The present invention is concerned with 3-aryl-isoxazole-4-carbonyl-benzofuran derivatives of formula (I) wherein R1 is hydrogen or halogen; R2 is hydrogen, halogen, hydroxy, lower alkoxy, OCF3, -OCH2-R, R3 is hydroxy or lower alkoxy; or R2 and R3 form together with the carbon atom to which they are attached a ring with -CH=CH-C=CH-; R is aryl or heteroaryl, optionally substituted by halogen or lower alkyl, or is C(O)NH-lower alkyl, or is -C(O)-heteroaryl, wherein the heteroaryl group is optionally substituted by lower alkyl or phenyl, and with their pharmaceutically acceptable acid addition salts. It has been found that this class of compounds show high affinity and selectivity for GABA A cc5 receptor binding sites and might be useful as cognitive enhancer or for the treatment of cognitive disorders like Alzheimer's disease.
The present invention is concerned with 3-aryl-isoxazole-4-carbonyl-benzofuran derivatives of formula

\[
\begin{align*}
\text{R}^1 & \quad \text{is hydrogen or halogen;} \\
\text{R}^2 & \quad \text{is hydrogen, halogen, hydroxy, lower alkoxy, } \text{OCF}_3, \text{-OCH}_2\text{-R,} \\
\text{R}^3 & \quad \text{is hydrogen or lower alkoxy; or} \\
\text{R}^2 \text{ and } \text{R}^3 \text{ form together with the carbon atom to which they are attached a ring with} \\
\text{CH}=\text{CH}=\text{CH}=-; \\
\text{R} & \quad \text{is aryl or heteroaryl, optionally substituted by halogen or lower alkyl, or is } \\
\text{C(O)NH-lower alkyl, or is } \text{-C(O)-heteroaryl, wherein the heteroaryl group is} \\
\text{optionally substituted by lower alkyl or phenyl,} \\
\text{and with their pharmaceutically acceptable acid addition salts.}
\end{align*}
\]

It has been found that this class of compounds show high affinity and selectivity for GABA_A receptor binding sites and might be useful as cognitive enhancer or for the treatment of cognitive disorders like Alzheimer's disease.

Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) GABA_A receptors, which are members of the ligand-gated ion channel superfamily and (2) GABA_B receptors, which are members of the G-protein linked receptor family. The GABA_A receptor complex which is a
membrane-bound heteropentameric protein polymer is composed principally of α, β and γ subunits.

Presently a total number of 21 subunits of the GABA A receptor have been cloned and sequenced. Three types of subunits (α, β and γ) are required for the construction of recombinant GABA A receptors which most closely mimic the biochemical, electrophysiological and pharmacological functions of native GABA A receptors obtained from mammalian brain cells. There is strong evidence that the benzodiazepine binding site lies between the α and γ subunits. Among the recombinant GABA A receptors, c2β2γ2 mimics many effects of the classical type-I BzR subtypes, whereas α2β2γ2,

c3β2γ2 and α5β2γ2 ion channels are termed type-II BzR.

It has been shown by McNamara and Skelton in *Psychobiology, 21:101-108* that the benzodiazepine receptor inverse agonist β-CCM enhance spatial learning in the Morris watermaze. However, β-CCM and other conventional benzodiazepine receptor inverse agonists are proconvulsant or convulsant which prevents their use as cognition enhancing agents in humans. In addition, these compounds are non-selective within the GABA A receptor subunits, whereas a GABA A c5 receptor partial or full inverse agonist which is relatively free of activity at GABA A α1 and/or c2 and/or c3 receptor binding sites can be used to provide a medicament which is useful for enhancing cognition with reduced or without proconvulsant activity. It is also possible to use GABA A c5 inverse agonists which are not free of activity at GABA A α1 and/or c2 and/or c3 receptor binding sites but which are functionally selective for c5 containing subunits. However, inverse agonists which are selective for GABA A c5 subunits and are relatively free of activity at GABA A α1, α2 and α3 receptor binding sites are preferred.

Objects of the present invention are compounds of formula I and pharmaceutically acceptable salts, the preparation of the above mentioned compounds, medicaments containing them and their manufacture as well as the use of the above mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders of the kind referred to earlier or in the manufacture of corresponding medicaments.

The most preferred indication in accordance with the present invention is Alzheimer's disease.
The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a straight- or branched-chain alkyl group containing from 1-7, preferably from 1-4 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, t-butyl and the like.

The term "aryl" denotes an unsaturated carbon ring, for example a phenyl, benzyl or naphthyl group. A preferred aryl group is phenyl.

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

The term "cycloalkyl" denotes a cyclic alkyl ring, having from 3 to 7 carbon atoms, for example, cyclopropyl, cyclopentyl or cyclohexyl.

