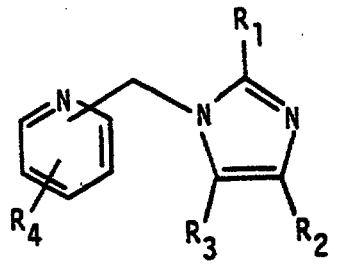
REPLACED SHEETS SG
☑ Description : paged ...1... to paged ...6...
☑ Claim(s) : paged ...7... to paged ...9...
☐ Drawing(s) : paged ..... to paged .....
☑ Abstract : paged ...10... to paged ...-...
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CASE 100-7825

IMIDAZOLYLMETHYL-PYRIDINES

The present invention relates to imidazolylmethyl-pyridines, their production and their use in therapeutic treatment.

More particularly the present invention provides compounds of formula I,



(I)

wherein

R_1 is alkyl (1-4 C), halogen with an atomic number of 9 to 35 or amino optionally mono- or disubstituted by alkyl (1-4 C),

R_2 and R_3 independently of one another are hydrogen or alkyl (1-4 C) and

R_4 is hydrogen, hydroxy, alkyl (1-4 C), alkoxy (1-4 C) or halogen with an atomic number of 9 to 35,

in free base or acid addition salt form, hereinafter referred to as new compounds.

Insofar as above-defined alkyl or alkoxy groups are present in the new compounds, these preferably have one or two carbon atoms and especially signify methyl or methoxy.

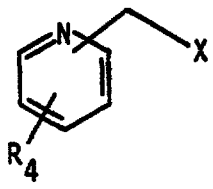
The imidazolylmethyl radical is preferably in position 2 of the pyridine.

R_1 is preferably methyl. R_2 and R_3 are preferably each hydrogen. R_4 is preferably hydrogen. The compound of Example 1 is preferred.

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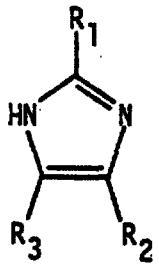
The invention particularly embraces a group of new compounds, wherein R_1 is alkyl (1-4 C), R_2 and R_3 independently of one another are hydrogen or alkyl (1-4 C) and R_4 is hydrogen, alkyl (1-4 C) or halogen with an atomic number of 9 to 35.

In accordance with the invention, the new compounds are obtained by reacting compounds of formula II,



(II)

wherein R_4 is defined as above, and X is halogen, with compounds of formula III,



(III)

wherein R_1, R_2 and R_3 are defined as above,

and recovering the resulting compounds of formula I in free base form or in acid addition salt form.

The reaction of the compounds of formula II with the compounds of formula III may take place in known manner, in a solvent which is inert under the reaction conditions, e.g. in dimethylformamide or a lower alcohol. In formula II, X is preferably chlorine.

Working up of the reaction mixtures obtained and purification of the compounds of formula I thus produced may take place in accordance with known methods.

The compounds of formula I may be present in free form or in the form of their acid

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addition salts. Acid addition salts may be produced from the free bases in known manner, and vice versa.

The starting compounds of formulae II and III are known or may be produced in accordance with known processes, resp. analogously to known processes.

The compounds of formula I and their physiologically acceptable salts, hereinafter referred to as compounds according to the invention, exhibit pharmacological activity and may therefore be used as pharmaceuticals.

In the sleep/wake cycle of the freely moving as well as the long-term implanted rat [for the method, see J.-M. Vigouret et al., J. Pharmacol 10, 503 (1978)], the compounds according to the invention when administered at 1 to 100 mg/kg p.o. effect an increase in vigilance by prolonging the wake phases.

Moreover after administration of 1 to 100 mg/kg p.o. to rats with bilateral lesions of the Locus coeruleus and the Nucleus basalis Meynert, the compounds according to the invention improve significantly the cognitive performance as measured by the ability to avoid an electric shock in the shuttle box.

The method is similar to that described by V. Haroutunian et al. in Brain Research 507 (1990) 261 - 266. Male OFA rats (300 g) are anaesthetized with pentobarbital and the lesions are carried out in a stereotaxic apparatus with a radio frequency generator at 60 ° C during 10 seconds. 5 weeks after lesioning, behavioral testing is performed, using a shuttle box as described by A.R. Dravid, A.-L. Jaton and E.B. Van Deusen in Experimental Brain Research, Suppl. 13, p. 249 (1986).

