3-substituted tetrahydropyridopyrimidinone derivatives, their preparation and use

The invention relates to 3-substituted tetrahydropyrido-pyrimidinone derivatives, their preparation and use for producing active ingredients for drugs.

Classical antidepressants and the newer selective serotonin reuptake inhibitors (SSRIs) develop their antidepressant effect inter alia by inhibiting active reuptake of the transmitter into the presynaptic nerve endings. Unfortunately, the antidepressant effect thereof does not have its onset until treatment has lasted at least 3 weeks, and, moreover, about 30% of patients are therapy-resistant.

Blockade of presynaptic serotonin autoreceptors increases, by abolishing negative coupling, the serotonin release and thus the current transmitter concentration in the synaptic cleft. This increase in the transmitter concentration is regarded as the principle of the antidepressant effect. This mechanism of action differs from previously known antidepressants which activate both the presynaptic and somatodendritic autoreceptors and therefore result in a delayed onset of action, only after desensitization of these autoreceptors. Direct autoreceptor blockade bypasses this effect.

The derivatives described in JP 08027149 and JP 04054181 are known.

According to current knowledge, the presynaptic serotonin autoreceptor is of the 5-HT_{1B} subtype (Fink et al., Arch. Pharmacol. 352 (1995), 451). Selective blockade thereof by 5-$HT_{1B/D}$ antagonists increases the serotonin release in the brain: G.W. Price et al., Behavioural Brain Research 73 (1996), 79-82; P.H. Hutson et al., Neuropharmacology Vol. 34, No. 4 (1995), 383-392.

However, surprisingly, the selective 5-HT_{1B} antagonist GR 127 935 reduces serotonin release in the cortex after systemic administration. One explanation might be stimulation of somatodendritic 5-HT_{1A} receptors in the raphe region by the released serotonin, which inhibits the firing rate of

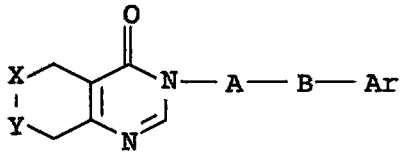
serotonergic neurons and thus serotonin release (M. Skingle et al., Neuropharmacology Vol. 34 No. 4 (1995), 377-382, 393-402).

One strategy for bypassing the autoinhibitory effects in serotonergic areas of origin thus aims at blockade of presynaptic 5-HT_{1B} receptors. This hypothesis is supported by the observation that the effect of paroxetine on serotonin release in the dorsal raphe nucleus of the rat is potentiated by the 5-HT_{1B} receptor antagonist GR 127 935 (Davidson and Stamford, Neuroscience Letts., 188 (1995), 41).

The second strategy includes blockade of both types of autoreceptors, namely the 5-HT_{1A} receptors, in order to intensify neuronal firing, and the 5-HT_{1B} receptors, in order to increase terminal serotonin release (Starkey and Skingle, Neuropharmacology 33 (3-4) (1994), 393).

5-$HT_{1B/D}$ antagonists, alone or coupled to a 5-HT_{1A} receptor antagonistic component, should therefore cause a greater increase in serotonin release in the brain and might therefore be associated with advantages in the therapy of depressions and related psychological disorders.

It has now been found that 3-substituted tetrahydropyrido-pyrimidinone derivatives of the formula I



(I),

where

one of the two radicals X and Y is CH_2 and the other is NR^1,

R^1 is hydrogen, (C_{1-6}) alkyl branched or unbranched, CO-(C_{1-4})-alkyl, CO_2tBu, CO-aryl and a phenylalkyl-C_1-C_4 radical which in turn may be substituted on the aromatic system by F, Cl, Br, I, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, hydroxyl, amino, cyano or nitro,

A is branched or unbranched (C_{1-10})-alkylene or straight-chain or branched (C_{2-10})-alkylene which comprises at least one group Z which is selected from O, S, NR^2, cyclopropyl, CHOH, a double or triple bond,

R^2 is hydrogen and C_1-C_4 alkyl,

B is 4-piperidine, 4-tetrahydro-1,2,3,6 pyridine, 4-piperazine or the corresponding cyclic compounds enlarged by one methylene group, with the linkage to A being via an N atom of B, and

Ar is phenyl which is unsubstituted or substituted by (C_{1-6}) alkyl branched or unbranched, O-(C_{1-6}) alkyl branched or unbranched, OH, F, Cl, Br, I, trifluoromethyl, NR^2_2, CO_2R^2, cyano or phenyl, or is tetralin, indan, fused aromatic systems such as naphthalene which is unsubstituted or substituted by (C_{1-4})-alkyl or O(C_{1-4})-alkyl, anthracene or 5- or 6-membered aromatic heterocycles having 1 or 2 heteroatoms which are selected, independently of one another, from O and N, which may be fused to other aromatic radicals,

and their salts with physiologically tolerated acids, have valuable pharmacological properties.

Particularly preferred compounds are those where

one of the two radicals X and Y is CH_2 and the other is NR^1,

R^1 is hydrogen, (C_{1-4})-alkyl branched or unbranched, CO-(C_{1-4})-alkyl, CO_2tBu, COPh or a phenylalkyl C_1-C_2 radical which in turn can be substituted on the aromatic system by F, Cl, Br, I, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, hydroxyl or cyano,

A is (C_{2-5}) alkylene branched or unbranched or (C_{2-5})-alkylene which comprises a group Z which is selected from CHOH, cyclopropyl, a double or a triple bond,

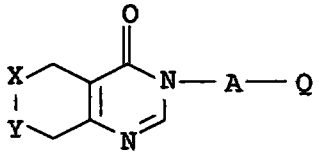
B is 4-piperidine, 4-tetrahydro-1,2,3,6 pyridine, 4-piperazine or homopiperazine, where the linkage to A takes place via an N atom of B, and

Ar is phenyl which is unsubstituted or substituted by (C_{1-6})-alkyl branched or unbranched, O-(C_{1-6})-alkyl branched or unbranched, F, Cl, Br, I, trifluoromethyl, CO_2R^2, NR^2_2, cyano or phenyl, or is tetralin, indan, fused aromatic systems such as naphthalene which is unsubstituted or substituted by (C_{1-4}) alkyl or O(C_{1-4}) alkyl, or 5- or 6-membered aromatic heterocycles having 1 or 2 nitrogen atoms, which may be fused to other aromatic radicals.

Particularly preferred compounds of the formula I are those listed in claim 3.

The compounds of the formula I may have one or more centers of asymmetry. The invention therefore includes not only the racemates but also the relevant enantiomers and diastereomers. The invention also includes the respective tautomeric forms.

The novel compounds of the formula I can be prepared by reacting a compound of the formula II

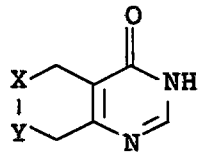


(II),

where A, X and Y have the abovementioned meanings, and Q is a group which can be eliminated (eg. Cl, Br, I, alkanesulfonyloxy or arylsulfonyloxy), with a compound of the formula III,

H-B-Ar (III),

where B and Ar have the abovementioned meanings, in a manner known per se, and converting the compound obtained in this way where appropriate into the addition salt with a physiologically tolerated acid. It is likewise possible to react a compound of the formula IV



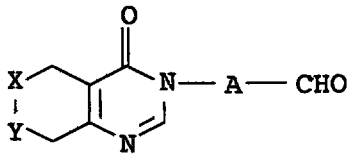
(IV)

with a compound of the formula V

Q-A-B-Ar (V)

in a manner known per se.

Another variant of the synthesis comprises linking a compound of the formula VI



(VI)

with a compound of the formula III by a reductive amination known per se.

Compounds of the formula III can be synthesized by

1. Linking compounds of the formula VII

$$W\text{-}B^1 \qquad (VII)$$

where B^1 is piperazine or homopiperazine and W is hydrogen or one of the usual amino protective groups (eg. Boc or Cbz), with a compound of the formula VIII

$$P\text{-}Ar \qquad (VIII),$$

where P is $B(OH)_2$, SnR_3, OTf, Br, Cl, or I, and R is C_1-C_4-alkyl, in a known manner; or

2. linking compounds of the formula IX

$$W\text{-}B^2\text{-}P^1 \qquad (IX),$$

where B^2 is 4-tetrahydro-1,2,3,6-pyridine and the corresponding cyclic compounds enlarged by one methylene group, and P^1 is Cl, Br, I, SnR_3, where R is C_1-C_4-alkyl, or OTf, with a compound of the formula X

P-Ar (X),

where W, P and Ar each have the abovementioned meanings, and the reactions take place by known processes as described, for example, in

S.L. Buchwald et al. *J. Am. Chem. Soc.* **1996**, *118*, 7215,
J.F. Hartwig et al. *Tetrahedron Lett.* **1995**, *36*, 3604 ,
J.K. Stille et al. *Angew. Chem.* **1986**, *98*, 504,
S.L. Buchwald et al. *Angew. Chem.* **1995**, *107*, 1456 or
J.F. Hartwig et al. *J. Am. Chem. Soc* **1996**, *118*, 7217 or
J.F. Hartwig et al. *J. Org. Chem.* **1997**, *62*, 1268,
S.L. Buchwald et al. *J. Org. Chem.* **1997**, *62*, 1264 and the literature cited therein or
S.L. Buchwald et al *J. Am. Chem. Soc* **1997**, *119*, 6054,
J.K. Stille, *Angew. Chem.* **1986**, *98*, 504 or
J.K.Stille et al. *J.Org. Chem.* **1990**, *55*, 3014,
M. Pereyre et al. "Tin in Organic Synthesis", Butterworth 1987; or

3. reducing compounds of the formula (XI)

$$W\text{-}B^2\text{-}Ar \qquad (XI),$$

where B^2 has the abovementioned meaning, to compounds of the formula XII

$$W\text{-}B^3\text{-}Ar \qquad (XII),$$

where B^3 is piperidines linked in the 1,4 positions, and the corresponding ring compounds enlarged by one methylene group; or

4. cyclizing compounds of the formula XIII

$$W\text{-}N\text{-}(C_2H_4Q)_2 \qquad (XIII),$$

where W and Q have the meanings described above, with a compound of the formula XIV

$$NH_2\text{-}Ar \qquad (XIV),$$

where Ar has the abovementioned meaning, to give compounds of the formula XV

$$W\text{-}B^1\text{-}Ar \qquad (XV).$$

The substances of the formulae III and V which are required as starting materials for synthesizing the novel compounds are known or can be synthesized by known processes (eg. *Organikum* Barth Dt. Verl. der Wiss. **1993** or A. R. Katritzky, C. W. Rees (ed.) *Comprehensive Heterocyclic Chemistry* Pergamon Press) from analogous precursors.

