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2-Substituted 1,2-benzothiazole derivatives, their preparation and use

- 5 The invention relates to 2-substituted 1,2-benzothiazole derivatives, their preparation and use for preparing active ingredients of drugs.

Classical antidepressants, and the newer selective serotonin reuptake inhibitors (SSRIs) exert their antidepressant effect inter alia by inhibiting active reuptake of the transmitter into the presynaptic nerve endings. Unfortunately, in this case the antidepressant effect has its onset only after treatment for at least 3 weeks, moreover, about 30% of patients are therapy-resistant.

Blockade of presynaptic serotonin autoreceptors increases, by abolishing negative coupling, the serotonin release and thus the instantaneous 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 that of previously disclosed 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.

It is known that although the thiazole derivatives described in DE 3620643 have affinity for 5-HT_{1A} receptors they have no 5-HT_{1B} affinity.

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 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 rate of firing of serotonergic neurones and thus serotonin excretion (M. Skingle et al., Neuropharmacology Vol. 34, No. 4 (1995), 377 - 382, 393 - 402).



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One strategy for bypassing the autoinhibitory effects in serotonergic areas of origin thus aims at blockade of the presynaptic 5-HT_{1B} [sic] 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).

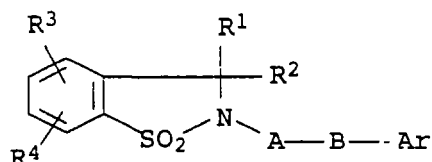
The second strategy includes blockade of both types of autoreceptors, namely the 5-HT_{1A} receptors, in order to enhance neuronal firing, and the 5-HT_{1B} receptors, in order to increase terminal serotonin release (Starkey and Skingle, Neuropharmacology 33 (3 - 4) (1994), 393).

5-HT_{1B/D} antagonists, alone or coupled to a 5-HT_{1A} receptor antagonist component, ought therefore to cause a greater increase in serotonin release in the brain and might therefore entail advantages in the therapy of depression and related psychological disorders.

20

It has now been found that 2-substituted 1,2-benzisothiazole derivatives of the formula I

25



I

30 where

R¹ and R² are, independently of one another (C₁₋₆) alkyl,

R³ and R⁴ are, independently of one another, hydrogen, (C₁₋₆) alkyl branched or unbranched, OH, O-(C₁₋₆)-alkyl branched or unbranched, F, Cl, Br, I, trifluoromethyl, NR⁵R⁶, CO₂R⁷, nitro, cyano, pyrrole, a phenylalkyl C₁-C₄ radical which in turn can be substituted on the aromatic system by F, Cl, Br, I, C₁-C₄ alkyl, C₁-C₄ alkoxy, trifluoromethyl, hydroxyl, amino, cyano or nitro ,

40

R⁵ and R⁶ are, independently of one another, hydrogen, (C₁₋₆) alkyl branched or unbranched, C₆H₅, CO₂tBu, CO-(C₁₋₄)-alkyl or together are a 5- or 6-membered ring which may contain a second nitrogen (e.g. piperazine),

45

R⁷ is hydrogen and (C₁₋₆) alkyl branched or unbranched,

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A is branched or unbranched (C₁₋₁₀)-alkylene or straight-chain or branched (C₂₋₁₀)-alkylene, which comprises at least one group Z which is selected from O, S, NR⁷, cyclopropyl, CHOH, a double or a triple bond,

5

B is 4-piperidine, 4-tetrahydro-1,2,3,6-pyridine, 4-piperazine and the corresponding cyclic compounds enlarged by one methylene group, the linkage to A taking place by one nitrogen atom of B, and

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Ar is phenyl which is unsubstituted or substituted by (C₁₋₆) alkyl branched or unbranched, O-(C₁₋₆)-alkyl branched or unbranched, OH, F, Cl, Br, I, trifluoromethyl, NR⁵R⁶, CO₂R⁷, cyano or phenyl or is tetralin, indan, fused aromatic systems such as naphthalene
15 which is unsubstituted or substituted by (C₁₋₄) alkyl or O(C₁₋₄) alkyl, or anthracene or 5- or 6-membered aromatic heterocycles having 1 or 2 heteroatoms which are selected, independently of one another, from O and N and which may also be fused to other aromatic radicals, for example quinoline, isoquinoline,
20 phthalazine, indole and quinazoline, which in turn may be substituted by phenyl,

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

25

Preferred compounds of the formula I are those where

R¹ and R² is [sic], independently of one another, methyl or ethyl,

30 R³ and R⁴ are, independently of one another, hydrogen, O-(C₁₋₄)-alkyl branched or unbranched, F, Cl, Br, trifluoromethyl, NR⁵R⁶, nitro, cyano and phenyl,

R⁵ and R⁶ are, independently of one another, hydrogen, C⁶H₅,

35 CO₂tBu, (C₁₋₆) alkyl branched or unbranched and CO-(C₁₋₄)-alkyl,

A is branched or unbranched (C₂₋₅) alkylene or straight-chain or branched (C₂₋₅) alkylene, which comprises a group Z which is selected from CHOH, cyclopropyl, a double or a triple bond,

40

B is 4-piperidine, 4-tetrahydro-1,2,3,6-pyridine, 4-piperazine or homopiperazine, the linkage to A taking place by one nitrogen atom of B, and

45 Ar is phenyl which is unsubstituted or substituted by (C₁₋₆) alkyl branched or unbranched, O-(C₁₋₆)-alkyl branched or unbranched, F, Cl, Br, I, trifluoromethyl, NR⁵R⁶, CO₂R⁷, cyano and phenyl, or

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tetralin, indan, fused aromatic systems such as naphthalene which is unsubstituted or substituted by (C₁₋₄) alkyl or O(C₁₋₄) alkyl, or anthracene and 5- or 6-membered aromatic heterocycles having 1 or 2 heteroatoms which are selected, independently of one another, from O and N, and which may be fused to other aromatic radicals.

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

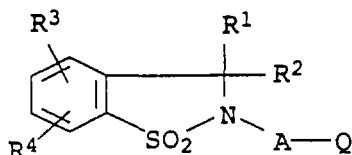
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The compounds of the formula I may have one or more centers of asymmetry. The invention therefore includes not only the racemates but also the relevant enantiomers and diastereomers. The invention also includes the respective tautomeric forms.

15

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

20



II

25 where R¹ to R⁴ and A have the meanings stated above, and Q is a group which can be eliminated (e.g. Cl, Br, I, alkanesulfonyloxy or arylsulfonyloxy), with a secondary amine of the formula III,

H-B-Ar

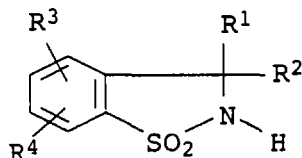
III

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where B and Ar have the meanings stated above, 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

35 the formula IV

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IV

with a compound of the formula V

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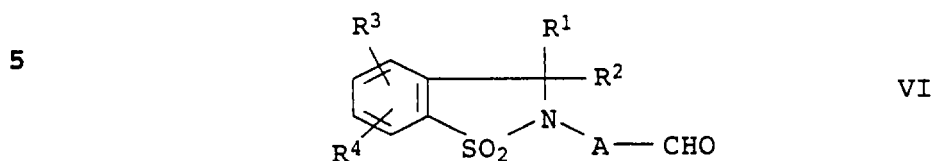
Q-A-B-Ar

V

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in a manner known per se. Another synthetic variant is linkage of a compound of the formula VI



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

Compounds of the formula III can be synthesized by

15 1. linking compounds of the formula VII



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



25 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



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 to a compound of the formula X

35



40 where W, P and Ar each have the abovementioned meanings, and the reactions are carried out 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

45 S.L. Buchwald et al. Angew. Chem. 1995, 107, 1456 or J.F.

J.F. Hartwig et al. J. Am. Chem. Soc. 1996, 118, 7217 or

J.F. Hartwig et al. J. Org. Chem. 1997, 62, 1268

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S.L. Buchwald et al. J.Org. Chem. 1997, 62, 1264 and literature cited therein or

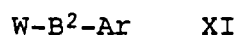
S.L. Buchwald et al J.Am. Chem. Soc 1997, 119, 6054

J.K. Stille, Angew. Chem. 1986, 98, 504 or

5 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)
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where B^2 has the meaning stated above, to compounds of the formula XII

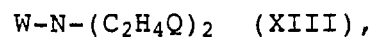
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where B^3 is piperidines linked in the 1,4 positions and the corresponding cyclic compounds enlarged by one methylene group, or
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4. cyclizing compounds of the formula XIII

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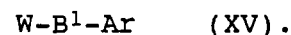
where W and Q have the meanings described above, with a compound of the formula XIV

30



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

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

Further reaction of the compounds prepared according to 1. or 4., with subsequent elimination of any protective groups,

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to give compounds of the formula V takes place by linkage to compounds of the formula XVI



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

The substances of the formulae II, IV, VI and of the formulae P-Ar, NH₂-Ar, W-B¹ and W-B²-P¹, which are required as starting materials for synthesizing the novel compounds, are known or can be synthesized from analogous precursors by processes described in the literature (e.g. B. Schulze, K. Illgen J. prakt. Chem. 1997, 339, 1 or K. Auer, E. Hungerbühler, R. W. Lang Chimia 1990, 44, 120 or A. Yokoo et al. Bull. Chem. Soc. Jpn. 1956, 29, 631 or 15 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).