In view of these activities the compounds according to the invention are useful for the treatment of senile dementia, Alzheimer's disease and further degenerative diseases such as Huntington's chorea, Morbus Parkinson, Steel-Richardson syndrome, tardive dyskinesias, hyperkinesia, acute confusion disorders, Down's syndrome, myasthenia gravis and

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Friedrich's ataxia, furthermore as antidepressants.

An indicated daily dosage for this therapeutical activity is in the range from about 1 mg to 100 mg of the compound, administered, for example, in divided doses up to four times a day.

The compounds according to the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

The present invention also provides pharmaceutical compositions comprising a compound according to the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.25 mg to about 50 mg of a compound according to this invention.

The following examples illustrate the invention. The temperatures are given in degrees Celsius and are uncorrected.

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EXAMPLE 1: [2-(2-methylimidazol-1-yl)methyl]pyridine

9.7 g (75 mM) of 2-(chloromethyl)pyridine and 42 g (512 mM) of 2-methyl-imidazole are suspended in 40 ml dimethylformamide, then stirred for 3 hours at 105°. The dimethylformamide is distilled off and the crystalline residue is diluted with ethyl acetate and a little hexane. Following filtration, the mother solution is concentrated by evaporation and the dimethylformamide distilled off, and then shaken out several times between water and methylene chloride. 10.3 g of the oily title compound are obtained.

9.3 g of the obtained base in ethanol are mixed with 12.7 g of fumaric acid. The resulting bis(base)-tris(hydrogen fumarate) crystallizes from ethanol/ethyl acetate and is recrystallized once from ethanol/ethyl acetate. It is uniform upon thin-layer chromatography and melts at 109 - 110°.

The following [2-(imidazol-1-yl)methyl]pyridines are produced analogously to example 1:

Example	R_1	R_2	R_3	R_4	M.p.
2	CH_3	H	H	6-CH_3	129 - 130° *
3	CH_3	CH_3	H	H	250 - 253° (decomp.)**
4	CH_3	H	CH_3	H	213 - 220° (decomp.)**

* fumarate

** dihydrochloride

as well as the following [4-(imidazol-1-yl)methyl]pyridine:

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Example	R_1	R_2	R_3	R_4	M.p.
5	CH_3	H	H	H	155 - 156° *

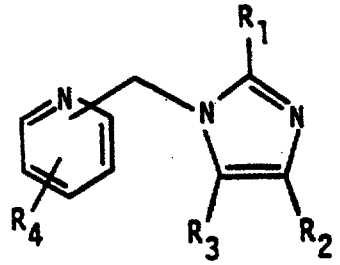
* fumarate

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PATENT CLAIMS FOR THE CONTRACTING STATES:
AT, BE, CH, LI, DE, DK, FR, GB, IE, IT, LU, NL, PT, SE

1. A compound which is of formula I,



(I)

wherein

R_1	is alkyl (1-4 C), halogen with an atomic number of 9 to 35 or amino optionally mono- or disubstituted by alkyl (1-4 C),
R_2 and R_3	independently of one another are hydrogen or alkyl (1-4 C) and
R_4	is hydrogen, hydroxy, alkyl (1-4 C), alkoxy (1-4 C) or halogen with an atomic number of 9 to 35,

in free base or acid addition salt form.

2. A compound of formula I according to claim 1 wherein R_1 is alkyl (1-4 C), R_2 and R_3 independently of one another are hydrogen or alkyl (1-4 C) and R_4 is hydrogen, alkyl (1-4 C) or halogen with an atomic number of 9 to 35, in free base or acid addition salt form.

3. A compound of formula I according to claim 1, wherein

- $R_1 = CH_3$, $R_2 = H$, $R_3 = H$, $R_4 = 6\text{-}CH_3$, or
- $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = H$, $R_4 = H$, or
- $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$, $R_4 = H$

and the imidazolylmethyl group in each compound is in position 2, or

- $R_1 = CH_3$, $R_2 = H$, $R_3 = H$, $R_4 = H$

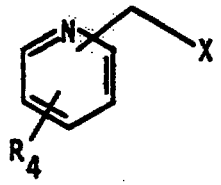
and the imidazolylmethyl group is in position 4,

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in free base form or in acid addition salt form.

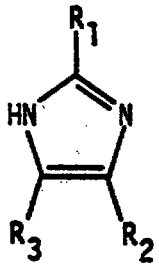
4. The [2-(2-methylimidazol-1-yl)methyl]pyridine, in free base or acid addition salt form.