Further reaction of the compounds

$$H\text{-}B\text{-}Ar \qquad (III)$$

prepared as in 1. to 4., with subsequent elimination of any protective groups, to give compounds of the formula V takes place by linkage with compounds of the formula XVI

$$Q\text{-}A\text{-}Q' \qquad (XVI),$$

where Q and Q' are leaving groups, under conditions known per se.

The substances of the formula II, IV, VI and of the formula P-Ar, NH_2-Ar, W-B^1 and W-B^2-P^1 required as starting materials for synthesizing the novel compounds are known or can be synthesized from similar precursors by methods described in the literature (eg. B. Dumaitre, N. Dodic *J. Med. Chem.* **1996**, *39*, 1635 or A. Yokoo et al. *Bull. Chem. Soc. Jpn.* **1956**, *29*, 631 or L. Börjeson et al. *Acta Chem. Chem.* [sic] **1991**, *45*, 621 or *Organikum* Barth Dt. Verl. der Wiss. **1993** or A. R. Katritzky, C. W. Rees (ed.) *Comprehensive Heterocyclic Chemistry* Pergamon Press

or *The Chemistry of Heterocyclic Compounds* J. Wiley & Sons Inc. NY and the literature cited in each of these).

The reactions described above generally take place in an inert organic solvent, eg. dimethylformamide, acetonitrile, dichloromethane, dimethyl sulfoxide, dimethoxyethane, toluene, ethyl acetate, xylene, a ketone such as acetone or methyl ethyl ketone, an alcohol such as ethanol or n-butanol, or a cyclic saturated ether, eg. tetrahydrofuran or dioxane.

The reactions generally take place at from 20°C to the boiling point of the solvent and are generally complete within 1 to 20 hours. If required, they take place in the presence of an acid-binding agent such as sodium or potassium carbonate, sodium methoxide, sodium ethoxide, sodium hydride, organometallic compounds (butyllithium, alkylmagnesium compounds), potassium t-butoxide, pyridine or triethylamine.

Where appropriate, the reactions take place with use of a catalyst such as transition metals and their complexes, eg. Pd-C, $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd(P(oTol)_3)_4$, $Pd_2(dba)_3$ or $Ni(COD)_2$.

The crude product is isolated in a conventional way, for example by filtration, removal of the solvent by distillation or extraction from the reaction mixture.

The novel compounds of the formula I can be purified either by recrystallization from conventional organic solvent or by column chromatography.

Besides the 3-substituted tetrahydropyridopyrimidinone derivatives, the invention also comprises the acid addition salts of the compounds of the formula I with physiologically tolerated acids. Examples of suitable physiologically tolerated organic and inorganic acids are hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, oxalic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, adipic acid or benzoic acid. Further acids which can be used are described in "Fortschritte der Arzneimittelforschung", Volume 10, pages 224 et seq., Birkhäuser Verlag, Basle and Stuttgart, 1966.

The acid addition salts are prepared in a conventional way by mixing the free base with the appropriate acid, where appropriate in solution in an organic solvent, eg. a lower alcohol such as methanol, ethanol or propanol, an ether such as methyl t-butyl

ether, a ketone such as acetone or methyl ethyl ketone, or an ester such as ethyl acetate.

The invention accordingly also relates to a therapeutic composition which comprises a compound of the formula I or its pharmacologically suitable acid addition salt as active ingredient in addition to conventional carriers and diluents, and to the use of the novel compounds for controlling diseases.

The novel compounds can be administered orally or parenterally, intravenously or intramuscularly, in a conventional way.

The dosage depends on the age, condition and weight of the patient and on the mode of administration. As a rule, the daily dose of active ingredient is about 1-100 mg/kg of body weight on oral administration and 0.1-10 mg/kg of body weight on parenteral administration.

The novel compounds can be used in conventional solid or liquid pharmaceutical forms, eg. as uncoated or (film)coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. The active ingredients can for this purpose be processed with conventional pharmaceutical auxiliaries such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or propellant gases (cf. H. Sucker et. al: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1978). The administration forms obtained in this way normally contain from 1 to 99% by weight of active ingredient.

The novel compounds have a high affinity for 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1A} serotonin receptors. Approximately the same degree of affinity, at least of the same order of magnitude, is shown for these receptors. In addition, some of the novel compounds show good inhibition of serotonin reuptake, a principle which is implemented in most antidepressants.

These compounds are suitable as drugs for treating pathological states in which the serotonin concentration is reduced and in which it is wished for therapeutic purposes to block specifically the activity of the presynaptic 5-HT_{1B}, 5-HT_{1A}, 5-HT_{1D} receptors without having a great effect on other receptors. An example of such a pathological state is depression.

The compounds of the present invention can also be of use for treating mood disturbances with a central nervous causation, such as seasonal affective disorders and dysthymia. These also include anxiety states such as generalized anxiety, panic attacks, sociophobia, obsessive-compulsive neuroses and post-traumatic stress symptoms, memory disturbances including dementia, amnesias and age-related loss of memory, and psychogenic eating disorders such as anorexia nervosa and bulimia nervosa.

The novel compounds can additionally be used to treat endocrine disorders such as hyperprolactinemia and to treat vasospasms (especially of the cerebral vessels), hypertension and gastrointestinal disorders associated with disturbances of motility and secretion. Another area of use comprises sexual disorders.

The following examples serve to illustrate the invention without restricting it.

Example 1:

3-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-3,5,7,8-tetrahydro-4-oxo-6-benzylpyrido[4,3-d]pyrimidine

Preparation of the starting materials

a) 3,5,7,8-Tetrahydro-4-oxo-6-benzylpyrido[4,3-d]pyrimidine

4.7 g of sodium were reacted in small portions with 250 ml of ethanol and then, at 5-10°C, a suspension of 14.2 g (0.05 mol) of methyl N-benzyl-4-piperidone-3-carboxylate in ethanol was added dropwise. After stirring for 30 minutes, 6 g (0.075 mol) of formamidine hydrochloride were slowly added and the reaction mixture was refluxed for 10 h. The solvent was removed under reduced pressure, and the residue was adjusted in 100 ml of water to pH = 6.5 - 7 with 2N hydrochloric acid so that the product precipitated. The crystals were filtered off with suction and dried in a vacuum oven, and 8 g (66%) were isolated in this way. Melting point 88°C.

3,5,7,8-Tetrahydro-4-oxo-6-benzylpyrido[3,4-d]pyrimidine (melting point 199°C) and 1,1-dimethyl [sic] 3,5,7,8-tetrahydro-4-oxopyrido[4,3-d]pyrimidine-6-carboxylate (melting point 160°C) were obtained in a similar way.

b) 1-(2-methoxyphenyl)-4-(2-chloroeth-1-yl)piperazine

19.2 g (0.1 mol) of o-methoxyphenylpiperazine and 13.8 g (0.1 mol) of potassium carbonate were dissolved in 200 ml of DMF at room temperature and, after 30 min, 30 ml (0.36 mol) of 1-bromo-2-chloroethane were added. The mixture was stirred at room temperature for 2 h. Pouring into ice-water was followed by extraction with methyl tert-butyl ether, and the organic phases were washed with water, dried with sodium sulfate and then concentrated. 30% strength isopropanolic HCl solution was added to the solution of the residue in ethyl acetate to precipitate the hydrochloride, which was filtered off with suction and dried in a vacuum drying oven at 40°C. 17 g (67%) of substance were obtained. Melting point 200°C.

1-(2-Methoxyphenyl)-4-(3-chloroprop-1-yl)piperazine (melting point 217°C, hydrochloride), 1-(3,4-dimethylphenyl)-4-(2-chloroeth-1-yl)piperazine (melting point 260°C, hydrochloride), 1-(2-pyrimidyl)-4-(2-chloroeth-1-yl)piperazine (melting point 270°C, hydrochloride), 1-(1-naphthyl)-4-(3-chloroprop-1-yl)- piperazine (melting point 217°C, hydrochloride) were obtained in a similar way.

Two examples of syntheses of the piperazines are indicated below.

1-(5-Tetralinyl)piperazine

14,7 g (0.1 mol) of 5-aminotetralin and 18 g (0.11 mol) of bis(β-chloroethyl)amine hydrochloride in 300 ml of n-butanol were refluxed for 48 h and cooled, 5.4 g of sodium carbonate were added and the mixture was refluxed for a further 20 h. The precipitate which resulted on cooling was filtered off with suction and taken up in water, and 2N sodium hydroxide solution was added. The aqueous phase was extracted with ethyl acetate, and washing with water was followed by drying over sodium sulfate and concentration under reduced pressure. 10.7 g (50%) of the product were isolated as an oil in this way.

4-(1-piperazinyl)isoquinoline

4.51 g (21.7 mmol) of 4-bromoisoquinoline, 4.65 g (25.0 mmol) of t-butyl piperazine-N-carboxylate, 0.1 g (0.11 mmol) of tris(dibenzylideneacetone) dipalladium, 0.11 g (0.18 mmol) of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and 2.92 g (30.4 mmol) of sodium t-butoxide were mixed in 50 ml of toluene and stirred at 75°C for 2 h. The reaction mixture was added to ice/sodium chloride and extracted with ethyl acetate, the organic phase was dried over sodium sulfate, and the solvent was removed in a rotary evaporator. The product crystallized out and was filtered off with suction and washed with pentane. 5.5 g (81%) of the Boc-protected piperazine (melting point 111°C) were obtained. 5.2 g (16.6 mmol) of this substance were taken up in 17 ml of dichloromethane and, at 0°C, 17 ml (0.22 mol) of trifluoroacetic acid were slowly added. The mixture was stirred at 0°C for 4 h, poured into ice-water and extracted with dichloromethane. The aqueous phase was filtered, made alkaline and extracted with dichloromethane. Drying over sodium sulfate and substantial removal of the solvent were followed by dilution with diethyl ether and precipitation of the hydrochloride with ethereal hydrochloric acid. 3.2 g (67%) of the product were obtained.(Melting point 293°C).

The following compounds were prepared by processes similar to the two described: 1-(1-naphthyl)azepan (85°C, hydrochloride), 1-(1-naphthylmethyl)piperazine (oil), 4-(1-piperazinyl)indan (oil), 1-(1-naphthyl)piperazine (82°C), 4-chloro-1-(1-piperazinyl)phthalazine (205°C, decomposition) and 4-(1-piperazinyl)quinazoline (320°C, hydrochloride). Other derivatives were commercially available.