The term "heteroaryl" denotes an aromatic 5 or 6 membered ring containing from one to three heteroatoms, such as N, O or S atoms. Examples of such aromatic heteroaryl groups are pyridinyl, triazolyl, isoxazolyl, furanyl, thiophenyl, imidazolyl, oxazolyl or pyrazinyl.

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 are compounds, which have a binding activity (hKi) of lower than 100 nM and are selective for GABA A cc5 subunits and are relatively free of activity at GABA A α1, cc2 and cc3 receptor binding sites. Most preferred are compounds which have a binding activity (hKi) of lower than 35 nM.

Preferred compounds of formula I are those, in which R1 is hydrogen. Especially preferred compounds from this group are those, wherein R3 is hydrogen and R2 is halogen, hydroxy, OCF₃ or lower alkoxy, for example the following compounds:

(7-bromo-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone,
(7-hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone,
(7-methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone,
(7-ethoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone,
(6-hydroxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone,
(6-methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone,
(5-methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone,
(5-methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone or
(5-methyl-3-phenyl-isoxazol-4-yl)-(5-trifluoromethoxy-benzofuran-2-yl)-methanone.

Preferred compounds of formula I are further those, in which R¹ and R³ are hydrogen and R² is \(-\text{OCH}_2\text{C(O)NH-lower alkyl or -OCH}_2\text{-heteroaryl, optionally substitut}\text{ed by halogen or lower alkyl, for example the following compounds}
\text{N-isopropyl-2-[2-(5-methyl-3-phenyl-isoxazole-4-carbonyl)-benzofuran-7-yloxy]-acetamide,}
(5-methyl-3-phenyl-isoxazol-4-yl)-[7-(pyridin-2-ylmethoxy)-benzofuran-2-yl]-methanone,
(5-methyl-3-phenyl-isoxazol-4-yl)-[7-(pyridin-3-ylmethoxy)-benzofuran-2-yl]-methanone,
(5-methyl-3-phenyl-isoxazol-4-yl)-[7-(pyridin-4-ylmethoxy)-benzofuran-2-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone.

Preferred compounds of formula I are further those, in which R¹ is hydrogen,
R³ is lower alkoxy and R² is lower alkoxy, for example the following compound
(4,6-dimethoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone.

Preferred compounds of formula I are those, in which R¹ is halogen.

Especially preferred are compounds, wherein R³ is hydrogen and R² is hydrogen,
hydroxy, lower alkoxy or -\text{OCH}_2\text{C(O)NH-lower alkyl}, for example the following compounds
benzofuran-2-yl-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-methanone,
[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-(7-methoxy-benzofuran-2-yl)-methanone,
[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-(7-ethoxy-benzofuran-2-yl)-methanone,
2-{2-[3-(4-bromo-phenyl)-5-methyl-isoxazole-4-carbonyl]-benzofuran-7-yloxy}]-\text{N-isopropyl-acetamide,}
[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-(6-hydroxy-benzofuran-2-yl)-methanone,
[3-(4-bromo-phenyl)-5-methylisoxazol-4-yl]-(6-methoxy-benzofuran-2-yl)-methanone,
[3-(4-bromo-phenyl)-5-methylisoxazol-4-yl]-(5-hydroxy-benzofuran-2-yl)-methanone
or
[3-(4-bromo-phenyl)-5-methylisoxazol-4-yl]-(5-methoxy-benzofuran-2-yl)-methanone.

Preferred compounds of formula I are further those, in which $R^1$ is halogen,
$R^3$ is lower alkoxy and $R^2$ is hydrogen, for example the following compound

[3-(4-bromo-phenyl)-5-methylisoxazol-4-yl]-(4-methoxy-benzofuran-2-yl)-methanone.

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

reacting a compound of formula

\[
\text{II}
\]

with a compound of formula

\[
\text{III}
\]

in the presence of potassium carbonate
to give a compound of formula

\[
\text{I}
\]

wherein $R^1$, $R^2$ and $R^3$ are as described above,
and, if desired, converting a compound of formula I into a pharmaceutically acceptable salt.

The starting materials of formulas II and III are known compounds or maybe prepared according to methods known in the art.

According to reaction step above, compounds of formula I maybe prepared as follows:
To a solution of the bromo ketone II (commercially available for $R^1=H$) in DMF at room temperature was added the appropriately substituted salicylaldehyde of formula III and the mixture stirred vigorously for about 2 h. Where $R^2=OH$ the products can then be further transformed as shown in Scheme 1.

![Scheme 1](image)

wherein $R^2$ is lower alkyl, CF$_3$, -CH$_2$-R for R being aryl or heteroaryl, optionally substituted by halogen or lower alkyl, or being C(O)NH-lower alkyl, or -C(O)-heteroaryl, wherein the heteroaryl group is optionally substituted by lower alkyl or phenyl.

