following abbreviation has been used:

15

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## Scheme 1



Compounds of general formula I can be prepared by reacting 4-aryl-substituted-1,2,3,6-tetrahydro-pyridine derivative of formula II with a corresponding acid of formula III (A: OH) in the presence of an activating agent like TBTU or with a corresponding activated acid of formula III (A: Cl). The acid of formula III can be prepared by reaction of an acid of formula IV with a nucleophile of formula R<sup>1</sup>H. 4-aryl-substituted-1,2,3,6-tetrahydro-pyridine derivatives of formula II can be prepared under Suzuki conditions (*Eastwood et al. tetrahedron Letters* (2000), 41,(19),3705-3708) by reacting boronic ester V with ArX in the presence of palladium catalyst followed by cleavage of the protective group as shown in scheme 1. The protective group is typically tert-butoxycarbonyl (Boc).

The acid addition salts of the basic compounds of formula I may be 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 pharmaceutically 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-1).

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 CaCl<sub>2</sub>, 2.5 mM KCl, 2.5 mM MgSO<sub>4</sub>, 10 mM (+) D-glucose.

Flp-in<sup>TM</sup>-CHO (Invitrogen Cat n° R758-07) cells stably transfected with mGlyT1b cDNA.

Glycine uptake inhibition assay (mGlyT-1b)

- 10 On day 1 mammalian cells, (Flp-in<sup>TM</sup>-CHO), transfected with mGlyT-1b 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
- 15 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<sub>50</sub>, the concentration of the competitor inhibiting glycine uptake of 50 %). A solution was then immediately added containing [<sup>3</sup>H]-glycine 60 nM (11-16 Ci/mmol) and 25 µM non-radioactive glycine. The plates were incubated with
- 20 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<sub>50</sub> (µM) at GlyT-1 < 0.9.

| Example No. | IC <sub>50</sub> (µM) | Example No. | IC <sub>50</sub> (µM) |
|-------------|-----------------------|-------------|-----------------------|
| 1           | 0.803                 | 6           | 0.251                 |
| 2           | 0.432                 | 7           | 0.870                 |
| 3           | 0.270                 | 8           | 0.201                 |
| 4           | 0.122                 | 9           | 0.28                  |

|   |       |    |       |
|---|-------|----|-------|
| 5 | 0.232 | 10 | 0.056 |
|---|-------|----|-------|

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I 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, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations.

10 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, dragées 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.

15 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 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/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 1000 mg per day of a compound of general formula I 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)

|    | <u>Item</u> | <u>Ingredients</u>           | <u>mg/tablet</u> |       |        |        |
|----|-------------|------------------------------|------------------|-------|--------|--------|
|    |             |                              | 5 mg             | 25 mg | 100 mg | 500 mg |
| 10 | 1.          | Compound of formula IA or IB | 5                | 25    | 100    | 500    |
|    | 2.          | Lactose Anhydrous DTG        | 125              | 105   | 30     | 150    |
|    | 3.          | Sta-Rx 1500                  | 6                | 6     | 6      | 30     |
|    | 4.          | Microcrystalline Cellulose   | 30               | 30    | 30     | 150    |
|    | 5.          | Magnesium Stearate           | 1                | 1     | 1      | 1      |
| 15 |             | Total                        | 167              | 167   | 167    | 831    |

#### 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.
- 20 4. Add item 5 and mix for three minutes; compress on a suitable press.

#### Capsule Formulation

|    | <u>Item</u> | <u>Ingredients</u>           | <u>mg/capsule</u> |       |        |        |
|----|-------------|------------------------------|-------------------|-------|--------|--------|
|    |             |                              | 5 mg              | 25 mg | 100 mg | 500 mg |
|    | 1.          | Compound of formula IA or IB | 5                 | 25    | 100    | 500    |
| 25 | 2.          | Hydrous Lactose              | 159               | 123   | 148    | ---    |
|    | 3.          | Corn Starch                  | 25                | 35    | 40     | 70     |
|    | 4.          | Talc                         | 10                | 15    | 10     | 25     |
|    | 5.          | Magnesium Stearate           | 1                 | 2     | 2      | 5      |
|    |             | Total                        | 200               | 200   | 300    | 600    |

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.

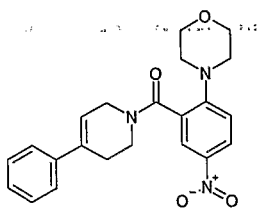
5       The following examples illustrate the present invention without limiting it. All temperatures are given in degree Celsius.