Preparation of the final product

2.9 g (10 mmol) of chloroethylpiperazine [b)] and 2.8 g (20 mmol) of potassium carbonate were added to a solution of 2.4 g (10 mmol) of tetrahydropyridopyrimidine [a)] in 40 ml of DMF. After reaction at 90°C for 2 hours, the mixture was poured onto ice-water and extracted with ethyl acetate. The organic phase was washed with saturated brine and dried over sodium sulfate, and the solvent was removed under reduced pressure. The remaining oil was taken up in acetone, and the hydrochloride was precipitated with isopropanol/HCl. 4 g (75%) of the product were obtained (melting point 205°C).

NMR: $CDCl_3$ δ 8.0 (s, 1H), 7.4 - 7.2 (m, 5H), 7.1 - 6.8 (m, 4H), 4.0 (t, 2H), 3.8 (s, 3H), 3.7 (s, 2H), 3.5 (s, 2H), 3.1 (br. s, 4H), 2.8 - 2.6 (m, 10H) ppm.

The following compounds were obtained in a similar way:

Example 2:

3-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-3,5,7,8-tetrahydro-4-oxo-6-benzylpyrido[3,4-d]pyrimidine (melting point 181°C, hydrochloride).

Example 3:

3-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-3,5,7,8-tetrahydro-4-oxo-6-benzylpyrido[4,3-d]pyrimidine (melting point 198°C, hydrochloride).

Example 4:

3-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-3,5,7,8-tetrahydro-4-oxo-6-benzylpyrido[3,4-d]pyrimidine (melting point 190°C, hydrochloride).

Example 5:

3-[3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-hydroxypropyl]-3,5,7,8-tetrahydro-4-oxo-6-benzylpyrido[4,3-d]pyrimidine.

Example 6:

1,1-dimethyl [sic] 3-[2-[4-(1-naphthyl)-1-piperazinyl]ethyl]-3,5,7,8-tetrahydro-4-oxo-pyrido[4,3-d]pyrimidine-6-carboxylate (melting point 170°C, hydrochloride).

Example 7:

3-[2-[4-(4-isoquinolinyl)-1-piperazinyl]ethyl]-3,5,7,8-tetrahydro-4-oxo-6-benzylpyrido[4,3-d]pyrimidine (melting point 268°C, hydrochloride).

Example 8:

3-[2-[4-(1-naphthyl)-1-piperazinyl]ethyl]-3,5,6,7,8-pentahydro-4-oxopyrido[4,3-d]pyrimidine (melting point 272°C, hydrochloride).

Example 9:

3-[2-[4-(4-quinazolinyl)-1-piperazinyl]ethyl]-3,5,7,8-tetrahydro-4-oxo-6-benzylpyrido[4,3-d]pyrimidine (melting point 258°C, hydrochloride).

Example 10:

3-[2-[4-(1-naphthyl)-1-piperazinyl]ethyl]-3,5,7,8-tetrahydro-4-oxo-6-benzylpyrido[4,3-d]pyrimidine (melting point 227°C, hydrochloride).

Example 11:

3-[2-[4-(1-naphthyl)-1,2,3,6-tetrahydro-1-pyridinyl]eth-1-yl]-3,5,7,8-tetrahydro-4-oxo-6-benzyl-pyrido[4,3-d]pyrimidine (melting point 216°C, hydrochloride).

Synthesis of the starting materials

a) N-Boc-4-(trifluoromethanesulfonyloxy)tetrahydro-1,2,3,6-pyridine

A solution of 13.2 g (0.13 mol) of diisopropylamine in 200 ml of THF was deprotonated at -78°C with 100 mol of nBuLi (1.6M in hexane) and, after 30 minutes at this temperature, 20.0 g (0.1 mol) of N-Boc-piperidone dissolved in 50 ml of THF were added dropwise. After a further 3 hours at -78°C, a solution of 39.3 g (0.11 mol) of N,N,-bistrifluoromethanesulfonyl-aniline in 50 ml of THF were added, and the mixture was allowed to reach room temperature overnight. For workup, water was added, the mixture was extracted with ether, the organic phases were washed with $NaHCO_3$ solution and water and dried over sodium sulfate, and the solvent was evaporated off. The crude product was purified by flash chromatography (silica gel, mobile phase heptane/ethyl acetate = 3/1).

Yield: 20.2 g (60% of theory)

1H-NMR:(270 MHz,$CDCl_3$)δ= 1.4 (s, 9H); 2.4(m, 2H); 3.6 (t, 2H); 4.1 (m, 2H); 5.8 (m, 1H)ppm

b) N-Boc-4-(1-naphthyl)tetrahydro-1,2,3,6-pyridine

22 ml of 2M sodium carbonate solution, 7.63 g (44.4 mmol) of naphthyl-1-boronic acid, 4.13 g (97.6 mmol) of lithium chloride, 0.85 g (4.44 mmol) of copper(I) iodide and 2.1 g (1.77 mmol) of tetrakistriphenylpalladium [sic] were successively added to 14.7 g (44.4 mmol) of the compound described above, dissolved in 115 ml of dimethoxyethane, and the mixture was boiled for 4 h. For workup, aqueous ammonia solution was added, extractive workup was carried out with water and ethyl acetate and, after drying over sodium sulfate and evaporation of the solvent, the residue was purified by flash chromatography (silica gel, mobile phase heptane/ethyl acetate = 4/1).

Yield: 8.2 g (57% of theory)

1H-NMR (270 MHz, $CDCl_3$): δ= 1.4 (s, 9H); 2.5 (m, 2H); 3.7(t, 2H); 4.1 (m, 2H); 5.8 (m, 1H); 7.2-7.5(m, 3H); 7.3-8.0 (m, 3H) ppm.

c) 4-(1-naphthyl)tetrahydro-1,2,3,6-pyridine

7.84 g (25.3 mmol) of N-Boc-4-(1-naphthyl)tetrahydro-1,2,3,6-pyridine were stirred with 200 ml of ethereal hydrochloric acid at room temperature overnight, and the precipitated product was filtered off and dried.

Yield: 5.5 g (88% of theory).

d) Preparation of the final compound

0.61 g (2 mmol) of 3-(2-chloroeth-1-yl)-3,5,7,8-tetrahydro-4-oxo-6-benzylpyrido[4,3-d]pyrimidine and 2 ml (17 mmol) of triethylamine were added to 0.51 g (2 mmol) of 4-(1-naphthyl)tetrahydro-1,2,3,6-pyridine dissolved in 30 ml of dry DMF, and the mixture was stirred at 120°C for 5 h. The organic phase was diluted with ether, washed with water and dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting crude product was purified by

chromatography to afford, after precipitation of the salt with ethereal hydrochloric acid solution, a white solid.

Yield: 0.2 g (20% of theory)

Melting point: 237°C.

Example 12

3-[2-[4-(1-naphthyl)-1-piperidinyl]eth-1-yl]-3,5,7,8-tetrahydro-4-oxo-6-benzylpyrido[4,3-d]pyrimidine

4-(1-naphthyl)piperidine

3.7 g (15.3 mmol) of 4-(1-naphthyl)tetrahydro-1,2,3,6-pyridine were dissolved in methanol and, after addition of 0.8 g of palladium on carbon, hydrogenated with hydrogen at room temperature for 48 h. The catalyst was filtered off, and the solvent was evaporated off.

Yield: 1.8 g (56% of theory)

1H-NMR (270 MHz, $CDCl_3$)δ = 1.6-1.8 (m, 2H); 2.0 (m, 2H); 2.9 (dt, 2H); 3.3 (d, 2H); 3.5 (tt, 1H); 7.4-7.6 (m, 4H); 7.7 (d, 1H); 7.9 (d, 1H); 8.1 (d, 1H) ppm.

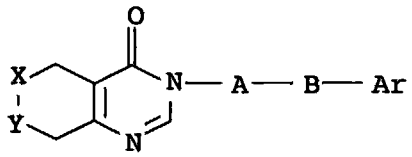
Preparation of the final compound

0.61 g (2 mmol) of 3-(2-chloroeth-1-yl)-3,5,7,8-tetrahydro-4-oxo-6-benzylpyrido[4,3-d]pyrimidine and 2 ml (17 mmol) of triethylamine were added to 0.42 g (2 mmol) of 4-(1-naphthyl)piperidine dissolved in 30 ml of dry DMF, and the mixture was stirred at 120°C for 5 h. The organic phase was diluted with ether, washed with water and dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting crude product was purified by chromatography to afford, after precipitation of the salt with ethereal hydrochloric acid solution, a white solid.

Yield: 0.24 g (27% of theory)

1H-NMR (270 MHz, $CDCl_3$)δ = 8.3 (s, 1H), 8.0 (d,1H), 7.8 (d, 1H), 7.7 (t, 1H), 7.5 - 7.2 (m, 9H), 4.5 (s, 2H), 4.0 (s, 2H), 3.7 - 2.3 (m, 15H), 2.1 (d, 2H) ppm.

Further preferred novel compounds of the formula I are listed in the following table.