To a solution of a compound of formula 1-1 in THF and the appropriate alcohol of formula HO-R$^2$, triphenylphosphine is added and the resulting mixture is cooled to 0 °C. Then diethyl azodicarboxylate is added and the reaction mixture allowed to warm up to room temperature overnight. Alternatively, the compound of formula 1-1 is dissolved in THF or DMF and potassium carbonate added followed by addition of the appropriate halide at room temperature and the resulting mixture is stirred overnight.

As mentioned earlier, the compounds of formula I and their pharmaceutically usable salts possess valuable pharmacological properties. It has been found that the compounds of the present invention are ligands for GABA A receptors containing the cc5 subunit and are therefore useful in the therapy where cognition enhancement is required.
The compounds were investigated in accordance with the test given hereinafter.

Membrane preparation and binding assay

The affinity of compounds at GABA A receptor subtypes was measured by competition for [3H]flumazenil (85 Ci/mmol; Roche) binding to HEK293 cells expressing rat (stably transfected) or human (transiently transfected) receptors of composition α1β3γ2, α2β3γ2, α3β3γ2 and α5β3γ2.

Cell pellets were suspended in Krebs-tris buffer (4.8 mM KCl, 1.2 mM CaC12, 1.2 mM MgCl2, 120 mM NaCl, 15 mM Tris; pH 7.5; binding assay buffer), homogenized by polytron for ca. 20 sec on ice and centrifuged for 60 min at 4 °C (50000 g; Sorvall, rotor: SM24 = 20000 rpm). The cell pellets were resuspended in Krebs-tris buffer and homogenized by polytron for ca. 15 sec on ice. Protein was measured (Bradford method, Bio-Rad) and aliquots of 1 mL were prepared and stored at -80 °C.

Radioligand binding assays were carried out in a volume of 200 mL (96-well plates) which contained 100 mL of cell memembranes, [3H]flumazenil at a concentration of 1 nM for α1, cc2, cc3 subunits and 0.5 nM for cc5 subunits and the test compound in the range of 10-10^{-3} x 10^{-6} M. Nonspecific binding was defined by 10^{-5} M diazepam and typically represented less than 5% of the total binding. Assays were incubated to equilibrium for 1 hour at 4 °C and harvested onto GF/C uni-filters (Packard) by filtration using a Packard harvester and washing with ice-cold wash buffer (50 mM Tris; pH 7.5). After drying, filter-retained radioactivity was detected by liquid scintillation counting. Ki values were calculated using Excel-Fit (Microsoft) and are the means of two determinations.

The compounds of the accompanying examples were tested in the above described assay, and the preferred compounds were found to possess a Ki value for displacement of [3H]flumazenil from α5 subunits of the rat GABA A receptor of 100 nM or less. In a preferred embodiment the compounds of the invention are binding selective for the cc5 subunit relative to the α1, α2 and α3 subunit.

|-------------|------------|-------------|------------|-------------|------------|


The compounds of formula I as well as their pharmaceutically usable acid addition salts 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 their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragees and hard gelatine capsules. Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semisolid and liquid polyols etc.

<p>| | | | | | |</p>
<table>
<thead>
<tr>
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<td>8.1</td>
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<td>13.8</td>
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<td>42</td>
<td>4.6</td>
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<tr>
<td>15</td>
<td>18.9</td>
<td>30</td>
<td>17.4</td>
<td>43</td>
<td>2.9</td>
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<td>3.7</td>
<td>31</td>
<td>3.7</td>
<td>44</td>
<td>4.8</td>
</tr>
</tbody>
</table>
Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can 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.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of general formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

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

**Example A**

Tablets of the following composition are manufactured in the usual manner:

<table>
<thead>
<tr>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance</td>
</tr>
<tr>
<td>Lactose</td>
</tr>
<tr>
<td>Corn starch</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
</tr>
<tr>
<td>Magnesium stearate</td>
</tr>
<tr>
<td>Tablet weight</td>
</tr>
</tbody>
</table>

**Example B**

Capsules of the following composition are manufactured:

<table>
<thead>
<tr>
<th>mg/capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance</td>
</tr>
<tr>
<td>Lactose</td>
</tr>
</tbody>
</table>
The active substance, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer, the talc is added thereto and mixed thoroughly. The mixture is filled by machine into hard gelatine capsules.

**Example C**

Suppositories of the following composition are manufactured:

<table>
<thead>
<tr>
<th></th>
<th>mg/supp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance</td>
<td>15</td>
</tr>
<tr>
<td>Suppository mass</td>
<td>1285</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1300</strong></td>
</tr>
</tbody>
</table>

The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45 °C. Thereupon, the finely powdered active substance is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool, the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

The following examples 1-44 are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

**Example 1**

Benzofuran-2-yl-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

To a solution of 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) in DMF (0.5 mL) was added salicylaldehyde (61 mg, 53 µL, 0.5 mmol) followed by potassium carbonate (138 mg, 1.0 mmol) and the resulting mixture stirred vigorously at room temperature for 2 h. The mixture was then poured onto ice-water, and extracted with ethyl acetate. The combined organic layers were then washed with water and brine, dried over Na$_2$SO$_4$ and evaporated. Purification by chromatography
(SiO₂, heptane:ethyl acetate: = 100:0 to 1:1) afforded the title compound (131 mg, 86%) as a white solid. MS m/e: 304.0 [M+H]⁺.