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The reactions described above generally take place in an inert organic solvent, e.g. dimethylformamide, acetonitrile, dichloromethane, dimethyl sulfoxide, dimethoxyethane, toluene, ethyl acetate, xylene, a ketone such as acetone or methyl ethyl 25 ketone, an alcohol such as ethanol or n-butanol, or a cyclic saturated ether, e.g. 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 30 hours. An acid-binding agent is present if required, such as sodium or potassium carbonate, sodium methoxide, sodium ethoxide, sodium hydride, organometallic compounds (butyllithium, alkylmagnesium compounds), potassium t-butoxide, pyridine or triethylamine.

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The reactions take place where appropriate with use of a catalyst such as transition metals and complexes thereof, e.g. Pd-C, Pd(PPh₃)₄, Pd(OAc)₂, Pd(P(oTol)₃)₄, Pd₂(dba)₃ or Ni(COD)₂.

40 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 45 recrystallization from conventional organic solvents or by column chromatography.

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The invention includes not only the free 2-substituted 1,2-benzothiazole derivatives but also the addition salts of compounds of the formula I with physiologically tolerated acids. Examples of suitable physiologically tolerated organic and
5 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
10 Verlag, Basel 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, for example a lower alcohol
15 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
20 composition which comprises a compound of the formula I or its pharmacologically acceptable acid addition salt as active ingredient in addition to conventional excipients and diluents, and to the use of the novel compounds for controlling diseases.

25 The novel compounds can be administered in a conventional way orally or parenterally, intravenously or intramuscularly. 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
30 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, e.g. as uncoated or (film-)coated tablets,
35 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, bulking agents, preservatives, tablet disintegrants, flow
40 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
45 weight of active ingredient.

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The novel compounds have a high affinity for the 5HT_{1B}, 5-HT_{1D} and 5-HT_{1A} serotonin receptors. The affinity for these receptors is moreover approximately the same, at least of the same order of magnitude. Furthermore, some of the novel compounds show good 5 serotonin reuptake inhibition, which is a principle 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 as part of a treatment to block specifically the activity of the 5-HT_{1B}, 5-HT_{1A} and 5-HT_{1D} presynaptic receptors without greatly affecting the other receptors at the same time. An example of a pathological state of this type is depression.

The compounds of the present invention may also be beneficial for treating mood disturbances with a central nervous causation, such as seasonal affective disorder 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 memory loss, and psychogenic eating disorders such as anorexia nervosa and bulimia nervosa.

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

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

Example 1

3,3-Dimethyl-2-[3-(4-(5-tetralinyl)-1-piperazinyl)prop-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide

Preparation of the starting materials

a) 3,3-Dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide

This compound was prepared in a manner known from the literature (K. Auer, E. Hungerbühler, R. W. Lang Chimia 1990, 44, 120).

3,3-Diethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting point 174°C) and 3,3-dimethyl-6-nitro-2,3-dihydro-1,2-

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benzothiazole 1,1-dioxide (melting point 187°C) were obtained in a similar way.

- 5 b) 2-(3-Chloroprop-1-yl)-3,3-dimethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide

A solution of 5.9 g (3 mmol) of 3,3-dimethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide in 150 ml of DMF at room temperature was, after addition of 3.7 g (3.3 mmol) of potassium
10 t-butoxide, heated under nitrogen to 80°C. Then 14.2 g (9 mmol) of 1-bromo-3-chloropropane were rapidly added and the mixture was stirred at 100°C for 30 min. Pouring into ice-water was followed by extraction with ether, and the organic phases were washed with water, dried with sodium sulfate and then evaporated so that the
15 product resulted as crystals which could be filtered off with suction. 6.7 g (82%) of substance were obtained. Melting point 107°C.

2-(3-Chloroprop-1-yl)-3,3-diethyl-2,3-dihydro-1,2-benzothiazole
20 e 1,1-dioxide (melting point 70°C), 2-(3-chloroprop-1-yl)-3,3-dimethyl-6-nitro-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (melting point 146°C), 2-(2-chloroethyl)-3,3-diethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (oil), 2-(2-chloroethyl)-4-chloro-3,3-dimethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide
25 (oil), 2-(3-chloro-2-methyleneprop-1-yl)-3,3-dimethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (melting point 115°C) and 2-(3-chloropropyl)-3,3-dimethyl-6-nitro-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (melting point 146°C) were obtained in a similar way.

30

- c) 1-(5-Tetralinyl)piperazine

14.7 g (0.1 mol) of 5-aminotetralin were refluxed with 18 g (0.11 mol) of bis(β-chloroethyl)amine hydrochloride in 300 ml of
35 n-butanol for 48 h and, after cooling, 5.4 g of sodium carbonate were added and the mixture was refluxed for a further 20 h. The precipitate which formed 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
40 washing with water and drying over sodium sulfate were followed by evaporation under reduced pressure. It was possible in this way to isolate 10.7 g (50%) of the product as an oil.

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4-(1-Piperazinyl)isoquinoline

- 4.51 g (21.7 mmol) of 4-bromoisquinoline, 4.65 g (25.0 mmol) of t-butyl piperazine-N-carboxylate, 0.1 g (0.11 mmol) of
- 5 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
- 10 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 were obtained (melting point 111°C). 5.2 g (16.6 mmol) of this substance were taken up in 17 ml of
- 15 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
- 20 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).
- 25 The following compounds were prepared by processes similar to the two described: 1-(1-naphthyl)diazepane (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
- 30 4-(1-piperazinyl)-quinazoline (320°C, hydrochloride). Other derivatives were commercially available.

Preparation of the final product

- 35 1.1 g (5.2 mmol) of 1-(5-tetralinyl)piperazine, 1.5 ml of triethylamine and a trace of potassium iodide were added to a solution of 1.64 g (6.0 mmol) of 2-(3-chloroprop-1-yl)-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide in 40 ml of DMF. The reaction mixture was stirred at 100°C for four
- 40 hours and then poured in ice-water, and the resulting precipitate was filtered off with suction. Purification took place by recrystallization from isopropanol to result in 1 g (43%) of the product (melting point 140°C).

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NMR: CDCl₃ δ 7.8 (d, 1H), 7.6 (dd, 1H), 7.5 (dd, 1H), 7.4 (d, 1H), 7.1 (dd, 1H), 6.9 (d, 1H), 6.8 (d, 1H), 3.4 (t, 2H), 3.0-2.5 (m, 14H), 2.1 (tt, 2H), 1.8-1.7 (m, 4H), 1.5 (s, 6H) ppm.

5 The following compounds were obtained in a similar way:

Example 2: 3,3-Dimethyl-2-[3-(4-(2-phenyl-4-quinazolinyl)-1-piperazinyl)prop-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting point 269°C, hydrochloride).

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Example 3: 3,3-Dimethyl-2-[3-(4-(2-quinolinyl)-1-piperazinyl)-prop-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting point 63°C).

15 Example 4: 3,3-Dimethyl-2-[3-(4-(1-naphthyl)-1-diazepanyl)-prop-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting point 126°C, hydrochloride).

Example 5: 3,3-Dimethyl-2-[3-(4-(4-chloro-1-phthalazinyl)-1-piperazinyl)-eth-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting point 190°C).

20

Example 6: 3,3-Dimethyl-2-[3-(4-(1-naphthyl)-1-piperazinyl)-2-methyleneprop-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting point 193°C).