No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
13.	NR^1	CH_2	H	C_2		4-piperazine	Ph	
14.	NR^1	CH_2	H	C_2		4-piperazine	2-OH-Ph	
15.	NR^1	CH_2	H	C_2		4-piperazine	2-OMe-Ph	
16.	NR^1	CH_2	H	C_2		4-piperazine	2-Me-Ph	
17.	NR^1	CH_2	H	C_2		4-piperazine	2-CN-Ph	
18.	NR^1	CH_2	H	C_2		4-piperazine	2-Cl-Ph	
19.	NR^1	CH_2	H	C_2	Me	4-piperazine	$3\text{-}NR^2{}_2\text{-Ph}$	
20.	NR^1	CH_2	H	C_2	Me	4-piperazine	$3\text{-}CO_2R^2\text{-Ph}$	
21.	NR^1	CH_2	H	C_2		4-piperazine	$3\text{-}CF_3\text{-Ph}$	
22.	NR^1	CH_2	H	C_2		4-piperazine	$3\text{-}NO_2\text{-Ph}$	
23.	NR^1	CH_2	H	C_2		4-piperazine	3-F-Ph	
24.	NR^1	CH_2	H	C_2		4-piperazine	$4\text{-}iC_3\text{-Ph}$	
25.	NR^1	CH_2	H	C_2		4-piperazine	4-I-Ph	
26.	NR^1	CH_2	H	C_2		4-piperazine	4-Br-Ph	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
27.	NR^1	CH_2	H	C_2		4-piperazine	4-O(n-C_4)-Ph	
28.	NR^1	CH_2	H	C_2		4-piperazine	4-t-Bn-Ph	
29.	NR^1	CH_2	H	C_2	H	4-piperazine	4-CO_2R^2-Ph	
30.	NR^1	CH_2	H	C_2	n-C_3	4-piperazine	4-NR^2_2-Ph	
31.	NR^1	CH_2	H	C_2		4-piperazine	3-Me,4-Me-Ph	
32.	NR^1	CH_2	H	C_2		4-piperazine	2-Cl,4-NO_2-Ph	
33.	NR^1	CH_2	H	C_2		4-piperazine	3-tBu,5-CF_3-Ph	
34.	NR^1	CH_2	H	C_2		4-piperazine	2-OMe,5-Ph-Ph	
35.	NR^1	CH_2	H	C_2		4-piperazine	2-OMe,4-Cl,5-Me-Ph	
36.	NR^1	CH_2	H	C_2		4-piperazine	5-tetralin	
37.	NR^1	CH_2	H	C_2		4-piperazine	4-indan	
38.	NR^1	CH_2	H	C_2		4-piperazine	1-naphthalene	
39.	NR^1	CH_2	H	C_2		4-piperazine	2-OMe-1-naphthalene	
40.	NR^1	CH_2	H	C_2		4-piperazine	2-Me-1-naphthalene	
41.	NR^1	CH_2	H	C_2		4-piperazine	8-OMe-1-naphthalene	
42.	NR^1	CH_2	H	C_2		4-piperazine	3-indolylnaphthalene	
43.	NR^1	CH_2	H	C_2		4-piperazine	2-quinazoline	
44.	NR^1	CH_2	H	C_2		4-piperazine	4-quinazoline	
45.	NR^1	CH_2	H	C_2		4-piperazine	2-quinoxaline	
46.	NR^1	CH_2	H	C_2		4-piperazine	1-phthalazine	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
47.	NR^1	CH_2	H	C_2		4-piperazine	4-quinoline	
48.	NR^1	CH_2	H	C_2		4-piperazine	1-isoquinoline	
49.	NR^1	CH_2	H	C_2		4-piperazine	4-isoquinoline	
50.	NR^1	CH_2	H	C_2		4-piperazine	7-benzofuran	
51.	NR^1	CH_2	H	C_2		4-piperazine	2-pyrimidine	
52.	NR^1	CH_2	H	C_2		4-piperazine	2-tBu,4-CF_3-6-pyrimidine	
53.	NR^1	CH_2	H	C_2		4-piperazine	2-pyridine	
54.	NR^1	CH_2	H	C_2		4-piperazine	2-Ph-4-quinazoline	
55.	NR^1	CH_2	H	C_2		4-piperazine	5-chroman	
56.	NR^1	CH_2	H	C_2		4-piperazine	3-isoxazole	
57.	NR^1	CH_2	H	C_2		4-piperazine	7-OMe-1-naphthalene	
58.	NR^1	CH_2	H	C_2		4-piperazine	1-tetralin	
59.	NR^1	CH_2	H	C_2		4-piperazine	2-Et-naphthalene	
60.	NR^1	CH_2	H	C_2		4-piperazine	2-quinoline	
61.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	Ph	
62.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-OH-Ph	
63.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-OMe-Ph	
64.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-Me-Ph	
65.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-CN-Ph	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
66.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-Cl-Ph	
67.	NR^1	CH_2	CH_2-Ph	C_2	Me	4-piperazine	3-NR^2_2-Ph	
68.	NR^1	CH_2	CH_2-Ph	C_2	Me	4-piperazine	3-CO_2R^2-Ph	
69.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	3-CF_3-Ph	
70.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	3-NO_2-Ph	
71.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	3-F-Ph	
72.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	4-iC_3-Ph	
73.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	4-I-Ph	
74.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	4-Br-Ph	
75.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	4-O(n-C_4)-Ph	
76.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	4-tBu-Ph	
77.	NR^1	CH_2	CH_2-Ph	C_2	H	4-piperazine	4-CO_2R^2-Ph	
78.	NR^1	CH_2	CH_2-Ph	C_2	n-C_3	4-piperazine	4-NR^2_2-Ph	
79.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	3-Me,4-Me-Ph	
80.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-Cl,4-NO_2-Ph	
81.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	3-tBu,5-CF_3-Ph	
82.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-OMe,5-Ph-Ph	
83.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-OMe,4-Cl,5-MePh	
84.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	5-tetralin	
85.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	4-indan	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
86.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	1-naphthalene	
87.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-OMe-1-naphthalene	
88.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-Me-1-naphthalene	
89.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	8-OMe-1-naphthalene	
90.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	3-indole	
91.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-quinazoline	
92.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	4-quinazoline	
93.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-quinoxaline	
94.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	1-phthalazine	
95.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	4-quinoline	
96.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	1-isoquinoline	
97.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	4-isoquinoline	
98.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	7-benzofuran	
99.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-pyrimidine	
100.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-tBu,4-CF_3-6-pyrimidine	
101.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-pyridine	
102.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-Ph-4-quinazoline	
103.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	5-chroman	
104.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	3-isoxazole	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
105.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	7-OMe-1-naphthalene	
106.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	1-tetralin	
107.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-Et-naphthalene	
108.	NR^1	CH_2	CH_2-Ph	C_2		4-piperazine	2-quinoline	
109.	NR^1	CH_2	Me	C_2		4-piperazine	Ph	
110.	NR^1	CH_2	Me	C_2		4-piperazine	2-OH-Ph	
111.	NR^1	CH_2	Me	C_2		4-piperazine	2-OMe-Ph	
112.	NR^1	CH_2	Me	C_2		4-piperazine	2-Me-Ph	
113.	NR^1	CH_2	Me	C_2		4-piperazine	2-CN-Ph	
114.	NR^1	CH_2	Me	C_2		4-piperazine	2-Cl-Ph	
115.	NR^1	CH_2	Me	C_2	Me	4-piperazine	3-NR^2_2-Ph	
116.	NR^1	CH_2	Me	C_2	Me	4-piperazine	3-CO_2R^2-Ph	
117.	NR^1	CH_2	Me	C_2		4-piperazine	3-CF_3-Ph	
118.	NR^1	CH_2	Me	C_2		4-piperazine	3-NO_2-Ph	
119.	NR^1	CH_2	Me	C_2		4-piperazine	3-F-Ph	
120.	NR^1	CH_2	Me	C_2		4-piperazine	4-iC_3-Ph	
121.	NR^1	CH_2	Me	C_2		4-piperazine	4-I-Ph	
122.	NR^1	CH_2	Me	C_2		4-piperazine	4-Br-Ph	
123.	NR^1	CH_2	Me	C_2		4-piperazine	4-O(n-C_4)-Ph	
124.	NR^1	CH_2	Me	C_2		4-piperazine	4-tBu-Ph	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
125.	NR^1	CH_2	Me	C_2	H	4-piperazine	$4-CO_2R^2-Ph$	
126.	NR^1	CH_2	Me	C_2	$n-C_3$	4-piperazine	$4-NR^2_2-Ph$	
127.	NR^1	CH_2	Me	C_2		4-piperazine	3-Me,4-Me-Ph	
128.	NR^1	CH_2	Me	C_2		4-piperazine	$2-Cl,4-NO_2-Ph$	
129.	NR^1	CH_2	Me	C_2		4-piperazine	$3-tBn,5-CF_3-Ph$	
130.	NR^1	CH_2	Me	C_2		4-piperazine	2-OMe,5-Ph-Ph	
131.	NR^1	CH_2	Me	C_2		4-piperazine	2-OMe,4-Cl,5-MePh	
132.	NR^1	CH_2	Me	C_2		4-piperazine	5-tetralin	
133.	NR^1	CH_2	Me	C_2		4-piperazine	4-indan	
134.	NR^1	CH_2	Me	C_2		4-piperazine	1-naphthalene	
135.	NR^1	CH_2	Me	C_2		4-piperazine	2-OMe-1-naphthalene	
136.	NR^1	CH_2	Me	C_2		4-piperazine	2-Me-1-naphthalene	
137.	NR^1	CH_2	Me	C_2		4-piperazine	8-OMe-1-naphthalene	
138.	NR^1	CH_2	Me	C_2		4-piperazine	3-indole	
139.	NR^1	CH_2	Me	C_2		4-piperazine	2-quinazoline	
140.	NR^1	CH_2	Me	C_2		4-piperazine	4-quinazoline	
141.	NR^1	CH_2	Me	C_2		4-piperazine	2-quinoxaline	
142.	NR^1	CH_2	Me	C_2		4-piperazine	1-phthalazine	
143.	NR^1	CH_2	Me	C_2		4-piperazine	4-quinoline	
144.	NR^1	CH_2	Me	C_2		4-piperazine	1-isoquinoline	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
145.	NR^1	CH_2	Me	C_2		4-piperazine	4-isoquinoline	
146.	NR^1	CH_2	Me	C_2		4-piperazine	7-benzofuran	
147.	NR^1	CH_2	Me	C_2		4-piperazine	2-pyrimidine	
148.	NR^1	CH_2	Me	C_2		4-piperazine	2-tBu,4-CF_3-6-pyrimidine	
149.	NR^1	CH_2	Me	C_2		4-piperazine	2-pyridine	
150.	NR^1	CH_2	Me	C_2		4-piperazine	2-Ph-4-quinazoline	
151.	NR^1	CH_2	Me	C_2		4-piperazine	5-chroman	
152.	NR^1	CH_2	Me	C_2		4-piperazine	3-isoxazole	
153.	NR^1	CH_2	Me	C_2		4-piperazine	7-OMe-1-naphthalene	
154.	NR^1	CH_2	Me	C_2		4-piperazine	1-tetralin	
155.	NR^1	CH_2	Me	C_2		4-piperazine	2-Et-naphthalene	
156.	NR^1	CH_2	Me	C_2		4-piperazine	2-quinoline	
157.	NR^1	CH_2	Boc	C_2		4-piperazine	Ph	
158.	NR^1	CH_2	Boc	C_2		4-piperazine	2-OMe-Ph	
159.	NR^1	CH_2	Boc	C_2		4-piperazine	2-Me-Ph	
160.	NR^1	CH_2	Boc	C_2		4-piperazine	2-Cl-Ph	
161.	NR^1	CH_2	Boc	C_2		4-piperazine	3-CN-Ph	
162.	NR^1	CH_2	Boc	C_2		4-piperazine	4-F-Ph	
163.	NR^1	CH_2	Boc	C_2		4-piperazine	3-tBu,5-CF_3-Ph	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
164.	NR^1	CH_2	Boc	C_2		4-piperazine	5-tetralin	
165.	NR^1	CH_2	Boc	C_2		4-piperazine	4-indan	
166.	NR^1	CH_2	Boc	C_2		4-piperazine	1-naphthalene	
167.	NR^1	CH_2	Boc	C_2		4-piperazine	2-OMe-naphthalene	
168.	NR^1	CH_2	Boc	C_2		4-piperazine	2-Me-naphthalene	
169.	NR^1	CH_2	Boc	C_2		4-piperazine	8-OMe-naphthalene	
170.	NR^1	CH_2	Boc	C_2		4-piperazine	4-quinazoline	
171.	NR^1	CH_2	Boc	C_2		4-piperazine	2-quinazoline	
172.	NR^1	CH_2	Boc	C_2		4-piperazine	1-phthalazine	
173.	NR^1	CH_2	Boc	C_2		4-piperazine	4-quinoline	
174.	NR^1	CH_2	Boc	C_2		4-piperazine	4-isoquinoline	
175.	NR^1	CH_2	Boc	C_2		4-piperazine	2-pyrimidine	
176.	NR^1	CH_2	Boc	C_2		4-piperazine	2-tBu,4-CF_3-6-pyrimidine	
177.	NR^1	CH_2	Boc	C_2		4-piperazine	2-pyridinyl	
178.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	Ph	
179.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	2-OMe-Ph	
180.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	2-Me-Ph	
181.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	2-Cl-Ph	
182.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	3-CN-Ph	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
183.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	4-F-Ph	
184.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	3-tBu,5-CF_3-Ph	
185.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	5-tetralin	
186.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	4-indan	
187.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	1-naphthalene	
188.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	2-OMe-naphthalene	
189.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	2-Me-1-naphthalene	
190.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	8-OMe-1-naphthalene	
191.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	4-quinazoline	
192.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	2-quinazoline	
193.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	1-phthalazine	
194.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	4-quinoline	
195.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	4-isoquinoline	
196.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	2-pyrimidine	
197.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	2-tBu,4-CF_3-6-pyrimidine	
198.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperazine	2-pyridine	
199.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	Ph	
200.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	2-OMe-Ph	
201.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	2-Me-Ph	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
202.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	2-Cl-Ph	
203.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	3-CN-Ph	
204.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	4-F-Ph	
205.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	3-tBu, 5-CF_3-Ph	
206.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	5-tetralin	
207.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	4-indan	
208.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	1-naphthalene	
209.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	2-OMe-1-naphthalene	
210.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	2-Me-1-naphthalene	
211.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	8-OMe-1-naphthalene	
212.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	4-quinazoline	
213.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	2-quinazoline	
214.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	1-phthalazine	
215.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	4-quinoline	
216.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	4-isoquinoline	
217.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	2-pyrimidine	
218.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	2-tBu,4-CF_3-pyrimidine	
219.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	2-pyridinalene	
220.	NR^1	CH_2	i-C_3	C_2		4-piperazine	1-naphthalene	
221.	NR^1	CH_2	C_2-Ph	C_2		4-piperazine	1-naphthalene	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
222.	NR^1	CH_2	C_2-(2-OMe)Ph	C_2		4-piperazine	1-naphthalene	
223.	NR^1	CH_2	C_3-(4-Cl)Ph	C_2		4-piperazine	1-naphthalene	
224.	NR^1	CH_2	C_2-(2-CF_3)Ph	C_2		4-piperazine	1-naphthalene	
225.	NR^1	CH_2	H	C_3		4-piperazine	5-tetralin	
226.	NR^1	CH_2	H	C_3		4-piperazine	1-naphthalene	
227.	NR^1	CH_2	H	C_3		4-piperazine	2-OMe-Ph	
228.	NR^1	CH_2	H	C_3		4-piperazine	4-isoquinoline	
229.	NR^1	CH_2	H	C_3		4-piperazine	2-pyrimidine	
230.	NR^1	CH_2	H	C_3		4-piperazine	2-OMe-naphthalene	
231.	NR^1	CH_2	CH_2-Ph	C_3		4-piperazine	5-tetralin	
232.	NR^1	CH_2	CH_2-Ph	C_3		4-piperazine	1-naphthalene	
233.	NR^1	CH_2	CH_2-Ph	C_3		4-piperazine	2-OMe-Ph	
234.	NR^1	CH_2	CH_2-Ph	C_3		4-piperazine	4-isoquinoline	
235.	NR^1	CH_2	CH_2-Ph	C_3		4-piperazine	2-pyridine	
236.	NR^1	CH_2	CH_2-Ph	C_3		4-piperazine	2-OMe-naphthalene	
237.	NR^1	CH_2	Me	C_3		4-piperazine	5-tetralin	
238.	NR^1	CH_2	Me	C_3		4-piperazine	1-naphthalene	
239.	NR^1	CH_2	Me	C_3		4-piperazine	2-OMe-Ph	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
240.	NR^1	CH_2	Me	C_3		4-piperazine	4-isoquinoline	
241.	NR^1	CH_2	Me	C_3		4-piperazine	2-pyrimidine	
242.	NR^1	CH_2	Me	C_3		4-piperazine	2-OMe-naphthalene	
243.	NR^1	CH_2	Boc	C_3		4-piperazine	5-tetralin	
244.	NR^1	CH_2	Boc	C_3		4-piperazine	1-naphthalene	
245.	NR^1	CH_2	Boc	C_3		4-piperazine	2-OMe-Ph	
246.	NR^1	CH_2	Boc	C_3		4-piperazine	4-isoquinoline	
247.	NR^1	CH_2	Boc	C_3		4-piperazine	2-pyrimidine	
248.	NR^1	CH_2	Boc	C_3		4-piperazine	2-OMe-naphthalene	
249.	NR^1	CH_2	CH_3-C=O	C_3		4-piperazine	5-tetralin	
250.	NR^1	CH_2	CH_3-C=O	C_3		4-piperazine	1-naphthalene	
251.	NR^1	CH_2	CH_3-C=O	C_3		4-piperazine	2-OMe-Ph	
252.	NR^1	CH_2	CH_3-C=O	C_3		4-piperazine	4-isoquinoline	
253.	NR^1	CH_2	CH_3-C=O	C_3		4-piperazine	2-pyrimidine	
254.	NR^1	CH_2	Ph-C=O	C_3		4-piperazine	2-OMe-naphthalene	
255.	NR^1	CH_2	Ph-C=O	C_3		4-piperazine	5-tetralin	
256.	NR^1	CH_2	Ph-C=O	C_3		4-piperazine	1-naphthalene	
257.	NR^1	CH_2	Ph-C=O	C_3		4-piperazine	2-OMe-Ph	
258.	NR^1	CH_2	Ph-C=O	C_3		4-piperazine	4-isoquinoline	
259.	NR^1	CH_2	Ph-C=O	C_3		4-piperazine	2-pyrimidine	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
260.	NR^1	CH_2	Ph-C=O	C_3		4-piperazine	2-OMe-naphthalene	
261.	NR^1	CH_2	H	C_2		4-piperidine	5-tetralin	
262.	NR^1	CH_2	H	C_2		4-piperidine	1-naphthalene	
263.	NR^1	CH_2	H	C_2		4-piperidine	2-OMe-Ph	
264.	NR^1	CH_2	H	C_2		4-piperidine	4-isoquinoline	
265.	NR^1	CH_2	H	C_2		4-piperidine	2-pyrimidine	
266.	NR^1	CH_2	H	C_2		4-piperidine	2-OMe-naphthalene	
267.	NR^1	CH_2	Me	C_2		4-piperidine	5-tetralin	
268.	NR^1	CH_2	Me	C_2		4-piperidine	1-naphthalene	
269.	NR^1	CH_2	Me	C_2		4-piperidine	2-OMe-Ph	
270.	NR^1	CH_2	Me	C_2		4-piperidine	4-isoquinoline	
271.	NR^1	CH_2	Me	C_2		4-piperidine	2-pyrimidine	
272.	NR^1	CH_2	Me	C_2		4-piperidine	2-OMe-naphthalene	
273.	NR^1	CH_2	CH_2-Ph	C_2		4-piperidine	5-tetralin	
274.	NR^1	CH_2	CH_2-Ph	C_2		4-piperidine	1-naphthalene	
275.	NR^1	CH_2	CH_2-Ph	C_2		4-piperidine	2-OMe-Ph	
276.	NR^1	CH_2	CH_2-Ph	C_2		4-piperidine	4-isoquinoline	
277.	NR^1	CH_2	CH_2-Ph	C_2		4-piperidine	2-pyrimidine	
278.	NR^1	CH_2	CH_2-Ph	C_2		4-piperidine	2-OMe-naphthalene	
279.	NR^1	CH_2	CH_3C=O	C_2		4-piperidine	5-tetralin	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
280.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperidine	1-naphthalene	
281.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperidine	2-OMe-Ph	