All starting materials are either commercially available, described in the literature or can be prepared by methods well known in the art.

10

Example 1

(2-Morpholin-4-yl-5-nitro-phenyl)-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-methanone

1a: 2-Morpholin-4-yl-5-nitro-benzoic acid

15       To a solution of 2-fluoro-5-nitrobenzoic acid (4.86 g, 26.2 mmol) in dioxane (50 ml) was added morpholine (11.5 ml). The mixture was stirred at room temperature for 2 hours. The solvent was removed in vacuo. The residue was dissolved in water and the mixture was acidified with HCl 2N. The solid was filtered, washed with water and dried to provide the title compound (6.2 g, 93%) as a yellow solid, MS (m/e): 251.2 (M-H, 100%).

1b: 2-Morpholin-4-yl-5-nitro-benzoyl chloride

20       To a suspension of 2-morpholin-4-yl-5-nitro-benzoic acid (4.0 g, 16 mmol) in toluene were added 2 drops of DMF and thionylchloride (5.7 ml, 79.3 mmol). The mixture was heated to 80°C for 50 minutes. The solvent was removed in vacuo, and the resulting solid was stirred in ether, filtered and dried to provide the title compound (4.0 g, 93%) as a yellow solid.

25       1c: (2-Morpholin-4-yl-5-nitro-phenyl)-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)-methanone

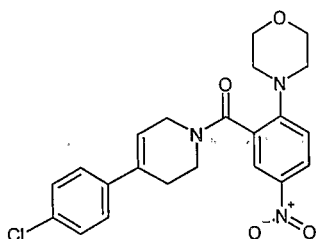
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A mixture of 40.6 mg (0.15 mmol) of 2-morpholin-4-yl-5-nitro-benzoyl chloride, 29 mg (0.18 mmol) 4-phenyl-1,2,3,6-tetrahydro-pyridine (commercial) and 62.5 ul (0.45 mmol)  $\text{NEt}_3$  in 1 ml DCM was stirred at room temperature for 16 h. After evaporation of the volatiles the residue was taken up in 1 ml  $\text{CH}_3\text{CN}/\text{DMF}/\text{HCOOH}$  3/5/2 and subjected to  
 5 preparative HPLC purification on reversed phase eluting with an acetonitrile / water gradient to yield after evaporation the title compound.

MS (m/e): 394.1 ( $\text{MH}^+$ , 100%)

### Example 2

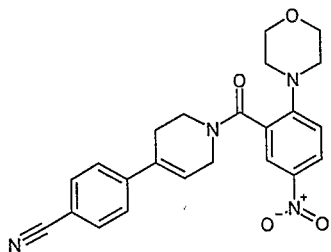
[4-(4-Chloro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-(2-morpholin-4-yl-5-nitrophenyl)  
 10 methanone



According to the procedure described for the synthesis of example 1, the title compound has been synthesised from 2-morpholin-4-yl-5-nitro-benzoyl chloride and 4-(4-Chloro-phenyl)-1,2,3,6-tetrahydro-pyridine hydrochloride (commercial). MS (m/e): 428.1  
 15 ( $\text{MH}^+$ , 100%)

### Example 3

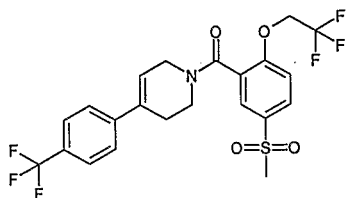
4-[1-(2-Morpholin-4-yl-5-nitro-benzoyl)-1,2,3,6-tetrahydro-pyridin-4-yl] benzonitrile



According to the procedure described for the synthesis of example 1, the title compound  
 20 has been synthesised from 2-morpholin-4-yl-5-nitro-benzoyl chloride and 4-(1,2,3,6-Tetrahydro-pyridin-4-yl)-benzonitrile (CAS: 460365-22-4). MS (m/e): 417.0 (M-H, 100%)

## Example 4

[5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl) 3,6-dihydro-2H-pyridin-1-yl]-methanone



5 4a:2-Chloro-5-sulfinobenzoic acid

A solution of 33.59 g (267 mmol) sodium sulfite in 100 ml water at 0 °C is treated with 21.2 g (89 mmol) 2-chloro-5-fluorosulfonylbenzoic acid and 26.6 ml of a 10 M aqueous NaOH solution (267 mmol). The mixture was allowed to stir for 3 h at room temperature, acidified with HCl conc. (pH = 4) and water was removed under vacuum.