**Example 2**

(7-Fluoro-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound (using 3-fluoro-2-hydroxybenzaldehyde instead of salicylaldehyde) which was obtained as a white solid (125 mg, 78%). MS m/e: 322.4 [M+H]⁺.

**Example 3**

(7-Bromo-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound (using 3-bromo-2-hydroxybenzaldehyde instead of salicylaldehyde) which was obtained as a white solid (1.4 g, 51%). MS m/e: 382.0/384.1 [M+H]⁺.

**Example 4**

(7-Hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone

As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (2.5 g, 359 mmol) was converted to the title compound (using 2,3-dihydroxybenzaldehyde instead of salicylaldehyde) which was obtained as a white solid (3.2 g, 55%). MS m/e: 318.0 [M-H]⁻. *Journal of Natural Products*, 1986, 49, 522-552.

**Example 5**

(7-Methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound (using o-vanillin instead of salicylaldehyde) which was obtained as a white solid (90 mg, 54%). MS m/e: 334.4 [M+H]⁺.

**Example 6**

(7-Ethoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

To a solution of (7-hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone (example 4) (100 mg, 0.31 mmol) in THF (3.1 mL) was added ethanol (19 mg, 24 µL, 0.42 mmol) and triphenylphosphine (109 mg, 0.42 mmol) at room temperature. The resulting mixture was then cooled to 0 °C and diethyl azodicarboxylate (73 mg, 65 µL, 0.42 mmol) added. The resulting mixture was
maintained at 0 °C for 30 min and then allowed to warm up to room temperature overnight. The mixture was then adsorbed onto SiO₂ and purification by chromatography (SiO₂, heptane:ethyl acetate: = 100:0 to 75:25) afforded the title compound (90 mg, 83%) as a white solid. MS m/e: 348.4 [M+H]⁺.

Example 7

(7-Benzyloxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

As described for example 6, (7-hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone (example 4) (100 mg, 0.31 mmol) was converted to the title compound (using benzyl alcohol instead of ethanol) which was obtained as a white solid (108 mg, 84%). MS m/e: 410.3 [M+H]⁺.

Example 8

(5-Methyl-3-phenyl-isoxazol-4-yl)-[7-(pyridin-2-ylmethoxy)-benzofuran-2-yl]-methanone

As described for example 6, (7-hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone (example 4) (100 mg, 0.31 mmol) was converted to the title compound [using 2-(hydroxymethyl)pyridine instead of ethanol] which was obtained as a white solid (85 mg, 66%). MS m/e: 411.0 [M+H]⁺.

Example 9

(5-Methyl-3-phenyl-isoxazol-4-yl)-[7-(pyridin-3-ylmethoxy)-benzofuran-2-yl]-methanone

As described for example 6, (7-hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone (example 4) (100 mg, 0.31 mmol) was converted to the title compound [using 3-(hydroxymethyl)pyridine instead of ethanol] which was obtained as a white solid (77 mg, 60%). MS m/e: 411.0 [M+H]⁺.

Example 10

(5-Methyl-3-phenyl-isoxazol-4-yl)-[7-(pyridin-4-ylmethoxy)-benzofuran-2-yl]-methanone

As described for example 6, (7-hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone (example 4) (100 mg, 0.31 mmol) was converted to the title compound [using 4-(hydroxymethyl)pyridine instead of ethanol] which was obtained as a white solid (54 mg, 42%). MS m/e: 411.0 [M+H]⁺.
Example 11

[7-(3-Fluoro-benzyloxy)-benzofuran-2-yl]-[5-methyl-3-phenyl-isoxazol-4-yl]-methanone

As described for example 6, (7-hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone (example 4) (100 mg, 0.31 mmol) was converted to the title compound (using 3-fluorobenzyl alcohol instead of ethanol) which was obtained as a white solid (94 mg, 70%). MS m/e: 428.3 [M+H]+.

Example 12

[7-(4-Fluoro-benzyloxy)-benzofuran-2-yl]-[5-methyl-3-phenyl-isoxazol-4-yl]-methanone

As described for example 6, (7-hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone (example 4) (100 mg, 0.31 mmol) was converted to the title compound (using 4-fluorobenzyl alcohol instead of ethanol) which was obtained as a white solid (77 mg, 57%). MS m/e: 428.3 [M+H]+.