282.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperidine	4-isoquinoline	
283.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperidine	2-pyrimidine	
284.	NR^1	CH_2	$CH_3C=O$	C_2		4-piperidine	2-OMe-naphthalene	
285.	NR^1	CH_2	Boc	C_2		4-piperidine	5-tetralin	
286.	NR^1	CH_2	Boc	C_2		4-piperidine	1-naphthalene	
287.	NR^1	CH_2	Boc	C_2		4-piperidine	2-OMe-Ph	
288.	NR^1	CH_2	Boc	C_2		4-piperidine	4-isoquinoline	
289.	NR^1	CH_2	Boc	C_2		4-piperidine	2-pyrimidine	
290.	NR^1	CH_2	Boc	C_2		4-piperidine	2-OMe-naphthalene	
291.	NR^1	CH_2	Ph-C=O	C_2		4-piperidine	5-tetralin	
292.	NR^1	CH_2	Ph-C=O	C_2		4-piperidine	1-naphthalene	
293.	NR^1	CH_2	Ph-C=O	C_2		4-piperidine	2-OMe-Ph	
294.	NR^1	CH_2	Ph-C=O	C_2		4-piperidine	4-isoquinoline	
295.	NR^1	CH_2	Ph-C=O	C_2		4-piperidine	2-pyrimidine	
296.	NR^1	CH_2	Ph-C=O	C_2		4-piperidine	2-OMe-naphthalene	
297.	NR^1	CH_2	H	C_2		4-tetrahydro-1,2,3,6-pyridine	5-tetralin	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
298.	NR^1	CH_2	H	C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
299.	NR^1	CH_2	H	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-Ph	
300.	NR^1	CH_2	H	C_2		4-tetrahydro-1,2,3,6-pyridine	4-isoquinoline	
301.	NR^1	CH_2	H	C_2		4-tetrahydro-1,2,3,6-pyridine	2-pyrimidine	
302.	NR^1	CH_2	H	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-naphthalene	
303.	NR^1	CH_2	Me	C_2		4-tetrahydro-1,2,3,6-pyridine	5-tetralin	
304.	NR^1	CH_2	Me	C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene.	
305.	NR^1	CH_2	Me	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-Ph	
306.	NR^1	CH_2	Me	C_2		4-tetrahydro-1,2,3,6-pyridine	4-isoquinoline	
307.	NR^1	CH_2	Me	C_2		4-tetrahydro-1,2,3,6-pyridine	2-pyrimidine	
308.	NR^1	CH_2	Me	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-naphthalene	
309.	NR^1	CH_2	CH_2-Ph	C_2		4-tetrahydro-1,2,3,6-pyridine	tetralin	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
310.	NR^1	CH_2	CH_2-Ph	C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
311.	NR^1	CH_2	CH_2-Ph	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-Ph	
312.	NR^1	CH_2	CH_2-Ph	C_2		4-tetrahydro-1,2,3,6-pyridine	4-isoquinoline	
313.	NR^1	CH_2	CH_2-Ph	C_2		4-tetrahydro-1,2,3,6-pyridine	2-pyrimidine	
314.	NR^1	CH_2	CH_2-Ph	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-naphthalene	
315.	NR^1	CH_2	Boc	C_2		4-tetrahydro-1,2,3,6-pyridine	tetralin	
316.	NR^1	CH_2	Boc	C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
317.	NR^1	CH_2	Boc	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-Ph	
318.	NR^1	CH_2	Boc	C_2		4-tetrahydro-1,2,3,6-pyridine	4-isoquinoline	
319.	NR^1	CH_2	Boc	C_2		4-tetrahydro-1,2,3,6-pyridine	2-pyrimidine	
320.	NR^1	CH_2	Boc	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-naphthalene	
321.	NR^1	CH_2	$CH_3C=O$	C_2		4-tetrahydro-1,2,3,6-pyridine	tetralin	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
322.	NR^1	CH_2	$CH_3C=O$	C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
323.	NR^1	CH_2	$CH_3C=O$	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-Ph	
324.	NR^1	CH_2	$CH_3C=O$	C_2		4-tetrahydro-1,2,3,6-pyridine	4-isoquinoline	
325.	NR^1	CH_2	$CH_3C=O$	C_2		4-tetrahydro-1,2,3,6-pyridine	2-pyrimidine	
326.	NR^1	CH_2	$CH_3C=O$	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-naphthalene	
327.	NR^1	CH_2	Ph-C=O	C_2		4-tetrahydro-1,2,3,6-pyridine	tetralin	
328.	NR^1	CH_2	Ph-C=O	C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene.	
329.	NR^1	CH_2	Ph-C=O	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-Ph	
330.	NR^1	CH_2	Ph-C=O	C_2		4-tetrahydro-1,2,3,6-pyridine	4-isoquinoline	
331.	NR^1	CH_2	Ph-C=O	C_2		4-tetrahydro-1,2,3,6-pyridine	2-pyrimidine	
332.	NR^1	CH_2	Ph-C=O	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-naphthalene	
333.	NR^1	CH_2	H	C_2		4-homopiperazine	1-naphthalene	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
334.	NR^1	CH_2	H	C_2		4-homopiperazine	2-OMe-Ph	
335.	NR^1	CH_2	H	C_2		4-homopiperazine	2-OMe-1-naphthalene	
336.	NR^1	CH_2	H	C_3		4-homopiperazine	2-pyrimidine	
337.	NR^1	CH_2	Me	C_2		4-homopiperazine	1-naphthalene	
338.	NR^1	CH_2	Me	C_2		4-homopiperazine	2-OMe-Ph	
339.	NR^1	CH_2	CH_2-Ph	C_2		4-homopiperazine	1-naphthalene	
340.	NR^1	CH_2	CH_2-Ph	C_3		4-homopiperazine	2-OMe-Ph	
341.	NR^1	CH_2	Boc	C_2		4-homopiperazine	1-naphthalene	
342.	NR^1	CH_2	Boc	C_2		4-homopiperazine	2-OMe-Ph	
343.	NR^1	CH_2	Boc	C_3		4-homopiperazine	2-OMe-1-naphthalene	
344.	NR^1	CH_2	CH_3-C=O	C_2		4-homopiperazine	1-naphthalene	
345.	NR^1	CH_2	CH_3-C=O	C_2		4-homopiperazine	2-OMe-Ph	
346.	NR^1	CH_2	Ph-C=O	C_2		4-homopiperazine	1-naphthalene	
347.	NR^1	CH_2	Ph-C=O	C_2		4-homopiperazine	1-OMe-Ph	
348.	NR^1	CH_2	Ph-C=O	C_2		4-homopiperazine	2-pyrimidine	
349.	NR^1	CH_2	H	C_2		azepan	1-naphthalene	
350.	NR^1	CH_2	H	C_2		azepan	2-OMe-Ph	
351.	NR^1	CH_2	H	C_2		azepan	2-OMe-1-naphthalene	
352.	NR^1	CH_2	H	C_3		azepan	2-pyrimidine	
353.	NR^1	CH_2	Me	C_2		azepan	1-naphthalene	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
354.	NR^1	CH_2	Me	C_2		azepan	2-OMe-Ph	
355.	NR^1	CH_2	CH_2-Ph	C_2		azepan	1-naphthalene	
356.	NR^1	CH_2	CH_2-Ph	C_2		azepan	2-OMe-Ph	
357.	NR^1	CH_2	Boc	C_2		azepan	1-naphthalene	
358.	NR^1	CH_2	Boc	C_2		azepan	2-OMe-Ph	
359.	NR^1	CH_2	Boc	C_3		azepan	2-OMe-1-naphthalene	
360.	NR^1	CH_2	CH_3-C=O	C_2		azepan	1-naphthalene	
361.	NR^1	CH_2	CH_3-C=O	C_2		azepan	2-OMe-Ph	
362.	NR^1	CH_2	Ph-C=O	C_2		azepan	1-naphthalene	
363.	NR^1	CH_2	Ph-C=O	C_2		azepan	2-OMe-Ph	
364.	NR^1	CH_2	Ph-C=O	C_2		azepan	2-pyrimidine	
365.	NR^1	CH_2	H	C_2		tetrahydro-2H-azepine	1-naphthalene	
366.	NR^1	CH_2	H	C_2		tetrahydro-2H-azepine	2-OMe-Ph	
367.	NR^1	CH_2	H	C_2		tetrahydro-2H-azepine	2-OMe-1-naphthalene	
368.	NR^1	CH_2	H	C_3		tetrahydro-2H-azepine	2-pyrimidine	
369.	NR^1	CH_2	Me	C_2		tetrahydro-2H-azepine	1-naphthalene	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
370.	NR^1	CH_2	H	C_2		tetrahydro-2H-azepine	2-OMe-Ph	
371.	NR^1	CH_2	CH_2-Ph	C_2		tetrahydro-2H-azepine	1-naphthalene	
372.	NR^1	CH_2	CH_2-Ph	C_2		tetrahydro-2H-azepine	2-OMe-Ph	
373.	NR^1	CH_2	Boc	C_2		tetrahydro-2H-azepine	1-naphthalene	
374.	NR^1	CH_2	Boc	C_2		tetrahydro-2H-azepine	2-OMe-Ph	
375.	NR^1	CH_2	Boc	C_3		tetrahydro-2H-azepine	2-OMe-1-naphthalene	
376.	NR^1	CH_2	CH_3-C=O	C_2		tetrahydro-2H-azepine	1-naphthalene	
377.	NR^1	CH_2	CH_3-C=O	C_2		tetrahydro-2H-azepine	2-OMe-Ph	
378.	NR^1	CH_2	Ph-C=O	C_2		tetrahydro-2H-azepine	1-naphthalene	
379.	NR^1	CH_2	Ph-C=O	C_2		tetrahydro-2H-azepine	2-OMe-Ph	
380.	NR^1	CH_2	Ph-C=O	C_2		tetrahydro-2H-azepine	2-pyrimidine	
381.	NR^1	CH_2	H	CH_2-C(CH_2)-CH_2		4-piperazine	2-OMe-Ph	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
382.	NR^1	CH_2	H	CH_2-C(CH_2)-CH_2		4-piperazine	1-naphthalene	
383.	NR^1	CH_2	H	CH_2-C(CH_2)-CH_2		4-piperidine	1-naphthalene	
384.	NR^1	CH_2	Me	CH_2-C(CH_2)-CH_2		4-piperazine	2-OMe-Ph	
385.	NR^1	CH_2	Me	CH_2-C(CH_2)-CH_2		4-piperazine	1-naphthalene	
386.	NR^1	CH_2	Me	CH_2-C(CH_2)-CH_2		4-homopiperazine	1-naphthalene	
387.	NR^1	CH_2	CH_2-Ph	CH_2-C(CH_2)-CH_2		4-piperazine	2-OMe-Ph	
388.	NR^1	CH_2	CH_2-Ph	CH_2-C(CH_2)-CH_2		4-piperazine	1-naphthalene	
389.	NR^1	CH_2	CH_2-Ph	CH_2-C(CH_2)-CH_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
390.	NR^1	CH_2	Boc	CH_2-C(CH_2)-CH_2		4-piperazine	2-OMe-Ph	
391.	NR^1	CH_2	Boc	CH_2-C(CH_2)-CH_2		4-piperazine	1-naphthalene	
392.	NR^1	CH_2	Boc	CH_2-C(CH_2)-CH_2		4-piperazine	2-pyrimidine	
393.	NR^1	CH_2	CH_3-C=O	CH_2-C(CH_2)-CH_2		4-piperazine	2-OMe-Ph	
394.	NR^1	CH_2	CH_3-C=O	CH_2-C(CH_2)-CH_2		4-piperazine	1-naphthalene	
395.	NR^1	CH_2	Ph-C=O	CH_2-C(CH_2)-CH_2		4-piperazine	2-OMe-Ph	
396.	NR^1	CH_2	Ph-C=O	CH_2-C(CH_2)-CH_2		4-piperazine	1-naphthalene	
397.	NR^1	CH_2	H	CH_2-C(OH)-CH_2		4-piperazine	2-OMe-Ph	
398.	NR^1	CH_2	H	CH_2-C(OH)-CH_2		4-piperazine	1-naphthalene	
399.	NR^1	CH_2	H	CH_2-C(OH)-CH_2		4-piperidine	1-naphthalene	
400.	NR^1	CH_2	Me	CH_2-C(OH)-CH_2		4-piperazine	2-OMe-Ph	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
401.	NR^1	CH_2	H	CH_2-C(OH)-CH_2		4-piperazine	1-naphthalene	
402.	NR^1	CH_2	H	CH_2-C(OH)-CH_2		4-homopiperazine	1-naphthalene	
403.	NR^1	CH_2	CH_2-Ph	CH_2-C(OH)-CH_2		4-piperazine	2-OMe-Ph	
404.	NR^1	CH_2	CH_2-Ph	CH_2-C(OH)-CH_2		4-piperazine	1-naphthalene	
405.	NR^1	CH_2	CH_2-Ph	CH_2-C(OH)-CH_2		4-tetra-hydro-1,2,3,6-pyridine	1-naphthalene	
406.	NR^1	CH_2	Boc	CH_2-C(OH)-CH_2		4-piperazine	2-OMe-Ph	
407.	NR^1	CH_2	Boc	CH_2-C(OH)-CH_2		4-piperazine	1-naphthalene	
408.	NR^1	CH_2	Boc	CH_2-C(OH)-CH_2		4-piperazine	2-pyrimidine	
409.	NR^1	CH_2	CH_3-C=O	CH_2-C(OH)-CH_2		4-piperazine	2-OMe-Ph	
410.	NR^1	CH_2	CH_3-C=O	CH_2-C(OH)-CH_2		4-piperazine	1-naphthalene	
411.	NR^1	CH_2	Ph-C=O	CH_2-C(OH)-CH_2		4-piperazine	2-OMe-Ph	
412.	NR^1	CH_2	Ph-C=O	CH_2-C(OH)-CH_2		4-piperazine	1-naphthalene	
413.	NR^1	CH_2	H	C_2-N(Me)-C_2		4-piperazine	2-OMe-Ph	
414.	NR^1	CH_2	H	C_2-N(Me)-C_2		4-piperazine	1-naphthalene	
415.	NR^1	CH_2	H	C_2-N(Me)-C_2		4-piperidine	1-naphthalene	
416.	NR^1	CH_2	Me	C_2-N(Me)-C_2		4-piperazine	2-OMe-Ph	
417.	NR^1	CH_2	Me	C_2-N(Me)-C_2		4-piperazine	1-naphthalene	
418.	NR^1	CH_2	Me	C_2-N(Me)-C_2		4-homopiperazine	1-naphthalene	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
419.	NR^1	CH_2	CH_2-Ph	C_2-N(Me)-C_2		4-piperazine	2-OMe-Ph	
420.	NR^1	CH_2	CH_2-Ph	C_2-N(Me)-C_2		4-piperazine	1-naphthalene	
421.	NR^1	CH_2	CH_2-Ph	C_2-N(Me)-C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
422.	NR^1	CH_2	Boc	C_2-N(Me)-C_2		4-piperazine	2-OMe-Ph	
423.	NR^1	CH_2	Boc	C_2-N(Me)-C_2		4-piperazine	1-naphthalene	
424.	NR^1	CH_2	Boc	C_2-N(Me)-C_2		4-piperazine	2-pyrimidine	
425.	NR^1	CH_2	CH_3-C=O	C_2-N(Me)-C_2		4-piperazine	2-OMe-Ph	
426.	NR^1	CH_2	CH_3-C=O	C_2-N(Me)-C_2		4-piperazine	1-naphthalene	
427.	NR^1	CH_2	Ph-C=O	C_2-N(Me)-C_2		4-piperazine	2-OMe-Ph	
428.	NR^1	CH_2	Ph-C=O	C_2-N(Me)-C_2		4-piperazine	1-naphthalene	
429.	NR^1	CH_2	H	CH_2-CH(CH_3)-CH_2		4-piperazine	2-OMe-Ph	
430.	NR^1	CH_2	H	CH_2-CH(CH_3)-CH_2		4-piperazine	1-naphthalene	
431.	NR^1	CH_2	H	CH_2-CH(CH_3)-CH_2		4-piperidine	1-naphthalene	
432.	NR^1	CH_2	Me	CH_2-CH(CH_3)-CH_2		4-piperazine	2-OMe-Ph	
433.	NR^1	CH_2	Me	CH_2-CH(CH_3)-CH_2		4-piperazine	1-naphthalene	
434.	NR^1	CH_2	Me	CH_2-CH(CH_3)-CH_2		4-homopiperazine	1-naphthalene	
435.	NR^1	CH_2	CH_2-Ph	CH_2-CH(CH_3)-CH_2		4-piperazine	2-OMe-Ph	
436.	NR^1	CH_2	CH_2-Ph	CH_2-CH(CH_3)-CH_2		4-piperazine	1-naphthalene	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
437.	NR^1	CH_2	CH_2-Ph	CH_2-CH(CH_3)-CH_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
438.	NR^1	CH_2	Boc	CH_2-CH(CH_3)-CH_2		4-piperazine	2-OMe-Ph	
439.	NR^1	CH_2	Boc	CH_2-CH(CH_3)-CH_2		4-piperazine	1-naphthalene	
440.	NR^1	CH_2	Boc	CH_2-CH(CH_3)-CH_2		4-piperazine	2-pyrimidine	
441.	NR^1	CH_2	CH_3-C=O	CH_2-CH(CH_3)-CH_2		4-piperazine	2-OMe-Ph	
442.	NR^1	CH_2	CH_3-C=O	CH_2-CH(CH_3)-CH_2		4-piperazine	1-naphthalene	
443.	NR^1	CH_2	Ph-C=O	CH_2-CH(CH_3)-CH_2		4-piperazine	2-OMe-Ph	
444.	NR^1	CH_2	Ph-C=O	CH_2-CH(CH_3)-CH_2		4-piperazine	1-naphthalene	
445.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	Ph	
446.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	2-OMe-Ph	
447.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	2-Me-Ph	
448.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	2-CN-Ph	
449.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	2-Cl-Ph	
450.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	3-CF_3-Ph	
451.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	4-iC_3-Ph	
452.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	3-Me, 4-Me-Ph	
453.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	5-tetralin	
454.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	4-indan	
455.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	1-naphthalene	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
456.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	2-OMe-1-naphthalene	
457.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	2-Me-1-naphthalene	
458.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	8-OMe-1-naphthalene	
459.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	2-quinazoline	
460.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	1-phthalazine	
461.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	4-quinoline	
462.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	4-isoquinoline	
463.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	2-pyrimidine	
464.	CH_2	NR^1	CH_2-Ph	C_2		4-piperazine	2-pyridine	
465.	CH_2	NR^1	H	C_2		4-piperazine	2-OMe-Ph	
466.	CH_2	NR^1	H	C_2		4-piperazine	2-F-Ph	
467.	CH_2	NR^1	H	C_2		4-piperazine	3-tBu-Ph	
468.	CH_2	NR^1	H	C_2		4-piperazine	5-tetralin	
469.	CH_2	NR^1	H	C_2		4-piperazine	1-naphthalene	
470.	CH_2	NR^1	H	C_2		4-piperazine	2-OMe-1-naphthalene	
471.	CH_2	NR^1	H	C_2		4-piperazine	2-Me-1-naphthalene	
472.	CH_2	NR^1	H	C_2		4-piperazine	1-isoquinoline	
473.	CH_2	NR^1	H	C_2		4-piperazine	2-Ph-4-quinazoline	
474.	CH_2	NR^1	Me	C_2		4-piperazine	2-OMe-Ph	
475.	CH_2	NR^1	Me	C_2		4-piperazine	1-naphthalene	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
476.	CH_2	NR^1	Me	C_2		4-piperazine	2-Me-1-naphthalene	
477.	CH_2	NR^1	Me	C_2		4-piperazine	2-pyrimidine	
478.	CH_2	NR^1	$CH_3C=O$	C_2		4-piperazine	2-OMe-Ph	
479.	CH_2	NR^1	$CH_3C=O$	C_2		4-piperazine	1-naphthalene	
480.	CH_2	NR^1	PhC=O	C_2		4-piperazine	2-OMe-Ph	
481.	CH_2	NR^1	PhC=O	C_2		4-piperazine	1-naphthalene	
482.	CH_2	NR^1	Boc	C_2		4-piperazine	2-OMe-Ph	
483.	CH_2	NR^1	Boc	C_2		4-piperazine	1-naphthalene	
484.	CH_2	NR^1	CH_2-Ph	C_3		4-piperazine	2-OMe-Ph	
485.	CH_2	NR^1	CH_2-Ph	C_3		4-piperazine	1-naphthalene	
486.	CH_2	NR^1	H	C_3		4-piperazine	2-OMe-Ph	
487.	CH_2	NR^1	H	C_3		4-piperazine	1-naphthalene	
488.	CH_2	NR^1	Me	C_3		4-piperazine	2-OMe-Ph	
489.	CH_2	NR^1	Me	C_3		4-piperazine	1-naphthalene	
490.	CH_2	NR^1	Boc	C_3		4-piperazine	2-OMe-Ph	
491.	CH_2	NR^1	Boc	C_3		4-piperazine	1-naphthalene	
492.	CH_2	NR^1	$CH_3C=O$	C_3		4-piperazine	2-OMe-Ph	
493.	CH_2	NR^1	$CH_3C=O$	C_3		4-piperazine	1-naphthalene	
494.	CH_2	NR^1	PhC=O	C_3		4-piperazine	2-OMe-Ph	
495.	CH_2	NR^1	PhC=O	C_3		4-piperazine	1-naphthalene	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
496.	CH_2	NR^1	CH_2-Ph	C_2-N(Me)-C_2		4-piperazine	1-naphthalene	
497.	CH_2	NR^1	H	C_2-N(Me)-C_2		4-piperazine	1-naphthalene	
498.	CH_2	NR^1	Me	C_2-N(Me)-C_2		4-piperazine	1-naphthalene	
499.	CH_2	NR^1	Boc	C_2-N(Me)-C_2		4-piperazine	1-naphthalene	
500.	CH_2	NR^1	CH_2-Ph	CH_2-C(CH_2)-CH_2		4-piperazine	1-naphthalene	
501.	CH_2	NR^1	H	CH_2-C(CH_2)-CH_2		4-piperazine	1-naphthalene	
502.	CH_2	NR^1	Me	CH_2-C(CH_2)-CH_2		4-piperazine	1-naphthalene	
503.	CH_2	NR^1	Boc	CH_2-C(CH_2)-CH_2		4-piperazine	1-naphthalene	
504.	CH_2	NR^1	CH_2-Ph	CH_2-CH(OH)-CH_2		4-piperazine	1-naphthalene	
505.	CH_2	NR^1	H	CH_2-CH(OH)-CH_2		4-piperazine	1-naphthalene	
506.	CH_2	NR^1	Me	CH_2-CH(OH)-CH_2		4-piperazine	1-naphthalene	
507.	CH_2	NR^1	Boc	CH_2-CH(OH)-CH_2		4-piperazine	1-naphthalene	
508.	CH_2	NR^1	CH_2-Ph	CH_2-CH(CH_3)CH_2		4-piperazine	1-naphthalene	
509.	CH_2	NR^1	H	CH_2-CH(CH_3)CH_2		4-piperazine	1-naphthalene	
510.	CH_2	NR^1	Me	CH_2-CH(CH_3)CH_2		4-piperazine	1-naphthalene	
511.	CH_2	NR^1	Boc	CH_2-CH(CH_3)CH_2		4-piperazine	1-naphthalene	
512.	CH_2	NR^1	CH_2-Ph	C_2		4-piperidine	5-tetralin	
513.	CH_2	NR^1	CH_2-Ph	C_2		4-piperidine	1-naphthalene	
514.	CH_2	NR^1	CH_2-Ph	C_2		4-piperidine	2-OMe-Ph	
515.	CH_2	NR^1	CH_2-Ph	C_2		4-piperidine	4-isoquinoline	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
516.	CH_2	NR^1	CH_2-Ph	C_2		4-piperidine	2-pyrimidine	
517.	CH_2	NR^1	CH_2-Ph	C_2		4-piperidine	2-OMe-naphthalene	
518.	CH_2	NR^1	H	C_2		4-piperidine	5-tetralin	
519.	CH_2	NR^1	H	C_2		4-piperidine	1-naphthalene	
520.	CH_2	NR^1	H	C_2		4-piperidine	2-OMe-Ph	
521.	CH_2	NR^1	H	C_2		4-piperidine	4-isoquinoline	
522.	CH_2	NR^1	H	C_2		4-piperidine	2-pyrimidine	
523.	CH_2	NR^1	H	C_2		4-piperidine	2-OMe-naphthalene	
524.	CH_2	NR^1	Me	C_2		4-piperidine	2-OMe-Ph	
525.	CH_2	NR^1	Me	C_2		4-piperidine	1-naphthalene	
526.	CH_2	NR^1	Me	C_3		4-piperidine	2-pyrimidine	
527.	CH_2	NR^1	CH_3-C=O	C_2		4-piperidine	2-OMe-Ph	
528.	CH_2	NR^1	CH_3-C=O	C_2		4-piperidine	1-naphthalene	
529.	CH_2	NR^1	Ph-C=O	C_2		4-piperidine	2-OMe-Ph	
530.	CH_2	NR^1	Ph-C=O	C_2		4-piperidine	1-naphthalene	
531.	CH_2	NR^1	CH_2-Ph	C_2		4-tetrahydro-1,2,3,6-pyridine	5-tetralin	
532.	CH_2	NR^1	CH_2-Ph	C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
533.	CH_2	NR^1	CH_2-Ph	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-Ph	