5. A process for the production of compounds of formula I as defined in claim 1, and their acid addition salts, characterized by reacting compounds of formula II,



(II)

wherein R_4 is as defined in claim 1 and X is halogen, with compounds of formula III,



(III)

wherein R_1, R_2 and R_3 are as defined in claim 1,

and recovering the resulting compound of formula I in free base form or in acid addition salt form.

6. A compound of any one of claims 1 to 4, in free base form or in physiologically acceptable acid addition salt form, for use as a pharmaceutical.

7. A compound of any one of claims 1 to 4, in free base form or in physiologically acceptable acid addition salt form, for the treatment of senile dementia, Alzheimer's

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disease, Huntington's chorea, Morbus Parkinson, Steel-Richardson syndrome, tardive dyskinesias, hyperkinesia, acute confusion disorders, Down's syndrome, myasthenia gravis and Friedrich's ataxia.

8. A compound of any one of claims 1 to 4, in free base form or physiologically acceptable acid addition salt form, for use as antidepressant.

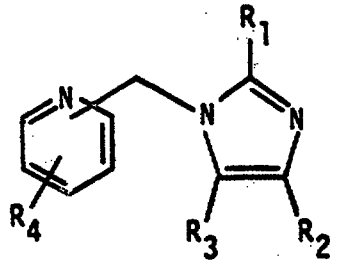
9. A pharmaceutical composition, containing a compound according to any one of claims 1 to 4, in free base form or physiologically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

10. The use of a compound of any one of claims 1 to 4, in free base form or in physiologically acceptable acid addition salt form, for the preparation of a pharmaceutical composition for the treatment of senile dementia, Alzheimer's disease, Huntington's chorea, Morbus Parkinson, Steel-Richardson syndrome, tardive dyskinesias, hyperkinesia, acute confusion disorders, Down's syndrome, myasthenia gravis, Friedrich's ataxia and for the treatment of depression.

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Abstract of the disclosure

Compounds of formula I,



(I)

wherein R_1 to R_4 possess the significances given in the description, may be used in the treatment of senile dementia, Alzheimer's disease and depression.

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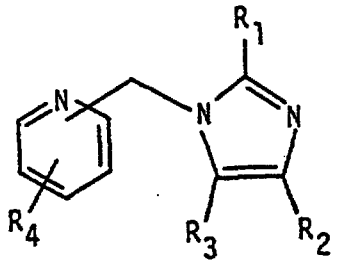
REPLACEMENT SHEETS SG
☑ Description : paged 1 to paged 6
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☐ Drawing(s) : paged ..... to paged .....
☑ Abstract : paged 10 to paged ...

DATE OF RECEIPT 9/9/96

IMIDAZOLYLMETHYL-PYRIDINES

The present invention relates to imidazolylmethyl-pyridines, their production and their use in therapeutic treatment.

More particularly the present invention provides compounds of formula I,



(I)

wherein

R_1 is alkyl (1-4 C), halogen with an atomic number of 9 to 35 or amino optionally mono- or disubstituted by alkyl (1-4 C),

R_2 and R_3 independently of one another are hydrogen or alkyl (1-4 C) and

R_4 is hydrogen, hydroxy, alkyl (1-4 C), alkoxy (1-4 C) or halogen with an atomic number of 9 to 35,

in free base or acid addition salt form, hereinafter referred to as new compounds.

Insofar as above-defined alkyl or alkoxy groups are present in the new compounds, these preferably have one or two carbon atoms and especially signify methyl or methoxy.

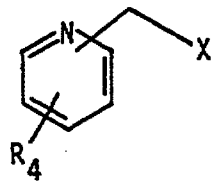
The imidazolylmethyl radical is preferably in position 2 of the pyridine.

R_1 is preferably methyl. R_2 and R_3 are preferably each hydrogen. R_4 is preferably hydrogen. The compound of Example 1 is preferred.

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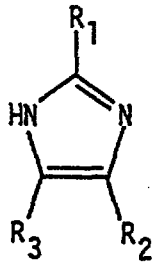
The invention particularly embraces a group of new compounds, wherein R_1 is alkyl (1-4 C), R_2 and R_3 independently of one another are hydrogen or alkyl (1-4 C) and R_4 is hydrogen, alkyl (1-4 C) or halogen with an atomic number of 9 to 35.