Example 13

N-Isopropyl-2-[2-(5-methyl-3-phenyl-isoxazole-4-carbonyl)-benzofuran-7-yloxy]-acetamide

To a solution of (7-hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone (example 4) (100 mg, 0.31 mmol) in DMF (5 mL) was added N-(chloroacetyl)isopropylamine (47 mg, 0.34 mmol) and potassium carbonate (173 mg, 1.25 mmol) and the reaction mixture was stirred at room temperature for 4 h. The mixture was then poured onto ice-water, and extracted with ethyl acetate. The combined organic layers were then washed with water and brine, dried over Na2SO4 and evaporated. Purification by chromatography (SiO2, heptane:ethyl acetate: = 100:0 to 1:1) afforded the title compound (37 mg, 28%) as a white solid. MS m/e: 419.3 [M+H]+.

Example 14

(5-Methyl-3-phenyl-isoxazol-4-yl)-[7-(2-methyl-2H-[1,2,4]triazol-3-ylmethoxy)-benzofuran-2-yl] -methanone

As described for example 13, (7-hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone (example 4) (100 mg, 0.31 mmol) was converted to the title compound [using 5-chloromethyl-l-methyl-lH-[1,2,4]triazole hydrochloride instead of N-(chloroacetyl)isopropylamine] which was obtained as a white solid (43 mg, 33%). MS m/e: 415.3 [M+H]+.

Example 15
[7-(3-Methyl-isoxazol-5-ylmethoxy)-benzofuran-2-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

As described for example 6, (7-hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone (example 4) (100 mg, 0.31 mmol) was converted to the title compound (using 5-(chloromethyl)-3-methylisoxazole instead of ethanol) which was obtained as a white solid (99 mg, 76%). MS m/e: 415.1 [M+H]+.

Example 16
(6-Hydroxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound (using 2,4-dihydroxybenzaldehyde instead of salicylaldehyde) which was obtained as a white solid (11 mg, 7%). MS m/e: 320.3 [M+H]+.

Example 17
(6-Methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound (using 2-hydroxy-4-methoxybenzaldehyde instead of salicylaldehyde) which was obtained as a white solid (95 mg, 57%). MS m/e: 334.1 [M+H]+.

Example 18
2-[2-(5-Methyl-3-phenyl-isoxazole-4-carbonyl)-benzofuran-6-yloxy]-l-(5-methyl-3-phenyl-isoxazol-4-yl)-ethanone

As described for example 16, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound (using 2,4-dihydroxybenzaldehyde instead of salicylaldehyde) which was obtained as a white solid (46 mg, 18%). MS m/e: 519.3 [M+H]+.

Example 19
(5-Chloro-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound (using 5-chlorosalicylaldehyde instead of salicylaldehyde) which was obtained as a white solid (114 mg, 68%). MS m/e: 338.1 [M+H]+.

Example 20
(5-Bromo-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone
As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound (using 5-bromosalicylaldehyde instead of salicylaldehyde) which was obtained as a white solid (145 mg, 76%). MS m/e: 384.1/382.0 [M+H]⁺.

Example 2

(5-Methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound (using 2,5-dihydroxybenzaldehyde instead of salicylaldehyde) which was obtained as a white solid (63 mg, 40%). MS m/e: 320.3 [M+H]⁺.

Example 22

(5-Methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound (2-hydroxy-5-methoxybenzaldehyde instead of salicylaldehyde) which was obtained as a white solid (73 mg, 44%). MS m/e: 334.1 [M+H]⁺.

Example 23

(5-Methyl-3-phenyl-isoxazol-4-yl)-(5-trifluoromethoxy-benzofuran-2-yl)-methanone

As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound [using 5-(trifluoromethoxy) salicylaldehyde instead of salicylaldehyde] which was obtained as a white solid (159 mg, 82%). MS m/e: 388.4 [M+H]⁺.

Example 24

2-[2-(5-Methyl-3-phenyl-isoxazole-4-carbonyl)-benzofuran-5-yloxy]-l-(5-methyl-3-phenyl-isoxazol-4-yl)-ethanone

As described for example 21, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound (using 2,5-dihydroxybenzaldehyde instead of salicylaldehyde) which was obtained as a white solid (27 mg, 10%). MS m/e: 519.3 [M+H]⁺.

Example 25

(4-Methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone
As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound using (2-hydroxy-6-methoxybenzaldehyde instead of salicylaldehyde) which was obtained as a white solid (93 mg, 56%). MS m/e: 334.1 [M+H]⁺.

Example 26
(4,6-Dimethoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound using (4,6-dimethoxysalicylaldehyde instead of salicylaldehyde) which was obtained as a white solid (129 mg, 71%). MS m/e: 364.3 [M+H]⁺.

Example 27
(5-Methyl-3-phenyl-isoxazol-4-yl)-naphtho[2,1-b]furan-2-yl-methanone

As described for example 1, 4-(bromoacetyl)-5-methyl-3-phenylisoxazole (commercially available) (140 mg, 0.5 mmol) was converted to the title compound using (2-hydroxy-1-naphthaldehyde instead of salicylaldehyde) which was obtained as a white solid (136 mg, 77%). MS m/e: 354.1 [M+H]⁺.