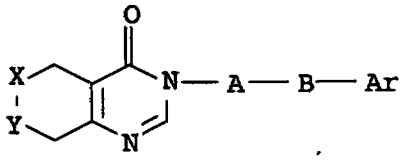
No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
534.	CH_2	NR^1	CH_2-Ph	C_2		4-tetrahydro-1,2,3,6-pyridine	4-isoquinoline	
535.	CH_2	NR^1	CH_2-Ph	C_2		4-tetrahydro-1,2,3,6-pyridine	2-pyrimidine	
536.	CH_2	NR^1	CH_2-Ph	C_2		4-tetrahydro-1,2,3,6-pyridine	2-OMe-naphthalene	
537.	CH_2	NR^1	H	C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
538.	CH_2	NR^1	Me	C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
539.	CH_2	NR^1	Boc	C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
540.	CH_2	NR^1	CH_3-C=O	C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
541.	CH_2	NR^1	Ph-C=O	C_2		4-tetrahydro-1,2,3,6-pyridine	1-naphthalene	
542.	CH_2	NR^1	CH_2-Ph	C_2		4-homopiperazine	1-naphthalene	
543.	CH_2	NR^1	H	C_2		4-homopiperazine	1-naphthalene	
544.	CH_2	NR^1	Me	C_2		4-homopiperazine	1-naphthalene	
545.	CH_2	NR^1	Boc	C_2		4-homopiperazine	1-naphthalene	
546.	CH_2	NR^1	CH_2-Ph	C_2		azepan	1-naphthalene	
547.	CH_2	NR^1	H	C_2		azepan	1-naphthalene	