- 10 Methanol was added, the precipitate filtered off and the filtrate concentrated. Methanol and diethylether were added and the precipitate was filtered off washed with ether and dried to yield 15 g (76.5%) of the title compound as white gum. MS (m/e): 219.1 (M-H, 100%)

4b: 2-Chloro-5-methanesulfonylbenzoic acid

- 15 A mixture of 1 g (4 mmol) 2-Chloro-5-sulfinobenzoic acid in 20 ml methanol and 20 ml water was treated with 10N NaOH to pH = 9 before adding 1.7 g (12 mmol) methyl iodide. The mixture was heated for 48 h to 80 °C with occasional addition of NaOH to maintain pH = 9. After removal of all volatiles HCl conc. was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried with
- 20 MgSO<sub>4</sub> and evaporated to dryness. The residue was taken up in methanol and subjected to reversed phase HPLC purification eluting with an acetonitrile / water gradient to yield after evaporation of the product fractions 323 mg (34 %) of the title compound. MS (m/e): 233.0 (M-H, 100%)

4c: 5-methanesulfonyl-2-(2,2,2-trifluoroethoxy)benzoic acid

- 25 A mixture of 2.13 mmol 2-chloro-5-methanesulfonylbenzoic acid, 0.64 mmol Cu(I)Br in 5 ml NEt<sub>3</sub> and 25 ml 2,2,2-trifluoroethanol was heated to 120 °C for 16 h in a sealed tube. The volatiles were removed under vacuum and the residue was taken up in 70 ml 1N HCl. Extraction with ethyl acetate drying of the combined organic fractions and

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evaporation yielded a residue which was purified by reversed phase preparative HPLC eluting with an acetonitrile / water gradient. Evaporation of the product fractions yielded the title compound. MS (m/e): 297.0 (M-H, 100%)

4d: 4-(4-Trifluoromethyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

To a solution of 0.97 mmol 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (CAS: 286961-14-6) in 6 ml dimethylformamide, 2.91 mmol potassium carbonate, 1.02 mmol p-bromobenzotrifluoride, and 0.06 mmol dichlor(1,1' bis(diphenylphosphino)ferrocene) palladium(II)dichloromethane complex were successively added. The reaction was then stirred at 80 °C for 6 hours, concentrated in vacuo and purified by column chromatography (SiO<sub>2</sub>, 20 g, heptane), to give the title compound. MS (m/e): 271.1 (M-isobuthylene)

4e: 4-(4-Trifluoromethyl-phenyl)-1,2,3,6-tetrahydro-pyridine

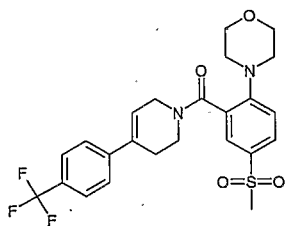
A mixture of 0.52 mmol 4-(4-trifluoromethyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester in 2 ml dichloromethane was treated with 0.2 ml trifluoroacetic acid. The mixture was stirred at 40 °C for 3 hrs then concentrated and treated with water/ NaOH and extracted with dichloromethane. The combined organic phases were washed with saturated NaCl, dried with MgSO<sub>4</sub> and evaporated to yield the title compound. MS (m/e): 228.3 (MH<sup>+</sup>, 100%)

4f: 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone

To a solution of 0.17 mmol 5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid in 0.75 ml dimethylformamide, 0.19 mmol TBTU, 0.855 mmol N-ethyl-diisopropylamine and 0.205 mmol 4-(4-trifluoromethyl-phenyl)-1,2,3,6-tetrahydro-pyridine were successively added. The reaction was then stirred at RT for 45 min., concentrated in vacuo and purified by column chromatography (SiO<sub>2</sub>, 10 g, heptane, ethylacetate 0 to 100%), to give the title compound. MS (m/e): 508.6 (MH<sup>+</sup>, 100%)

### Example 5

(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone



5a: 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid

A mixture of 163.8 mg (0.7 mmol) 2-chloro-5-methanesulfonyl-benzoic acid (example 4 step b) in 2 ml morpholine was heated for 16 h to 100 °C. After evaporation of all  
 5 volatiles the residue was taken up in 2 ml methanol/formic acid 3/1 and subjected to reversed phase HPLC purification eluting with an acetonitrile / water gradient to yield after evaporation of the product fractions the title compound. MS (m/e): 284.1 (M-H, 100%)