Example 28
Benzofuran-2-yl-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-methanone

(E)- and/or (Z)-4-Bromo-benzaldehyde-oxime
To a suspension of 4-bromobenzaldehyde (20.0 g, 108 mmol) and hydroxylamine hydrochloride (8.2 g, 119 mmol) in EtOH (8 mL) and water (24 mL) was added ice (46 g). Then a solution of NaOH (10.81 g, 270 mmol) in water (11 mL) was added dropwise within a 10 min period (temperature rises from -8 °C to + 7 °C) whereupon most of the solid dissolves. After 30 min stirring at room temperature a white solid precipitated and the resulting mixture was then diluted with water and acidified with 4 N HCl. The white precipitate was then filtered off, washed with water and dried under high vacuum to afford the title compound (20.7 g, 96%). MS m/e: 198.0/200.1 [M-H]⁻.

(E)- and/or (Z)-4-Bromo-N-hydroxy-benzenecarboximidoyl chloride
To a solution of (E)- and/or (Z)-4-bromo-benzaldehyde-oxime (7.15 g, 36 mmol) in DMF (36 mL) was added N-chlorosuccinimide (4.77 g, 45 mmol) portionwise over 1 h, keeping the temperature below 35 °C. The reaction mixture was stirred under at room
temperature overnight. The mixture was then poured onto ice-water, and extracted with ethyl acetate. The combined organic layers were then washed with water and brine, dried over Na₂SO₄ and evaporated to afford the title compound (7.6 g, 91%) as a light yellow solid after trituration from heptane. MS m/e (EI): 233.0/234.9 [M]+.

Example 2

Sample

1-[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone

Acetylacetone (1.25 mL, 12 mmol) was added to a sodium ethoxide solution 3.09 N (3.95 mL, 12 mmol) in EtOH (22 mL) at room temperature. The resulting yellow solution was cooled with a ice-bath and a cloudy solution of (E)- and/or (Z)-4-bromo-N-hydroxy-benzencarboximidoyl chloride (2.35 g, 10 mmol) in EtOH (8 mL) was added dropwise within 10 min keeping the temperature below 5 °C. The light yellow suspension was stirred at room temperature for 3 h and then acidified with 6 N HCl and then evaporated. The resulting mixture was extracted with ethyl acetate and the combined organic layers were then washed with water and brine, dried over Na₂SO₄ and evaporated. Purification by chromatography (SiO₂, heptane:ethyl acetate: = 100:0 to 7:3) afforded the title compound (2.35 g, 84%) as a light yellow oil. MS m/e: 280.1/282.1 [M+H]+.

2-Bromo-1-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone

To a solution of 1-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (2.49 g, 8.89 mmol) in carbontetrachloride (5.8 mL) and AcOH (0.3 mL) at 48 °C was added a solution of bromine (0.48 mL, 8.89 mmol) in carbontetrachloride (4.7 mL) over 10 min keeping the temperature below 50 °C. After addition the reaction mixture was allowed to cool down to room temperature and poured into ice-water (20 mL). The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic layers were then washed with water and brine, dried over Na₂SO₄ and evaporated. Purification by chromatography (SiO₂, heptane:ethyl acetate: = 8:2) afforded the title compound (1.49 g, 47%) as a light yellow oil. MS m/e: 355.9/358.1/360.0 [M+H]+.

Benzofuran-2-yl-1-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-methanone

As described for example 1, 2-bromo-l-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (180 mg, 0.5 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenylisoxazole] was converted to the title compound which was obtained as a white solid (122 mg, 63%). MS m/e: 384.1/382.0 [M+H]+.

Example 29

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl)-(7-fluoro-benzofuran-2-yl)-methanone
As described for example 2, 2-bromo-l-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (180 mg, 0.5 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenylisoxazole] was converted to the title compound which was obtained as a white solid (162 mg, 81%). MS m/e: 402.2/400.1 [M+H]^+.

Example 30

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-(7-hydroxy-benzofuran-2-yl)-methanone

As described for example 4, 2-bromo-l-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (180 mg, 0.5 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenylisoxazole] was converted to the title compound which was obtained as a white solid (37 mg, 19%). MS m/e: 400.1/398.1 [M+H]^+.

Example 31

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-(7-methoxy-benzofuran-2-yl)-methanone

As described for example 5, 2-bromo-l-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (180 mg, 0.5 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenylisoxazole] was converted to the title compound which was obtained as a white solid (142 mg, 69%). MS m/e: 414.2/412.1 [M+H]^+.

Example 32

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-(7-ethoxy-benzofuran-2-yl)-methanone

As described for example 28, 2-bromo-l-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (180 mg, 0.5 mmol) was converted to the title compound using (3-ethoxysalicylaldehyde instead of salicylaldehyde) which was obtained as a white solid (126 mg, 59%). MS m/e: 428.2/426.0 [M+H]^+.