In accordance with the invention, the new compounds are obtained by reacting compounds of formula II,



(II)

wherein R_4 is defined as above, and X is halogen, with compounds of formula III,



(III)

wherein R_1, R_2 and R_3 are defined as above,

and recovering the resulting compounds of formula I in free base form or in acid addition salt form.

The reaction of the compounds of formula II with the compounds of formula III may take place in known manner, in a solvent which is inert under the reaction conditions, e.g. in dimethylformamide or a lower alcohol. In formula II, X is preferably chlorine.

Working up of the reaction mixtures obtained and purification of the compounds of formula I thus produced may take place in accordance with known methods.

The compounds of formula I may be present in free form or in the form of their acid

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09 SEP 1996

addition salts. Acid addition salts may be produced from the free bases in known manner, and vice versa.

The starting compounds of formulae II and III are known or may be produced in accordance with known processes, resp. analogously to known processes.

The compounds of formula I and their physiologically acceptable salts, hereinafter referred to as compounds according to the invention, exhibit pharmacological activity and may therefore be used as pharmaceuticals.

In the sleep/wake cycle of the freely moving as well as the long-term implanted rat [for the method, see J.-M. Vigouret et al., J. Pharmacol 10, 503 (1978)], the compounds according to the invention when administered at 1 to 100 mg/kg p.o. effect an increase in vigilance by prolonging the wake phases.

Moreover after administration of 1 to 100 mg/kg p.o. to rats with bilateral lesions of the Locus coeruleus and the Nucleus basalis Meynert, the compounds according to the invention improve significantly the cognitive performance as measured by the ability to avoid an electric shock in the shuttle box.

The method is similar to that described by V. Haroutunian et al. in Brain Research 507 (1990) 261 - 266. Male OFA rats (300 g) are anaesthetized with pentobarbital and the lesions are carried out in a stereotaxic apparatus with a radio frequency generator at 60 ° C during 10 seconds. 5 weeks after lesioning, behavioral testing is performed, using a shuttle box as described by A.R. Dravid, A.-L. Jaton and E.B. Van Deusen in Experimental Brain Research, Suppl. 13, p. 249 (1986).

In view of these activities the compounds according to the invention are useful for the treatment of senile dementia, Alzheimer's disease and further degenerative diseases such as Huntington's chorea, Morbus Parkinson, Steel-Richardson syndrome, tardive dyskinesias, hyperkinesia, acute confusion disorders, Down's syndrome, myasthenia gravis and

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09 SEP 1996

Friedrich's ataxia, furthermore as antidepressants.

An indicated daily dosage for this therapeutical activity is in the range from about 1 mg to 100 mg of the compound, administered, for example, in divided doses up to four times a day.

The compounds according to the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

The present invention also provides pharmaceutical compositions comprising a compound according to the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.25 mg to about 50 mg of a compound according to this invention.

The following examples illustrate the invention. The temperatures are given in degrees Celsius and are uncorrected.

REPLACEMENT SHEET
09 SEP 1996

EXAMPLE 1: [2-(2-methylimidazol-1-yl)methyl]pyridine

9.7 g (75 mM) of 2-(chloromethyl)pyridine and 42 g (512 mM) of 2-methyl-imidazole are suspended in 40 ml dimethylformamide, then stirred for 3 hours at 105°. The dimethylformamide is distilled off and the crystalline residue is diluted with ethyl acetate and a little hexane. Following filtration, the mother solution is concentrated by evaporation and the dimethylformamide distilled off, and then shaken out several times between water and methylene chloride. 10.3 g of the oily title compound are obtained.

9.3 g of the obtained base in ethanol are mixed with 12.7 g of fumaric acid. The resulting bis(base)-tris(hydrogen fumarate) crystallizes from ethanol/ethyl acetate and is recrystallized once from ethanol/ethyl acetate. It is uniform upon thin-layer chromatography and melts at 109 - 110°.