25

Example 7: 3,3-Dimethyl-2-[2-(4-(4-quinazolinyl)-1-piperazinyl)-eth-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting point 178°C, hydrochloride).

30

Example 8: 3,3-Dimethyl-2-[2-(4-(1-naphthyl)-1-piperazinyl)-eth-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting point 282°C, hydrochloride).

35 Example 9: 3,3-Dimethyl-2-[2-(4-isoquinolin-4-yl)-1-piperazinyl)-eth-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting point 243°C, hydrochloride).

Example 10: 3,3-Diethyl-2-[2-(4-(1-naphthyl)-1-piperazinyl)-eth-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (oil).

Example 11: 3,3-Dimethyl-2-[3-(4-(1-naphthyl)-1-piperazinyl)-prop-1-yl]-6-(1-pyrrolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting point 269°C, hydrochloride).

40

45 The pyrrole ring was assembled by reacting 3,3-dimethyl-2-[3-(4-(1-naphthyl)-1-piperazinyl)prop-1-yl]-6-amino-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide with

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2,5-dimethoxytetrahydrofuran in glacial acetic acid at 100°C (1h)
in 86% yield.

Example 12: 3,3-Dimethyl-2-[3-(4-(1-naphthyl)-1-piperazinyl)-
5 prop-1-yl]-6-benzoylamido-2,3-dihydro-1,2-benzisothiazole
1,1-dioxide (melting point 127°C).

Example 13: 3,3-Dimethyl-2-[3-(4-(1-naphthyl)-1-piperazinyl)-
prop-1-yl]-6-nitro-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide
10 (melting point 203°C).

Example 14: 3,3-Dimethyl-2-[2-(4-(2,3-dimethylphenyl)-1-
piperazinyl)eth-1-yl]-2,3-dihydro-1,2-benzisothiazole
1,1-dioxide (melting point 291°C, hydrochloride).

15 Example 15: 3,3-Dimethyl-2-[2-(4-(4-indanyl)-1-piperazinyl)-
eth-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting
point 271°C, hydrochloride).

20 Example 16: 3,3-Dimethyl-2-[3-(4-(4-chloro-1-naphthyl)-1-
piperazinyl)prop-1-yl]-2,3-dihydro-1,2-benzisothiazole
1,1-dioxide (melting point 151°C).

Example 17: 3,3-Dimethyl-2-[3-(4-(2-pyrimidinyl)-1-piperazinyl)-
25 prop-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting
point 263°C, hydrochloride).

Example 18: 3,3-Dimethyl-2-[2-(4-(4-methoxyphenyl)-1-
piperazinyl)eth-1-yl]-2,3-dihydro-1,2-benzisothiazole
30 1,1-dioxide (melting point 207°C, hydrochloride).

Example 19: 3,3-Dimethyl-2-[3-(4-(2-methoxyphenyl)-1-
piperazinyl)-2-hydroxy-prop-1-yl]-2,3-dihydro-1,2-benziso-
thiazole 1,1-dioxide (melting point 160°C).

35 Example 20: 3,3-Diethyl-2-[3-(4-(1-naphthyl)-1-piperazinyl)-
prop-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (melting
point 179°C).

40 Example 21: 3,3-Dimethyl-2-[3-(4-(2,5-dimethylphenyl)-1-
piperazinyl)prop-1-yl]-2,3-dihydro-1,2-benzisothiazole
1,1-dioxide (melting point 218°C, hydrochloride).

Example 22: 3,3-Dimethyl-2-[2-(4-(2-cyanophenyl)-1-
45 piperazinyl)eth-1-yl]-2,3-dihydro-1,2-benzisothiazole
1,1-dioxide (melting point 228°C, hydrochloride).

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Example 23: 3,3-Dimethyl-2-[2-(4-(1-naphthyl)-1-piperazinyl)-eth-1-yl]-4-chloro-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide.

Preparation of the starting materials

5

a) 4-Chloro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide. This compound was prepared as in Example 1 a). Yield 7.8 g (70%). (Melting point 121°C)

10 b) 2-(2,2-Diethoxyeth-1-yl)-4-chloro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide

7.7 g (33 mmol) of 4-chloro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide, 8.25 ml (55 mmol) of bromoacetaldehyde diethyl acetal and 7.0 g of potassium carbonate were taken up in 100 ml of dry DMF and stirred at 120°C for 5 h. The reaction mixture was poured into ice-water and then extracted with ethyl acetate, and the organic phase was washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure, the crude product was purified by column chromatography. 7.5 g (65%) of the product were obtained as an oil in this way.

20 c) 2-(2-Oxoeth-1-yl)-4-chloro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide

7.5 g (21.5 mmol) of 2-(2,2-diethoxyeth-1-yl)-4-chloro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide and 25 ml of concentrated hydrochloric acid were taken up in 25 ml of water and 150 ml of THF and stirred at 40°C for 1.5 h [sic]. The reaction mixture was neutralized with sodium hydroxide solution and extracted with ether, and the organic phase was dried over sodium sulfate and concentrated under reduced pressure. 5.8 g (98%) of the product were isolated as oil in this way.

Preparation of the final product

1.5 g (5.5 mmol) of the aldehyde 24 c), 1.06 g (5 mmol) of naphthylpiperazine (prepared as in Example 1 c)) and 0.42 g (7 mmol) of glacial acetic acid in 50 ml of ethanol were stirred at room temperature for 30 min and then 0.5 g (8 mmol) of sodium cyanoborohydride was slowly added. The mixture was stirred at room temperature for 2 h and then poured into an ice/salt mixture and extracted with dichloromethane. Drying with sodium sulfate, removal of the solvent by distillation and subsequent

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recrystallization from ethanol resulted in 0.9 g (39%) of colorless crystals (melting point 156°C).

NMR:CDCl₃ δ = 8.3 (m, 1H), 7.8 (m, 1H), 7.7 (d, 1H), 7.6 - 7.3 (m, 5 6H), 7.1 (d, 1H), 3.5 (t, 2H), 3.2 (m, 4H), 3.0 - 2.8 (m, 6H), 1.8 (s, 6H) ppm.

Example 24

- 10 Preparation of 3,3-dimethyl-2-[2-(4-(1-naphthyl)tetrahydro-1,2,3,6-pyridin-1-yl)eth-1-yl] 2,3-dihydro-1,2-benzisothiazole 1,1-dioxide

Synthesis of the starting materials

15

- 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
 20 THF was deprotonated at -78°C with 100 ml 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 three hours at -78°C, a solution of 39.3 g (0.11 mol) of N,N,-bistrifluoromethanesulfonylaniline in 50 ml of
 25 THF was 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 NaHCO₃ solution and water and dried over sodium sulfate, and the solvent was evaporated off. The crude product was purified by
 30 flash chromatography (silica gel, mobile phase heptane/ethyl acetate = 3/1).

Yield: 20.2g (60% of theory)

¹H-NMR:(270MHz,CDCl₃ [sic]) δ = 1.4 (s, 9H); 2.4(m, 2H); 3.6 (t, 2H); 4.1 (m, 2H); 5.8 (m, 1H) ppm.

35

- 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,
 40 0.85 g (4.44 mmol) of copper(I) iodide and 2.1 g (1.77 mmol) of tetrakis(triphenyl)palladium [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 and extractive workup
 45 was carried out with water and ethyl acetate, and the residue obtained after drying over sodium sulfate and evaporation of the solvent was purified by flash chromatography (silica gel, mobile

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phase heptane/ethyl acetate = 4/1).

Yield: 8.2 g (57% of theory)

¹H-NMR (270 MHz, CDCl₃ [sic]): 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

5 (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)-3,6-dihydro-2H-

10 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).

15 d) Preparation of the final compound

1.0 g (4.1 mmol) of the compound 24c described above was

dissolved in 20 ml of methanol and, in the presence of 2.22 g

(16.8 mmol) of zinc(II) chloride, firstly 1.27g (5.3 mmol) of the

20 aldehyde described in Example 23c and then 0.5 g (8.14 mmol) of

sodium cyanoborohydride were added. After 16 h at room

temperature, workup was carried out as described, and the

resulting crude product was purified by chromatography (silica gel, mobile phase dichloromethane/methanol = 97/3). A white solid

25 was obtained by precipitating the salt with ethereal hydrochloric acid solution.