Example 33

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-(7-isopropoxy-benzofuran-2-yl)-methanone

As described for example 6, 2-bromo-l-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (120 mg, 0.30 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenylisoxazole] was converted to the title compound [using 2-propoanol instead of ethanol] which was obtained as a white solid (88 mg, 66%). MS m/e: 440.2/442.2 [M+H]^+.

Example 34

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-[7-(pyridin-2-ylmethoxy)-benzofuran-2-yl]-methanone
As described for example 8, 2-bromo-l-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (120 mg, 0.3 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenylisoxazole] was converted to the title compound which was obtained as a white solid (114 mg, 78%).

**Example 35**

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-[7-(pyridin-3-ylmethoxy)-benzofuran-2-yl]-methanone

As described for example 9, 2-bromo-l-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (120 mg, 0.3 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenylisoxazole] was converted to the title compound which was obtained as a white solid (93 mg, 63%).

**Example 36**

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-[7-(pyridin-4-ylmethoxy)-benzofuran-2-yl]-methanone

As described for example 10, 2-bromo-l-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (120 mg, 0.3 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenylisoxazole] was converted to the title compound which was obtained as a white solid (81 mg, 55%).

**Example 37**

2-{2-[3-(4-Bromo-phenyl)-5-methyl-isoxazole-4-carbonyl]-benzofuran-7-yloxy}-N-isopropyl-acetamide

As described for example 13, 2-bromo-l-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (120 mg, 0.3 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenylisoxazole] was converted to the title compound which was obtained as a white solid (82 mg, 55%).

**Example 38**

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-[7-(2-methyl-2H-[1,2,4]triazol-3-ylmethoxy)-benzofuran-2-yl]-methanone

As described for example 14, 2-bromo-l-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (120 mg, 0.3 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenylisoxazole] was converted to the title compound which was obtained as a white solid (82 mg, 55%).

MS m/e: 495.3/493.2 [M+H]+.
Example 39

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-[7-(3-methyl-isoxazol-5-ylmethoxy)benzofuran-2-yl]-methanone

As described for example 15, 2-bromo-1-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (120 mg, 0.3 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenyliosozazole] was converted to the title compound which was obtained as a white solid (90 mg, 61%). MS m/e: 495.3/493.2 [M+H]+.

Example 40

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-[6-hydroxy-benzofuran-2-yl]-methanone

As described for example 16, 2-bromo-1-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (180 mg, 0.5 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenyliosozazole] was converted to the title compound which was obtained as a white solid (8 mg, 4%). MS m/e: 400.0/398.1 [M+H]+.

Example 41

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-[6-hydroxy-benzofuran-2-yl]-methanone

As described for example 17, 2-bromo-1-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (180 mg, 0.5 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenyliosozazole] was converted to the title compound which was obtained as a white solid (144 mg, 70%). MS m/e: 414.2/412.1 [M+H]+.

Example 42

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-[6-methoxy-benzofuran-2-yl]-methanone

As described for example 21, 2-bromo-1-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (180 mg, 0.5 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenyliosozazole] was converted to the title compound which was obtained as a white solid (101 mg, 51%). MS m/e: 400.3/398.0 [M+H]+.

Example 43

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-[6-methoxy-benzofuran-2-yl]-methanone

As described for example 22, 2-bromo-1-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (180 mg, 0.5 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenyliosozazole] was converted to the title compound which was obtained as a white solid (159 mg, 77%). MS m/e: 414.2/412.1 [M+H]+.

Example 44

[3-(4-Bromo-phenyl)-5-methyl-isoxazol-4-yl]-[4-methoxy-benzofuran-2-yl]-methanone

As described for example 25, 2-bromo-1-[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-ethanone (180 mg, 0.5 mmol) [instead of 4-(bromoacetyl)-5-methyl-3-phenyliosozazole]
was converted to the title compound which was obtained as a white solid (109 mg, 53%).
MS m/e: 414.2/412.1 [M+H]^+.
Claims

1. 3-Aryl-isoxazole-4-carbonyl-benzofuran derivatives of formula

   \[
   \begin{align*}
   \text{wherein} \\
   R^1 & \text{ is hydrogen or halogen;} \\
   R^2 & \text{ is hydrogen, halogen, hydroxy, lower alkoxy, OCF}_3, -OCH_2-R; \\
   R^3 & \text{ is hydrogen or lower alkoxy; or} \\
   \text{R}^2 \text{ and } R^3 \text{ form together with the carbon atom to which they are attached a ring with} \\
   & -\text{CH} = \text{CH} = \text{CH} = \text{CH} =; \\
   \text{R} & \text{ is aryl or heteroaryl, optionally substituted by halogen or lower alkyl, or is} \\
   & \text{C(O)NH-lower alkyl, or is -C(O)-heteroaryl, wherein the heteroaryl group is} \\
   & \text{optionally substituted by lower alkyl or phenyl,} \\
   \text{and with their pharmaceutically acceptable acid addition salts.}
   \end{align*}
   \]

2. Compounds of formula I according to claim 1, wherein \( R^1 \) is hydrogen.

3. Compounds of formula I according to claim 2, wherein \( R^3 \) is hydrogen and \( R^2 \) is halogen, hydroxy, OCF\(_3\) or lower alkoxy.