The following [2-(imidazol-1-yl)methyl]pyridines are produced analogously to example 1:

Example	R_1	R_2	R_3	R_4	M.p.
2	CH_3	H	H	6-CH_3	129 - 130° *
3	CH_3	CH_3	H	H	250 - 253° (decomp.)**
4	CH_3	H	CH_3	H	213 - 220° (decomp.)**

* fumarate

** dihydrochloride

as well as the following [4-(imidazol-1-yl)methyl]pyridine:

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Example	R_1	R_2	R_3	R_4	M.p.
5	CH_3	H	H	H	155 - 156° *

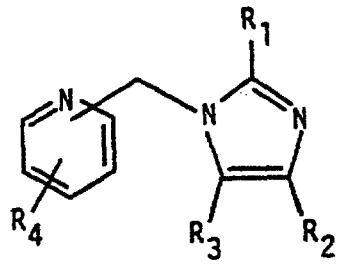
* fumarate

* C L M S *

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PATENT CLAIMS FOR THE CONTRACTING STATES:
AT, BE, CH, LI, DE, DK, FR, GB, IE, IT, LU, NL, PT, SE

1. A compound which is of formula I,



(I)

wherein

R_1 is alkyl (1-4 C), halogen with an atomic number of 9 to 35 or amino optionally mono- or disubstituted by alkyl (1-4 C),

R_2 and R_3 independently of one another are hydrogen or alkyl (1-4 C) and

R_4 is hydrogen, hydroxy, alkyl (1-4 C), alkoxy (1-4 C) or halogen with an atomic number of 9 to 35,

in free base or acid addition salt form.

2. A compound of formula I according to claim 1 wherein R_1 is alkyl (1-4 C), R_2 and R_3 independently of one another are hydrogen or alkyl (1-4 C) and R_4 is hydrogen, alkyl (1-4 C) or halogen with an atomic number of 9 to 35, in free base or acid addition salt form.

3. A compound of formula I according to claim 1, wherein

- $R_1 = CH_3$, $R_2 = H$, $R_3 = H$, $R_4 = 6\text{-}CH_3$, or
- $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = H$, $R_4 = H$, or
- $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$, $R_4 = H$

and the imidazolylmethyl group in each compound is in position 2, or

- $R_1 = CH_3$, $R_2 = H$, $R_3 = H$, $R_4 = H$

and the imidazolylmethyl group is in position 4,

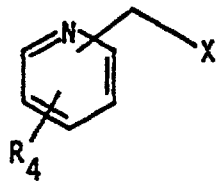
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in free base form or in acid addition salt form.

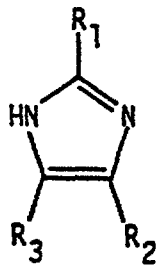
4. The [2-(2-methylimidazol-1-yl)methyl]pyridine, in free base or acid addition salt form.

5. A process for the production of compounds of formula I as defined in claim 1, and their acid addition salts, characterized by reacting compounds of formula II,



(II)

wherein R_4 is as defined in claim 1 and X is halogen, with compounds of formula III,



(III)

wherein R_1, R_2 and R_3 are as defined in claim 1,

and recovering the resulting compound of formula I in free base form or in acid addition salt form.

6. A compound of any one of claims 1 to 4, in free base form or in physiologically acceptable acid addition salt form, for use as a pharmaceutical.

7. A compound of any one of claims 1 to 4, in free base form or in physiologically acceptable acid addition salt form, for the treatment of senile dementia, Alzheimer's

* C L M S *

disease, Huntington's chorea, Morbus Parkinson, Steel-Richardson syndrome, tardive dyskinesias, hyperkinesia, acute confusion disorders, Down's syndrome, myasthenia gravis and Friedrich's ataxia.

8. A compound of any one of claims 1 to 4, in free base form or physiologically acceptable acid addition salt form, for use as antidepressant.

9. A pharmaceutical composition, containing a compound according to any one of claims 1 to 4, in free base form or physiologically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

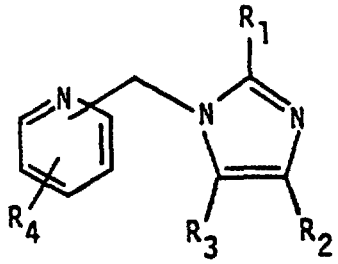
10. The use of a compound of any one of claims 1 to 4, in free base form or in physiologically acceptable acid addition salt form, for the preparation of a pharmaceutical composition for the treatment of senile dementia, Alzheimer's disease, Huntington's chorea, Morbus Parkinson, Steel-Richardson syndrome, tardive dyskinesias, hyperkinesia, acute confusion disorders, Down's syndrome, myasthenia gravis, Friedrich's ataxia and for the treatment of depression.

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IMIDAZOLYLMETHYL-PYRIDINES

Abstract of the disclosure

Compounds of formula I,



(I)

wherein R_1 to R_4 possess the significances given in the description, may be used in the treatment of senile dementia, Alzheimer's disease and depression.

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