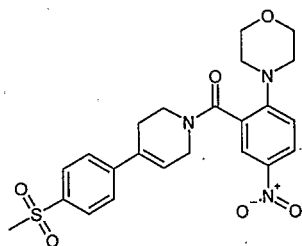
5b: (5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-3,6  
 10 dihydro-2H-pyridin-1-yl]-methanone

According to the procedure described for the synthesis of example 4, step f, the title compound has been synthesised from 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid and 4-(4-Trifluoromethyl-phenyl)-1,2,3,6-tetrahydro-pyridine. MS (m/e): 495.4 (MH<sup>+</sup>, 100%)

15

**Example 6**

[4-(4-Methanesulfonyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone



6a: 4-(4-Methanesulfonyl-phenyl)-1,2,3,6-tetrahydro-pyridine

20 The title compound has been synthesised from 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester and 4-bromomethylsulfone following procedures described in example 4 step d and e. MS (m/e): 336.0 (M-H, 100%)

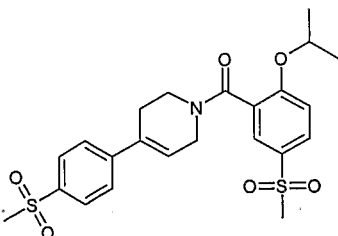
- 16 -

6b: [4-(4-Methanesulfonyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

According to the procedure described for the synthesis of example 4, step f, the title compound has been synthesised from 2-Morpholin-4-yl-5-nitro-benzoic acid and 4-(4-Methanesulfonyl-phenyl)-1,2,3,6-tetrahydro-pyridine. MS (m/e): 470.1 (M-H, 100%)

Example 7

(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-methanesulfonyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone



7a: 2-Isopropoxy-5-methanesulfonyl-benzoic acid

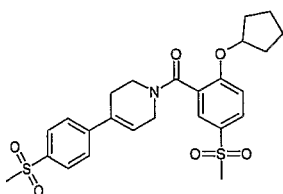
According to the procedure described for the synthesis of example 4, step c, the title compound has been synthesised from 2-chloro-5-methanesulfonyl-benzoic acid and isopropanol. MS (m/e): 257.0 (M-H, 100%)

7b: (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-methanesulfonyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone

According to the procedure described for the synthesis of example 4, step f, the title compound has been synthesised 2-isopropoxy-5-methanesulfonyl-benzoic acid and 4-(4-Methanesulfonyl-phenyl)-1,2,3,6-tetrahydro-pyridine. MS (m/e): 495.4 (M+NH<sub>4</sub><sup>+</sup>, 100%)

Example 8

(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-methanesulfonyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone



8a: 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid

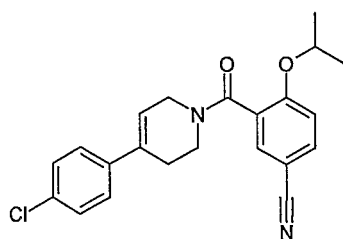
According to the procedure described for the synthesis of example 4, step c, the title compound has been synthesised from 2-chloro-5-methanesulfonyl-benzoic acid and  
 5 cyclopentanol. MS (m/e): 282.9 (M-H, 100%)

8b: (2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-methanesulfonyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone

According to the procedure described for the synthesis of example 4, step f, the title compound has been synthesised from 2-cyclopentyloxy-5-methanesulfonyl-benzoic acid  
 10 and 4-(4-Methanesulfonyl-phenyl)-1,2,3,6-tetrahydro-pyridine. MS (m/e): 503.9 (M<sup>+</sup>, 100%)

### Example 9

3-[4-(4-Chloro-phenyl)-3,6-dihydro-2H-pyridine-1-carbonyl]-4-isopropoxy-benzonitrile



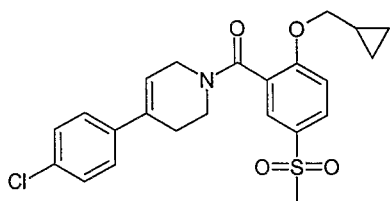
15

According to the procedure described for the synthesis of example 4, step f, the title compound has been synthesised from 5-cyano-2-isopropoxy-benzoic acid (CAS: 845616-14-0) and 4-(4-chloro-phenyl)-1,2,3,6-tetrahydro-pyridine hydrochloride (commercial). MS (m/e): 381.1 (MH<sup>+</sup>, 100%).