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
548.	CH_2	NR^1	Me	C_2		azepan	1-naphthalene	
549.	CH_2	NR^1	Boc	C_2		azepan	1-naphthalene	
550.	CH_2	NR^1	CH_2-Ph	C_2		tetrahydro-2H-azepine	1-naphthalene	
551.	CH_2	NR^1	H	C_2		tetrahydro-2H-azepine	1-naphthalene	
552.	CH_2	NR^1	Me	C_2		tetrahydro-2H-azepine	1-naphthalene	
553.	CH_2	NR^1	Boc	C_8		tetrahydro-2H-azepine	1-naphthalene	
554.	CH_2	NR^1	CH_2-Ph	C_2		tetrahydro-2H-azepine	1-naphthalene	
555.	NR^1	CH_2	CH_2-Ph	C_2		tetrahydro-2H-azepine	1-naphthalene	
556.	NR^1	CH_2	Me	C_2		4-piperazine	1-naphthalene	235°C
557.	NR^1	CH_2	CH_3-C=O	C_2		4-piperazine	1-naphthalene	236°C
558.	NR^1	CH_2	Ph-C=O	C_2		4-piperazine	1-naphthalene	245°C
559.	NR^1	CH_2	Boc	C_2		4-piperazine	4-quinazoline	270°C
560.	NR^1	CH_2	H	C_2		4-piperazine	4-quinazoline	260°C
561.	NR^1	CH_2	Boc	C_2		4-piperazine	4-isoquinoline	286°C
562.	NR^1	CH_2	H	C_2		4-piperazine	4-isoquinoline	290°C
563.	NR^1	CH_2	Ph-CH_2	C_4		4-piperazine	2-pyrimidine	265°C