Yield: 0.9 g (47% of theory)

¹H-NMR (270 MHz, DMSO-d₆ [sic]): δ = 1.6 (m, 6H); 2.6 (m, 1H); 3.1

(m, 1H); 3.4-3.6 (m, 6H); 4.0-4.2 (m, 2H); 5.8 (sbr, 1H); 7.6-8.0

30 (m, 7H); 8.2 (d, 1H); 12.0 (s, 1H) ppm.

Example 25

Preparation of 3,3-dimethyl-2-[2-(4-(1-naphthyl)-1-

35 piperidiny]eth-1-yl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide

a) 4-(1-Naphthyl)piperidine

40 3.7 g (15.3 mmol) of 4-(1-naphthyl)-1,2,3,6-tetrahydropyridine

were dissolved in methanol and hydrogenated, with the addition of

0.8 g of palladium on carbon, with hydrogen at room temperature

for 48 h. The catalyst was filtered off, and the solvent was evaporated off.

45 Yield: 1.8 g (56% of theory)

¹H-NMR (270MHz, CDCl₃ [sic]) δ = 1.6-1.8 (m, 2H); 2.0 (m, 2H); 2.9

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(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

5

1.5 g (7.1 mmol) of the amine 25a were dissolved in 20 ml of methanol and firstly 3.8 g (28.4 mmol) of zinc chloride and 2.21 g (9.2 mmol) of the aldehyde described in Example 23c, dissolved in 15 ml of methanol, were added, and then 0.89 g (14.2
10 mmol) of sodium cyanoborohydride was added in portions. After stirring for six hours, insolubles were filtered off, and the mother liquid was concentrated and taken up in ethyl acetate. The organic phase was washed with water and saturated brine, dried over sodium sulfate, filtered and concentrated to afford a
15 yellowish oil.

Yield: 2.2 g (65% of theory)

¹H-NMR (270 MHz, CDCl₃): δ = 1.7-1.9 (m, 8H); 2.0 (m, 2H); 2.7-3.0 (m, 4H); 3.2 (m, 2H); 3.5 (m, 1H); 3.7 (t, 2H); 7.1 (d, 1H); 7.3-7.7 (m, 9H); 8.2 (d, 1H) ppm.

20

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

25

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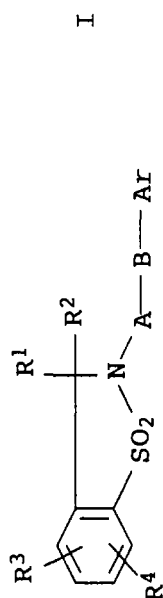
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No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
26	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Me-Ph
27	Me	H	H	/	/	/	C ₂	4-Piperazine	2-OH-Ph
28	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Br-Ph
29	Me	H	H	/	/	/	C ₂	4-Piperazine	2-CF ₃ -Ph
30	Me	H	H	/	/	/	C ₂	4-Piperazine	2-OEt-Ph
31	Me	H	H	Me	Me	/	C ₂	4-Piperazine	2-NR ⁵ R ⁶ -Ph
32	Me	H	H	/	/	/	C ₂	4-Piperazine	2-O(n-C ₄)-Ph
33	Me	H	H	/	/	/	C ₂	4-Piperazine	2-NO ₂ -Ph
34	Me	H	H	/	/	/	C ₂	4-Piperazine	2-F-Ph
35	Me	H	H	/	/	/	C ₂	4-Piperazine	2-OMe-Ph
36	Me	H	H	/	/	/	C ₂	4-Piperazine	2-CN-Ph
37	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Cl-Ph
38	Me	H	H	/	/	H	C ₂	4-Piperazine	2-CO ₂ R ⁷ -Ph
39	Me	H	H	/	/	Me	C ₂	4-Piperazine	2-CO ₂ R ⁷ -Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
40	Me	H	H	H	H	/	C ₂	4-Piperazine	2-NR ⁵ R ⁶ -Ph
41	Me	H	H	n-C ₃	n-C ₃	/	C ₂	4-Piperazine	2-NR ⁵ R ⁶ -Ph
42	Me	H	H	i-C ₃	i-C ₃	/	C ₂	4-Piperazine	2-NR ⁵ R ⁶ -Ph
43	Me	H	H	/	/	/	C ₂	4-Piperazine	2-I-Ph
44	Me	H	H	/	/	i-C ₃	C ₂	4-Piperazine	2-CO ₂ R ⁷ -Ph
45	Me	H	H	/	/	/	C ₂	4-Piperazine	Ph
46	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Et-Ph
47	Me	H	H	/	/	/	C ₂	4-Piperazine	2-iC ₃ -Ph
48	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Ph-Ph
49	Me	H	H	/	/	/	C ₂	4-Piperazine	3-tBu-Ph
50	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Et-Ph
51	Me	H	H	/	/	Et	C ₂	4-Piperazine	3-CO ₂ R ⁷ -Ph
52	Me	H	H	/	/	/	C ₂	4-Piperazine	3-I-Ph
53	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Cl-Ph
54	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Br-Ph
55	Me	H	H	/	/	/	C ₂	4-Piperazine	3-F-Ph
56	Me	H	H	/	/	/	C ₂	4-Piperazine	3-CF ₃ -Ph
57	Me	H	H	/	/	/	C ₂	4-Piperazine	3-OH-Ph
58	Me	H	H	/	/	H	C ₂	4-Piperazine	3-CO ₂ R ⁷ -Ph
59	Me	H	H	H	H	/	C ₂	4-Piperazine	3-NR ⁵ R ⁶ -Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
60	Me	H	H	Me	Me	/	C ₂	4-Piperazine	3-NR ⁵ R ⁶ -Ph
61	Me	H	H	i-C ₃	i-C ₃	/	C ₂	4-Piperazine	3-NR ⁵ R ⁶ -Ph
62	Me	H	H	/	/	/	C ₂	4-Piperazine	3-CN-Ph
63	Me	H	H	/	/	/	C ₂	4-Piperazine	3-OMe-Ph
64	Me	H	H	/	/	/	C ₂	4-Piperazine	3-NO ₂ -Ph
65	Me	H	H	/	/	/	C ₂	4-Piperazine	3-OEt-Ph
66	Me	H	H	/	/	/	C ₂	4-Piperazine	3-O(n-C ₅)Ph
67	Me	H	H	/	/	/	C ₂	4-Piperazine	4-Ph-Ph
68	Me	H	H	/	/	/	C ₂	4-Piperazine	4-iC ₃ -Ph
69	Me	H	H	/	/	/	C ₂	4-Piperazine	4-nC ₃ -Ph
70	Me	H	H	/	/	/	C ₂	4-Piperazine	4-nC ₆ -Ph
71	Me	H	H	/	/	/	C ₂	4-Piperazine	4-I-Ph
72	Me	H	H	/	/	/	C ₂	4-Piperazine	4-F-Ph
73	Me	H	H	/	/	/	C ₂	4-Piperazine	4-Br-Ph
74	Me	H	H	/	/	/	C ₂	4-Piperazine	4-Cl-Ph
75	Me	H	H	/	/	/	C ₂	4-Piperazine	4-OH-Ph
76	Me	H	H	/	/	/	C ₂	4-Piperazine	4-CN-Ph
77	Me	H	H	/	/	/	C ₂	4-Piperazine	4-CF ₃ -Ph
78	Me	H	H	/	/	/	C ₂	4-Piperazine	4-NO ₂ -Ph
79	Me	H	H	H	H	/	C ₂	4-Piperazine	4-NR ⁵ R ⁶ -Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
80	Me	H	H	Me	Me	/	C ₂	4-Piperazine	4-NR ⁵ R ⁶ -Ph
81	Me	H	H	n-C ₄	n-C ₄	/	C ₂	4-Piperazine	4-NR ⁵ R ⁶ -Ph
82	Me	H	H	Me	Et	/	C ₂	4-Piperazine	4-NR ⁵ R ⁶ -Ph
83	Me	H	H	/	/	H	C ₂	4-Piperazine	4-CO ₂ R ⁷ -Ph
84	Me	H	H	/	/	Me	C ₂	4-Piperazine	4-CO ₂ R ⁷ -Ph
85	Me	H	H	/	/	n-C ₅	C ₂	4-Piperazine	4-CO ₂ R ⁷ -Ph
86	Me	H	H	/	/	/	C ₂	4-Piperazine	4-OMe-Ph
87	Me	H	H	/	/	/	C ₂	4-Piperazine	4-OEt-Ph
88	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Cl, 4-NO ₂ -Ph
89	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Cl, 4-Me-Ph
90	Me	H	H	/	/	/	C ₂	4-Piperazine	2-CN, 6-CN-Ph
91	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Me, 6-Me-Ph
92	Me	H	H	/	/	/	C ₂	4-Piperazine	2-NO ₂ , 4-CF ₃ -Ph
93	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Cl, 4-Cl-Ph
94	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Me, 3-Me-Ph
95	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Et, 3-Et-Ph
96	Me	H	H	H	H	/	C ₂	4-Piperazine	2-NR ⁵ R ⁶ , 4-Cl-Ph
97	Me	H	H	H	H	/	C ₂	4-Piperazine	2-NR ⁵ R ⁶ , 4-Me-Ph
98	Me	H	H	Me	Me	/	C ₂	4-Piperazine	2-NR ⁵ R ⁶ , 4-Cl-Ph
99	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Me, 4-Me-Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
100	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Cl, 5-Cl-Ph
101	Me	H	H	/	/	/	C ₂	4-Piperazine	2-OMe, 4-OMe-Ph
102	Me	H	H	/	/	/	C ₂	4-Piperazine	3-tBu, 5-tBu-Ph
103	Me	H	H	/	/	/	C ₂	4-Piperazine	3-tBu, 5-CF ₃ -Ph
104	Me	H	H	/	/	/	C ₂	4-Piperazine	2-OMe, 5-Cl-Ph
105	Me	H	H	/	/	/	C ₂	4-Piperazine	2-OMe, 5-OMe-Ph
106	Me	H	H	/	/	/	C ₂	4-Piperazine	2-OMe, 5-Ph-Ph
107	Me	H	H	/	/	/	C ₂	4-Piperazine	2-OMe, 4-OMe-Ph
108	Me	H	H	/	/	/	C ₂	4-Piperazine	3-CF ₃ , 4-Cl-Ph
109	Me	H	H	/	/	/	C ₂	4-Piperazine	2-NO ₂ , 4-CF ₃ , 5-NO ₂ -Ph
110	Me	H	H	H	H	/	C ₂	4-Piperazine	2-NR ⁵ R ⁶ , 4-Me, 5-Cl-Ph
111	Me	H	H	/	/	/	C ₂	4-Piperazine	2-OMe, 3-Cl, 5-Cl-Ph
112	Me	H	H	/	/	/	C ₂	4-Piperazine	2-OMe, 4-NO ₂ , 5-Me-Ph
113	Me	H	H	/	/	/	C ₂	4-Piperazine	2-OMe, 4-Cl, 5-Me-Ph
114	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Me, 4-Cl, 5-CF ₃ -Ph
115	Me	H	H	/	/	/	C ₂	4-Piperazine	5-Tetralin
116	Me	H	H	/	/	/	C ₂	4-Piperazine	4-Indan
117	Me	H	H	/	/	/	C ₂	4-Piperazine	1-Tetralin
118	Me	H	H	/	/	/	C ₂	4-Piperazine	1-Indan
119	Me	H	H	/	/	/	C ₂	4-Piperazine	1-Naphthalene