20

### Example 10

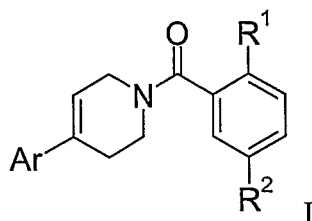
[4-(4-Chloro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone



According to the procedure described for the synthesis of example 4, step f, the title compound has been synthesised from 2-cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (CAS: 845616-03-7) and 4-(4-chloro-phenyl)-1,2,3,6-tetrahydro-pyridine  
5 hydrochloride (commercial). MS (m/e): 446.0 (MH<sup>+</sup>, 100%).

Claims

## 1. Compounds of general formula



wherein

- 5     R<sup>1</sup>           is a non aromatic heterocycle or OR';  
       R'           is lower alkyl, lower alkyl substituted by halogen or is -(CH<sub>2</sub>)<sub>n</sub>-cycloalkyl;  
       R<sup>2</sup>           is NO<sub>2</sub>, CN or SO<sub>2</sub>R'';  
       R''          is lower alkyl;  
 10    Ar          is phenyl, optionally substituted by halogen, cyano, lower alkyl substituted by  
                   halogen or SO<sub>2</sub>R'';  
       n          is 0, 1 or 2;  
       and pharmaceutically active acid addition salts.

- 15           2. Compounds of formula I according to claim 1, wherein R<sup>1</sup> is morpholine.

3. Compounds of formula I according to claim 2, which compounds are  
       4-[1-(2-morpholin-4-yl-5-nitro-benzoyl)-1,2,3,6-tetrahydro-pyridin-4-yl] benzonitrile,  
       (5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(4-trifluoromethyl-phenyl)-3,6  
 20    dihydro-2H-pyridin-1-yl]-methanone or  
       [4-(4-methanesulfonyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-(2-morpholin-4-yl-5-  
       nitro-phenyl)-methanone.

4. Compounds of formula I according to claim 1, wherein R<sup>1</sup> is -O-lower alkyl,  
 25    substituted by halogen.

5. A compound of formula I according to claim 4, which compound is  
       [5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)  
       3,6-dihydro-2H-pyridin-1-yl]-methanone.

6. Compounds of formula I according to claim 1, wherein R<sup>1</sup> is -O-lower alkyl.

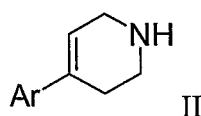
7. A compound of formula I according to claim 6, which compound is 3-[4-(4-chloro-phenyl)-3,6-dihydro-2H-pyridine-1-carbonyl]-4-isopropoxy-benzonitrile.

8. Compounds of formula I according to claim 1, wherein R<sup>1</sup> is  
 5 -O-(CH<sub>2</sub>)<sub>n</sub>-cycloalkyl.

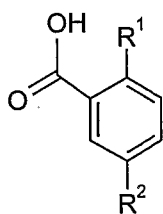
9. A compound of formula I according to claim 8, which compound is  
 (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-methanesulfonyl-phenyl)-3,6-  
 dihydro-2H-pyridin-1-yl]-methanone or  
 [4-(4-chloro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-(2-cyclopropylmethoxy-5-  
 10 methanesulfonyl-phenyl)-methanone.

10. A process for preparing a compound of formula I as defined in claim 1, which process comprises

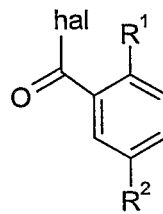
a) reacting a compound of formula



15 with a compound of formula

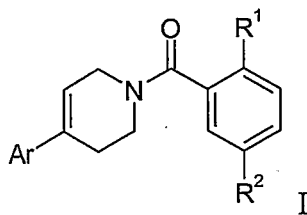


or



in the presence of an activating agent for compounds of formula III-1,

to a compound of formula



20 wherein hal is a halogen atom and Ar, R<sup>1</sup> and R<sup>2</sup> are as defined above, and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

11. A compound according to any one of claims 1 – 9, whenever prepared by a process as claimed in claim 10 or by an equivalent method.

5        12. A medicament containing one or more compounds as claimed in any one of claims 1 – 9 and pharmaceutically acceptable excipients.

13. A medicament according to claim 12 for the treatment of Alzheimer's disease.

14. The use of a compound in any one of claims 1 – 9 for the manufacture of medicaments for the treatment of Alzheimer's disease.

10        15. The invention as hereinbefore described.

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