4. Compounds of formula I according to claim 3, wherein the compounds are

   (7-bromo-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone,
   (7-hydroxy-2-benzofuranyl)(5-methyl-3-phenyl-4-isoxazolyl)methanone,
   (7-methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone,
   (7-ethoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone,
   (6-hydroxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone,
   (6-methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone,
   (5-methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone,
(5-methoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone or (5-methyl-3-phenyl-isoxazol-4-yl)-(5-trifluoromethoxy-benzofuran-2-yl)-methanone.

5. Compounds of formula I according to claim 2, wherein R³ is hydrogen and R² is

- OCH₂-C(O)NH-lower alkyl or -OCH₂-heteroaryl, optionally substituted by halogen or lower alkyl.

6. Compounds of formula I according to claim 5, wherein the compounds are

- N-isopropyl-2-[2-(5-methyl-3-phenyl-isoxazole-4-carbonyl)-benzofuran-7-yloxy]-acetamide,
- (5-methyl-3-phenyl-isoxazol-4-yl)-[7-(pyridin-2-ylmethoxy)-benzofuran-2-yl]-methanone,
- (5-methyl-3-phenyl-isoxazol-4-yl)-[7-(pyridin-3-ylmethoxy)-benzofuran-2-yl]-methanone,
- (5-methyl-3-phenyl-isoxazol-4-yl)-[7-(pyridin-4-ylmethoxy)-benzofuran-2-yl]-methanone or
- [7-(3-methyl-isoxazol-5-ylmethoxy)-benzofuran-2-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone.

7. Compounds of formula I according to claim 2, wherein R³ is lower alkoxy and R² is lower alkoxy.

8. Compounds of formula I according to claim 7, wherein the compound is

(4,6-dimethoxy-benzofuran-2-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone.

9. Compounds of formula I according to claim 1, wherein R¹ is halogen.

10. Compounds of formula I according to claim 9, wherein R³ is hydrogen and R² is hydrogen, hydroxy, lower alkoxy or -OCH₂-C(O)NH-lower alkyl.

11. Compounds of formula I according to claim 10, wherein the compounds are

- benzofuran-2-yl [3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-methanone,
- [3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-[7-methoxy-benzofuran-2-yl]-methanone,
- [3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-[7-ethoxy-benzofuran-2-yl]-methanone,
2-{2-[3-(4-bromo-phenyl)-5-methyl-isoxazole-4-carbonyl]-benzofuran-7-yloxy}N-isopropyl-acetamide,
[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-(6-hydroxy-benzofuran-2-yl)-methanone,
[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-(6-methoxy-benzofuran-2-yl)-methanone,
[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-(5-hydroxy-benzofuran-2-yl)-methanone or
[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-(5-methoxy-benzofuran-2-yl)-methanone.

12. Compounds of formula I according to claim 9, wherein R3 is lower alkoxy and R2 is hydrogen.

13. Compounds of formula I according to claim 12, wherein the compound is
[3-(4-bromo-phenyl)-5-methyl-isoxazol-4-yl]-(4-methoxy-benzofuran-2-yl)-methanone.

14. A process for preparation of compounds of formula I as defined in claim 1, which process comprises reacting a compound of formula

\[
\begin{align*}
\text{II} & \quad \text{with a compound of formula} \\
\text{III} & \quad \text{in the presence of potassium carbonate} \\
\text{to give a compound of formula} \\
\text{I}
\end{align*}
\]
wherein $R^1$, $R^2$ and $R^3$ are as described above, and, if desired, converting a compound of formula I into a pharmaceutically acceptable salt.

15. A compound of formula I according to claim 1, whenever prepared by a process as claimed in claim 14 or by an equivalent method.

16. A medicament containing one or more compounds of formula I in accordance with claim 1 and pharmaceutically acceptable excipients.

17. A medicament according to claim 16 for the treatment of diseases related to the GABA $\alpha_{5}$ subunit selected from cognitive enhancer or cognitive disorders.

18. A medicament according to claim 17 for the treatment of Alzheimer's disease.

19. The use of a compound of formula I according to claim 1 for the preparation of a medicament for the treatment of cognitive enhancer or cognitive disorders.

20. The use of a compound of formula I according to claim 1 for the preparation of a medicament for the treatment of Alzheimer's disease.

21. The invention as hereinbefore described.