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
120	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Ome-1-Naphthalene
121	Me	H	H	/	/	/	C ₂	4-Piperazine	2-OEt-1-Naphthalene
122	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Me-1-Naphthalene
123	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Et-1-Naphthalene
124	Me	H	H	/	/	/	C ₂	4-Piperazine	8-Ome-1-Naphthalene
125	Me	H	H	/	/	/	C ₂	4-Piperazine	8-Me-1-Naphthalene
126	Me	H	H	/	/	/	C ₂	4-Piperazine	9-Anthracene
127	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Indole
128	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Quinazoline
129	Me	H	H	/	/	/	C ₂	4-Piperazine	4-Quinazoline
130	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Quinoxaline
131	Me	H	H	/	/	/	C ₂	4-Piperazine	1-Phthalazine
132	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Quinoline
133	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Quinoline
134	Me	H	H	/	/	/	C ₂	4-Piperazine	4-Quinoline
135	Me	H	H	/	/	/	C ₂	4-Piperazine	5-Quinoline
136	Me	H	H	/	/	/	C ₂	4-Piperazine	1-Isoquinoline
137	Me	H	H	/	/	/	C ₂	4-Piperazine	4-Isoquinoline
138	Me	H	H	/	/	/	C ₂	4-Piperazine	8-Isoquinoline
139	Me	H	H	/	/	/	C ₂	4-Piperazine	7-Benzofuran