No.	X	Y	R^1	A	R^2	B	Ar	M.p. hydro-chloride
564.	NR^1	CH_2	Ph-CH_2	C_3		4-piperazine	4-indan	281°C
565.	NR^1	CH_2	Ph-CH_2	C_2		4-piperazine	2-Cl-Ph	225°C
566.	NR^1	CH_2	Ph-CH_2	C_2		4-piperazine	2-pyrimidine	250°C

We claim:

1. A 3-substituted tetrahydropyridopyrimidinone derivative of the formula I



(I),

where

one of the two radicals X and Y is CH_2 and the other is NR^1,

R^1 is hydrogen, (C_{1-6}) alkyl branched or unbranched, $CO-(C_{1-4})$-alkyl, CO_2tBu, CO-aryl and a phenylalkyl-C_1-C_4 radical which in turn may be substituted on the aromatic system by F, Cl, Br, I, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, hydroxyl, amino, cyano or nitro,

A is branched or unbranched (C_{1-10})-alkylene or straight-chain or branched (C_{2-10})-alkylene which comprises at least one group Z which is selected from O, S, NR^2, cyclopropyl, CO_2, CHOH, a double or triple bond,

R^2 is hydrogen and C_1-C_4 alkyl,

B is 4-piperidine, 4-tetrahydro-1,2,3,6 pyridine, 4-piperazine or the corresponding cyclic compounds enlarged by one methylene group, with the linkage to A being via an N atom of B, and

Ar is phenyl which is unsubstituted or substituted by (C_{1-6}) alkyl branched or unbranched, $O-(C_{1-6})$-alkyl branched or unbranched, OH, F, Cl, Br, I, trifluoromethyl, NR^2_2, CO_2R^2, cyano or phenyl, or is tetralin, indan, fused aromatic systems such as naphthalene which is unsubstituted or substituted by (C_{1-4}) alkyl or $O(C_{1-4})$ alkyl, anthracene or 5- or 6-membered aromatic heterocycles having 1 or 2 heteroatoms which are selected, independently of one another, from O and N, which may be fused to other aromatic radicals,



and their salts with physiologically tolerated acids.

2. A 3-substituted tetrahydropyridopyrimidinone derivative as claimed in claim 1, where

one of the two radicals X and Y is CH_2 and the other is NR^1,

R^1 is hydrogen, (C_{1-4}) alkyl branched or unbranched, CO-(C_{1-4})-alkyl, CO_2tBu, COPh or a phenylalkyl C_1-C_2 radical which in turn can be substituted on the aromatic system by F, Cl, Br, I, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, hydroxyl or cyano,

A is (C_{2-5}) alkylene branched or unbranched or (C_{2-5}) alkylene which comprises a group Z which is selected from CHOH, cyclopropyl, a double or a triple bond,

B is 4-piperidine, 4-tetrahydro-1,2,3,6 pyridine, 4-piperazine or homopiperazine, where the linkage to A takes place via an N atom of B, and

Ar is phenyl which is unsubstituted or substituted by (C_{1-6}) alkyl branched or unbranched, O-(C_{1-6})-alkyl branched or unbranched, F, Cl, Br, I, trifluoromethyl, CO_2R^2, NR^2_2, cyano or phenyl, or is tetralin, indan, fused aromatic systems such as naphthalene which is unsubstituted or substituted by (C_{1-4}) alkyl or O(C_{1-4}) alkyl, or 5- or 6-membered aromatic heterocycles having 1 or 2 nitrogen atoms, which may be fused to other aromatic radicals.

3. A 3-substituted tetrahydropyridopyrimidinone derivative of the formula I as claimed in claim 1, where

one of the two radicals X and Y is CH_2 and the other is NR^1,

R^1 is hydrogen, (C_{1-2}) alkyl, CO-(C_{1-4})-alkyl or a phenylalkyl C_1-C_2 radical,

A is (C_{2-3}) alkyl,

B is 4-piperidine, 4-piperazine or 4-tetrahydro-1,2,3,6 pyridine and

Ar is pyrimidine, phenyl which is unsubstituted or substituted by $O(C_{1-2})$ alkyl in the ortho position, tetralin, indan or naphthalene which is unsubstituted or substituted by (C_{1-4}) alkyl or $O(C_{1-2})$ alkyl.

4. The use of compounds as claimed in claim 1-3 for producing drugs.

5. The use as claimed in claim 4 for the treatment of depression and related disorders.

6. The use of compounds as claimed in claim 1-3 as selective $5\text{-}HT_{1B}$ and $5\text{-}HT_{1A}$ antagonists.

7. The use as claimed in claim 6, where the selective serotonin antagonism is supplemented by inhibition of serotonin reuptake.