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
140	Me	H	H	/	/	/	C ₂	4-Piperazine	3-2H-Chromene
141	Me	H	H	/	/	/	C ₂	4-Piperazine	5-Chroman
142	Me	H	H	/	/	/	C ₂	4-Piperazine	8-Chroman
143	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Pyrimidine
144	Me	H	H	/	/	/	C ₂	4-Piperazine	2-tBu,4-CF ₃ -6-Pyrimidine
145	Me	H	H	/	/	/	C ₂	4-Piperazine	5-OMe-4-Pyrimidine
146	Me	H	H	/	/	/	C ₂	4-Piperazine	4-Pyrimidine
147	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Pyrazine
148	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Isoxazole
149	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Pyridine
150	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Pyridine
151	Me	H	H	/	/	/	C ₂	4-Piperazine	3-Pyrrole
152	Me	H	H	/	/	/	C ₂	4-Piperazine	2-Ph-4-Quinazoline
153	Me	H	H	/	/	/	C ₂	4-Piperazine	6-iC ₃ -4-Pyrimidine
154	Me	H	H	/	/	/	C ₂	4-Piperazine	7-OMe-1-Naphthalene
155	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Me-Ph
156	Me	H	H	/	/	/	C ₂	4-Piperidine	2-OH-Ph
157	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Br-Ph
158	Me	H	H	/	/	/	C ₂	4-Piperidine	2-CF ₃ -Ph
159	Me	H	H	/	/	/	C ₂	4-Piperidine	2-OEt-Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
160	Me	H	H	Me	Me	/	C ₂	4-Piperidine	2-NR ⁵ R ⁶ -Ph
161	Me	H	H	/	/	/	C ₂	4-Piperidine	2-O(n-C ₄)-Ph
162	Me	H	H	/	/	/	C ₂	4-Piperidine	2-NO ₂ -Ph
163	Me	H	H	/	/	/	C ₂	4-Piperidine	2-F-Ph
164	Me	H	H	/	/	/	C ₂	4-Piperidine	2-OMe-Ph
165	Me	H	H	/	/	/	C ₂	4-Piperidine	2-CN-Ph
166	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Cl-Ph
167	Me	H	H	/	/	H	C ₂	4-Piperidine	2-CO ₂ R ⁷ -Ph
168	Me	H	H	/	/	Me	C ₂	4-Piperidine	2-CO ₂ R ⁷ -Ph
169	Me	H	H	H	H	/	C ₂	4-Piperidine	2-NR ⁵ R ⁶ -Ph
170	Me	H	H	n-C ₃	n-C ₃	/	C ₂	4-Piperidine	2-NR ⁵ R ⁶ -Ph
171	Me	H	H	i-C ₃	i-C ₃	/	C ₂	4-Piperidine	2-NR ⁵ R ⁶ -Ph
172	Me	H	H	/	/	/	C ₂	4-Piperidine	2-I-Ph
173	Me	H	H	/	/	i-C ₃	C ₂	4-Piperidine	2-CO ₂ R ⁷ -Ph
174	Me	H	H	/	/	/	C ₂	4-Piperidine	Ph
175	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Et-Ph
176	Me	H	H	/	/	/	C ₂	4-Piperidine	2-iC ₃ -Ph
177	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Ph-Ph
178	Me	H	H	/	/	/	C ₂	4-Piperidine	3-tBu-Ph
179	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Et-Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
180	Me	H	H	/	/	Et	C ₂	4-Piperidine	3-CO ₂ R ⁷ -Ph
181	Me	H	H	/	/	/	C ₂	4-Piperidine	3-I-Ph
182	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Cl-Ph
183	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Br-Ph
184	Me	H	H	/	/	/	C ₂	4-Piperidine	3-F-Ph
185	Me	H	H	/	/	/	C ₂	4-Piperidine	3-CF ₃ -Ph
186	Me	H	H	/	/	/	C ₂	4-Piperidine	3-OH-Ph
187	Me	H	H	/	/	H	C ₂	4-Piperidine	3-CO ₂ R ⁷ -Ph
188	Me	H	H	H	H	/	C ₂	4-Piperidine	3-NR ⁵ R ⁶ -Ph
189	Me	H	H	Me	Me	/	C ₂	4-Piperidine	3-NR ⁵ R ⁶ -Ph
190	Me	H	H	i-C ₃	i-C ₃	/	C ₂	4-Piperidine	3-NR ⁵ R ⁶ -Ph
191	Me	H	H	/	/	/	C ₂	4-Piperidine	3-CN-Ph
192	Me	H	H	/	/	/	C ₂	4-Piperidine	3-OMe-Ph
193	Me	H	H	/	/	/	C ₂	4-Piperidine	3-NO ₂ -Ph
194	Me	H	H	/	/	/	C ₂	4-Piperidine	3-OEt-Ph
195	Me	H	H	/	/	/	C ₂	4-Piperidine	3-O(n-C ₅)Ph
196	Me	H	H	/	/	/	C ₂	4-Piperidine	4-Ph-Ph
197	Me	H	H	/	/	/	C ₂	4-Piperidine	4-iC ₃ -Ph
198	Me	H	H	/	/	/	C ₂	4-Piperidine	4-nC ₃ -Ph
199	Me	H	H	/	/	/	C ₂	4-Piperidine	4-nC ₆ -Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
200	Me	H	H	/	/	/	C ₂	4-Piperidine	4-I-Ph
201	Me	H	H	/	/	/	C ₂	4-Piperidine	4-F-Ph
202	Me	H	H	/	/	/	C ₂	4-Piperidine	4-Br-Ph
203	Me	H	H	/	/	/	C ₂	4-Piperidine	4-Cl-Ph
204	Me	H	H	/	/	/	C ₂	4-Piperidine	4-OH-Ph
205	Me	H	H	/	/	/	C ₂	4-Piperidine	4-CN-Ph
206	Me	H	H	/	/	/	C ₂	4-Piperidine	4-CF ₃ -Ph
207	Me	H	H	/	/	/	C ₂	4-Piperidine	4-NO ₂ -Ph
208	Me	H	H	/	/	/	C ₂	4-Piperidine	4-NR ⁵ R ⁶ -Ph
209	Me	H	H	Me	Me	/	C ₂	4-Piperidine	4-NR ⁵ R ⁶ -Ph
210	Me	H	H	n-C ₄	n-C ₄	/	C ₂	4-Piperidine	4-NR ⁵ R ⁶ -Ph
211	Me	H	H	Me	Et	/	C ₂	4-Piperidine	4-NR ⁵ R ⁶ -Ph
212	Me	H	H	/	/	H	C ₂	4-Piperidine	4-CO ₂ R ⁷ -Ph
213	Me	H	H	/	/	Me	C ₂	4-Piperidine	4-CO ₂ R ⁷ -Ph
214	Me	H	H	/	/	n-C ₅	C ₂	4-Piperidine	4-CO ₂ R ⁷ -Ph
215	Me	H	H	/	/	/	C ₂	4-Piperidine	4-OMe-Ph
216	Me	H	H	/	/	/	C ₂	4-Piperidine	4-OEt-Ph
217	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Cl, 4-NO ₂ -Ph
218	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Cl, 4-Me-Ph
219	Me	H	H	/	/	/	C ₂	4-Piperidine	2-CN, 6-CN-Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
220	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Me, 6-Me-Ph
221	Me	H	H	/	/	/	C ₂	4-Piperidine	2-NO ₂ , 4-CF ₃ -Ph
222	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Cl, 4-Cl-Ph
223	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Me, 3-Me-Ph
224	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Et, 3-Et-Ph
225	Me	H	H	H	H	/	C ₂	4-Piperidine	2-NR ⁵ R ⁶ , 4-Cl-Ph
226	Me	H	H	H	H	/	C ₂	4-Piperidine	2-NR ⁵ R ⁶ , 4-Cl-Ph
227	Me	H	H	Me	Me	/	C ₂	4-Piperidine	2-NR ⁵ R ⁶ , 4-Cl-Ph
228	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Me, 4-Me-Ph
229	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Cl, 5-Cl-Ph
230	Me	H	H	/	/	/	C ₂	4-Piperidine	2-OMe, 4-OMe-Ph
231	Me	H	H	/	/	/	C ₂	4-Piperidine	3-tBu, 5-tBu-Ph
232	Me	H	H	/	/	/	C ₂	4-Piperidine	3-tBu, 5-CF ₃ -Ph
233	Me	H	H	/	/	/	C ₂	4-Piperidine	2-OMe, 5-Cl-Ph
234	Me	H	H	/	/	/	C ₂	4-Piperidine	2-OMe, 5-OMe-Ph
235	Me	H	H	/	/	/	C ₂	4-Piperidine	2-OMe, 5-Ph-Ph
236	Me	H	H	/	/	/	C ₂	4-Piperidine	3-OMe, 4-OMe-Ph
237	Me	H	H	/	/	/	C ₂	4-Piperidine	3-CF ₃ , 4-Cl-Ph
238	Me	H	H	/	/	/	C ₂	4-Piperidine	2-NO ₂ , 4-CF ₃ , 5-NO ₂ -Ph
239	Me	H	H	H	H	/	C ₂	4-Piperidine	2-NR ⁵ R ⁶ , 4-Me, 5-Cl-Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
240	Me	H	H	/	/	/	C ₂	4-Piperidine	2-OMe, 3-Cl, 5-Cl-Ph
241	Me	H	H	/	/	/	C ₂	4-Piperidine	2-OMe, 4-NO ₂ , 5-Me-Ph
242	Me	H	H	/	/	/	C ₂	4-Piperidine	2-OMe, 4-Cl, 5-Me-Ph
243	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Me, 4-Cl, 5-CF ₃ -Ph
244	Me	H	H	/	/	/	C ₂	4-Piperidine	5-Tetralin
245	Me	H	H	/	/	/	C ₂	4-Piperidine	4-Indan
246	Me	H	H	/	/	/	C ₂	4-Piperidine	1-Tetralin
247	Me	H	H	/	/	/	C ₂	4-Piperidine	1-Indan
248	Me	H	H	/	/	/	C ₂	4-Piperidine	1-Naphthalene
249	Me	H	H	/	/	/	C ₂	4-Piperidine	2-OMe-1-Naphthalene
250	Me	H	H	/	/	/	C ₂	4-Piperidine	2-OEt-1-Naphthalene
251	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Me-1-Naphthalene
252	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Et-1-Naphthalene
253	Me	H	H	/	/	/	C ₂	4-Piperidine	8-OMe-1-Naphthalene
254	Me	H	H	/	/	/	C ₂	4-Piperidine	8-Me-1-Naphthalene
255	Me	H	H	/	/	/	C ₂	4-Piperidine	9-Anthracene
256	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Indole
257	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Quinazoline
258	Me	H	H	/	/	/	C ₂	4-Piperidine	4-Quinazoline
259	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Quinoxaline

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
260	Me	H	H	/	/	(	C ₂	4-Piperidine	1-Phthalazine
261	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Quinoline
262	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Quinoline
263	Me	H	H	/	/	/	C ₂	4-Piperidine	4-Quinoline
264	Me	H	H	/	/	/	C ₂	4-Piperidine	5-Quinoline
265	Me	H	H	/	/	/	C ₂	4-Piperidine	1-Isoquinoline
266	Me	H	H	/	/	/	C ₂	4-Piperidine	4-Isoquinoline
267	Me	H	H	/	/	/	C ₂	4-Piperidine	8-Isoquinoline
268	Me	H	H	/	/	/	C ₂	4-Piperidine	7-Benzofuran
269	Me	H	H	/	/	/	C ₂	4-Piperidine	3-2H-Chromene
270	Me	H	H	/	/	/	C ₂	4-Piperidine	5-Chroman
271	Me	H	H	/	/	/	C ₂	4-Piperidine	8-Chroman
272	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Pyrimidine
273	Me	H	H	/	/	/	C ₂	4-Piperidine	2-tBu,4-CF ₃ -6-Pyrimidine
274	Me	H	H	/	/	/	C ₂	4-Piperidine	5-OMe-4-Pyrimidine
275	Me	H	H	/	/	/	C ₂	4-Piperidine	4-Pyrimidine
276	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Pyrazine
277	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Isoxazole
278	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Pyridine
279	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Pyridine

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
280	Me	H	H	/	/	/	C ₂	4-Piperidine	3-Pyrrole
281	Me	H	H	/	/	/	C ₂	4-Piperidine	2-Ph-4-Quinazoline
282	Me	H	H	/	/	/	C ₂	4-Piperidine	6-iC ₃ -4-Pyrimidine
283	Me	H	H	/	/	/	C ₂	4-Piperidine	7-OMe-1-Naphthalene
284	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Me-Ph
285	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OH-Ph
286	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Br-Ph
287	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-CF ₃ -Ph
288	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OEt-Ph
289	Me	H	H	Me	Me	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-NR ⁵ R ⁶ -Ph
290	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-O(n-C ₄)-Ph
291	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-NO ₂ -Ph
292	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-F-Ph
293	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OMe-Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
294	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-CN-Ph
295	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Cl-Ph
296	Me	H	H	/	/	H	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-CO ₂ R ⁷ -Ph
297	Me	H	H	/	/	Me	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-CO ₂ R ⁷ -Ph
298	Me	H	H	H	H	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-NR ⁵ R ⁶ -Ph
299	Me	H	H	n-C ₃	n-C ₃	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-NR ⁵ R ⁶ -Ph
300	Me	H	H	i-C ₃	i-C ₃	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-NR ⁵ R ⁶ -Ph
301	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-I-Ph
302	Me	H	H	/	/	i-C ₃	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-CO ₂ R ⁷ -Ph
303	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	Ph
304	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Et-Ph
305	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-iC ₃ -Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
306	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Ph-Ph
307	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-tBu-Ph
308	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Et-Ph
309	Me	H	H	/	/	Et	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-CO ₂ R ⁷ -Ph
310	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-I-Ph
311	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Cl-Ph
312	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Br-Ph
313	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-F-Ph
314	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-CF ₃ -Ph
315	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-OH-Ph
316	Me	H	H	/	/	H	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-CO ₂ R ⁷ -Ph
317	Me	H	H	H	H	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-NR ⁵ R ⁶ -Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
318	Me	H	H	Me	Me	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-NR ⁵ R ⁶ -Ph
319	Me	H	H	i-C ₃	i-C ₃	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-NR ⁵ R ⁶ -Ph
320	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-CN-Ph
321	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-OMe-Ph
322	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-NO ₂ -Ph
323	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-OEt-Ph
324	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-O(n-C ₅)Ph
325	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-Ph-Ph
326	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-iC ₃ -Ph
327	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-nC ₃ -Ph
328	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-nC ₆ -Ph
329	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-I-Ph

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No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
330	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-F-Ph
331	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-Br-Ph
332	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-Cl-Ph
333	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-OH-Ph
334	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-CN-Ph
335	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-CF ₃ -Ph
336	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-NO ₂ -Ph
337	Me	H	H	H	H	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-NR ⁵ R ⁶ -Ph
338	Me	H	H	Me	Me	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-NR ⁵ R ⁶ -Ph
339	Me	H	H	n-C ₄	n-C ₄	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-NR ⁵ R ⁶ -Ph
340	Me	H	H	Me	Me	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-NR ⁵ R ⁶ -Ph
341	Me	H	H	/	/	H	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-CO ₂ R ⁷ -Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
342	Me	H	H	/	/	Me	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-CO ₂ R ⁷ -Ph
343	Me	H	H	/	/	n-C ₅	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-CO ₂ R ⁷ -Ph
344	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-OMe-Ph
345	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-OEt-Ph
346	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Cl,2,3,6-NO ₂ -Ph
347	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Cl,2,3,6-Me-Ph
348	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-CN,6-CN-Ph
349	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Me,6-Me-Ph
350	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-NO ₂ ,2,3,6-CF ₃ -Ph
351	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Cl,2,3,6-Cl-Ph
352	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Me,3-Me-Ph
353	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Et,3-Et-Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
354	Me	H	H	H	H	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-NR ⁵ R ⁶ ,2,3,6-Cl-Ph
355	Me	H	H	H	H	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-NR ⁵ R ⁶ ,2,3,6-Me-Ph
356	Me	H	H	Me	Me	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-NR ⁵ R ⁶ ,2,3,6-Cl-Ph
357	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Me,2,3,6-Me-Ph
358	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Cl,5-Cl-Ph
359	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OMe,2,3,6-OMe-Ph
360	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-tBu,5-tBu-Ph
361	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-tBu,5-CF ₃ -Ph
362	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OMe,5-Cl-Ph
363	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OMe,5-OMe-Ph
364	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OMe,5-Ph-Ph
365	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OMe,2,3,6-OMe-Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
366	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-CF ₃ ,2,3,6-Cl-Ph
367	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-NO ₂ ,2,3,6-CF ₃ ,5-NO ₂ -Ph
368	Me	H	H	H	H	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-NR ⁵ R ⁶ ,2,3,6-Me,5-Cl-Ph
369	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OMe,3-Cl,5-Cl-Ph
370	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OMe,2,3,6-NO ₂ ,5-Me-Ph
371	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OMe,2,3,6-Cl,5-Me-Ph
372	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Me,2,3,6-Cl,5-CF ₃ -Ph
373	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-Tetraline
374	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-Indan
375	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	1-Tetralin
376	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	1-Indan
377	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	1-Naphthalene

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
378	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OMe-1-Naphthalene
379	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-OEt-1-Naphthalene
380	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Me-1-Naphthalene
381	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Et-1-Naphthalene
382	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	8-OMe-1-Naphthalene
383	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	8-Me-1-Naphthalene
384	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	9-Anthracene
385	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Indole
386	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Quinazoline
387	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-Quinazoline
388	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Quinoxaline
389	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	1-Phthalazine

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
390	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Quinoline
391	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Quinoline
392	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-Quinoline
393	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	5-Quinoline
394	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	1-Isoquinoline
395	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-Isoquinoline
396	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	8-Isoquinoline
397	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	7 Benzoferan [sic]
398	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-2H-Chromene
399	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	5-Chroman
400	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	8-Chroman
401	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Pyrimidine

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
402	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-tBu,2,3,6-CF ₃ -6-pyrimidine
403	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	5-OMe-4-Pyrimidine
404	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	4-Pyrimidine
405	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Pyrazine
406	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Isioxazole
407	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Pyridine
408	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Pyridine
409	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	3-Pyrrole
410	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	2-Ph-4-Quinazoline
411	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	6-iC ₃ -4-Pyrimidine
412	Me	H	H	/	/	/	C ₂	4-Tetrahydro-1,2,3,6-pyridine	7-OMe-1-Naphthalene

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
413	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-Me-Ph
414	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-OH-Ph
415	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-Br-Ph
416	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-CF ₃ -Ph
417	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-OMe-Ph
418	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-CN-Ph
419	Me	H	H	/	/	/	C ₂	4-Homopiperazine	Ph
420	Me	H	H	H	H	/	C ₂	4-Homopiperazine	2-NR ⁵ R ⁶ -Ph
421	Me	H	H	Me	Me	/	C ₂	4-Homopiperazine	2-NR ⁵ R ⁶ -Ph
422	Me	H	H	/	/	H	C ₂	4-Homopiperazine	2-CO ₂ R ⁷ -Ph
423	Me	H	H	/	/	Me	C ₂	4-Homopiperazine	2-CO ₂ R ⁷ -Ph
424	Me	H	H	/	/	/	C ₂	4-Homopiperazine	3-tBu-Ph
425	Me	H	H	/	/	/	C ₂	4-Homopiperazine	3-Me-Ph
426	Me	H	H	/	/	/	C ₂	4-Homopiperazine	3-CF ₃ -Ph
427	Me	H	H	/	/	/	C ₂	4-Homopiperazine	3-Cl-Ph
428	Me	H	H	/	/	/	C ₂	4-Homopiperazine	3-OMe-Ph
429	Me	H	H	/	/	/	C ₂	4-Homopiperazine	4-NO ₂ -Ph
430	Me	H	H	/	/	/	C ₂	4-Homopiperazine	4-Ph-Ph
431	Me	H	H	/	/	/	C ₂	4-Homopiperazine	4-F-Ph
432	Me	H	H	/	/	/	C ₂	4-Homopiperazine	3-Cl, 4-Me Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
433	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-Me,6-Me Ph
434	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-Me,3-Me Ph
435	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-Et,3,-Et Ph
436	Me	H	H	/	/	/	C ₂	4-Homopiperazine	3t-Bu,5-CF ₃ Ph
437	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-OMe,5-Ph Ph
438	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-OMe,4-Cl,5-Me Ph
439	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-Me,4-Cl,5-CF ₃ Ph
440	Me	H	H	/	/	/	C ₂	4-Homopiperazine	5-Tetralin
441	Me	H	H	/	/	/	C ₂	4-Homopiperazine	4-Indan
442	Me	H	H	/	/	/	C ₂	4-Homopiperazine	1-Naphthalene
443	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-OMe-1-Naphthalene
444	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-Me-1-Naphthalene
445	Me	H	H	/	/	/	C ₂	4-Homopiperazine	7-OMe-1-Naphthalene
446	Me	H	H	/	/	/	C ₂	4-Homopiperazine	8-Me-1-Naphthalene
447	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-Quinazoline
448	Me	H	H	/	/	/	C ₂	4-Homopiperazine	3-Indole
449	Me	H	H	/	/	/	C ₂	4-Homopiperazine	1-Phthalazine
450	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-Quinoline
451	Me	H	H	/	/	/	C ₂	4-Homopiperazine	1-Isoquinoline
452	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-Pyrimidine

NO	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
453	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-tBu,4-CF ₃ -6-Pyrimidine
454	Me	H	H	/	/	/	C ₂	4-Homopiperazine	2-Pyridine
455	Me	H	H	/	/	/	C ₂	Azepan	2-Me-Ph
456	Me	H	H	/	/	/	C ₂	Azepan	Ph
457	Me	H	H	/	/	/	C ₂	Azepan	2-OMe-Ph
458	Me	H	H	/	/	/	C ₂	Azepan	2-Cl-Ph
459	Me	H	H	H	H	/	C ₂	Azepan	2-NR ⁵ R ⁶ Ph
460	Me	H	H	/	/	Me	C ₂	Azepan	2-CO ₂ R ⁷ Ph
461	Me	H	H	/	/	/	C ₂	Azepan	3-tBu Ph
462	Me	H	H	/	/	/	C ₂	Azepan	4-Ph-Ph
463	Me	H	H	/	/	/	C ₂	Azepan	2-Me,3-Me-Ph
464	Me	H	H	/	/	/	C ₂	Azepan	2-Me,4-Cl,5-CF ₃ Ph
465	Me	H	H	/	/	/	C ₂	Azepan	4-Tetralin
466	Me	H	H	/	/	/	C ₂	Azepan	4-Indan
467	Me	H	H	/	/	/	C ₂	Azepan	1-Naphthalene
468	Me	H	H	/	/	/	C ₂	Azepan	2-OMe-1-Naphthalene
469	Me	H	H	/	/	/	C ₂	Azepan	2-Pyrimidine
470	Me	H	H	/	/	/	C ₂	Azepan	2-Quinoline
471	Me	H	H	/	/	/	C ₂	Azepan	1-Phthalazine
472	Me	H	H	/	/	/	C ₂	Azepan	2-tBu,4-CF ₃ -6-Pyrimidine

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
473	Me	H	H	/	/	/	C ₂		2-Pyridine
474	Me	H	H	/	/	/	C ₂	Azepan	4-NO ₂ -Ph
475	Me	H	H	/	/	/	C ₂	Azepan	2-OH-Ph
476	Me	H	H	/	/	/	C ₂	Tetrahydro-2H-azepine	2-Me-Ph
477	Me	H	H	/	/	/	C ₂	Tetrahydro-2H-azepine	Ph
478	Me	H	H	/	/	/	C ₂	Tetrahydro-2H-azepine	2-OMe-Ph
479	Me	H	H	/	/	/	C ₂	Tetrahydro-2H-azepine	2-Cl-Ph
480	Me	H	H	H	H	/	C ₂	Tetrahydro-2H-azepine	2-NR ⁵ R ⁶ -Ph
481	Me	H	H	/	/	Me	C ₂	Tetrahydro-2H-azepine	2-CO ₂ R ⁷ -Ph
482	Me	H	H	/	/	/	C ₂	Tetrahydro-2H-azepine	3-tBu-Ph
483	Me	H	H	/	/	/	C ₂	Tetrahydro-2H-azepine	4-Ph-Ph
484	Me	H	H	/	/	/	C ₂	Tetrahydro-2H-azepine	2-Me, 3-Me-Ph
485	Me	H	H	/	/	/	C ₂	Tetrahydro-2H-azepine	2-Me, 4-Cl, 5-CF ₃ Ph
486	Me	H	H	/	/	/	C ₂	Tetrahydro-2H-azepine	5-Tetralin

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
487	Me	H	H	/	/	/	C ₂	Tetrahydro- 2H-azepine	4-Indan
488	Me	H	H	/	/	/	C ₂	Tetrahydro- 2H-azepine	1-Naphthalene
489	Me	H	H	/	/	/	C ₂	Tetrahydro- 2H-azepine	2-OMe-1-Naphthalene
490	Me	H	H	/	/	/	C ₂	Tetrahydro- 2H-azepine	2-Pyrimidine
491	Me	H	H	/	/	/	C ₂	Tetrahydro- 2H-azepine	2-Quinoline
492	Me	H	H	/	/	/	C ₂	Tetrahydro- 2H-azepine	1-Phthalazine
493	Me	H	H	/	/	/	C ₂	Tetrahydro- 2H-azepine	2-tBu, 4-CF ₃ -6- Pyrimidine
494	Me	H	H	/	/	/	C ₂	Tetrahydro- 2H-azepine	2-Pyridine
495	Me	H	H	/	/	/	C ₂	Tetrahydro- 2H-azepine	4-NO ₂ -Ph
496	Me	H	H	/	/	/	C ₂	Tetrahydro- 2H-azepine	2-OH-Ph
497	Me	H	H	/	/	/	C ₃	Piperazine	2-Me-Ph
498	Me	H	H	/	/	/	C ₃	Piperazine	2-OMe-Ph
499	Me	H	H	H	H	/	C ₃	Piperazine	2-NR ⁵ R ⁶ -Ph
500	Me	H	H	/	/	Me	C ₃	Piperazine	2-CO ₂ R ⁷ -Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
501	Me	H	H	/	/	/	C ₃	Piperazine	3-tBu-Ph
502	Me	H	H	/	/	/	C ₃	Piperazine	2-Me, 3-Me-Ph
503	Me	H	H	/	/	/	C ₃	Piperazine	5-Tetralin
504	Me	H	H	/	/	/	C ₃	Piperazine	4-Indan
505	Me	H	H	/	/	/	C ₃	Piperazine	1-Naphthalene
506	Me	H	H	/	/	/	C ₃	Piperazine	2-Me-1-Naphthalene
507	Me	H	H	/	/	/	C ₃	Piperazine	2-Pyrimidine
508	Me	H	H	/	/	/	C ₃	Piperazine	1-Phthalazine
509	Me	H	H	/	/	/	C ₃	Piperidine	2-Me-Ph
510	Me	H	H	/	/	/	C ₃	Piperidine	2-OMe-Ph
511	Me	H	H	H	H	/	C ₃	Piperidine	2-NR ⁵ R ⁶ -Ph
512	Me	H	H	/	/	Me	C ₃	Piperidine	2-CO ₂ R ⁷ -Ph
513	Me	H	H	/	/	/	C ₃	Piperidine	3-tBu-Ph
514	Me	H	H	/	/	/	C ₃	Piperidine	2-Me, 3-Me-Ph
515	Me	H	H	/	/	/	C ₃	Piperidine	5-Tetralin
516	Me	H	H	/	/	/	C ₃	Piperidine	4-Indan
517	Me	H	H	/	/	/	C ₃	Piperidine	1-Naphthalene
518	Me	H	H	/	/	/	C ₃	Piperidine	2-Me-1-Naphthalene
519	Me	H	H	/	/	/	C ₃	Piperidine	2-Pyrimidine
520	Me	H	H	/	/	/	C ₃	Piperidine	1-Phthalazine

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
521	Me	H	H	/	/	/	C ₃	4-Tetrahydro-1,2,3,6-pyridine	2-Me-Ph
522	Me	H	H	/	/	/	C ₃	4-Tetrahydro-1,2,3,6-pyridine	2-OMe-Ph
523	Me	H	H	H	H	/	C ₃	4-Tetrahydro-1,2,3,6-pyridine	2-NR ⁵ R ⁶ -Ph
524	Me	H	H	/	/	Me	C ₃	4-Tetrahydro-1,2,3,6-pyridine	2-CO ₂ R ⁷ -Ph
525	Me	H	H	/	/	/	C ₃	4-Tetrahydro-1,2,3,6-pyridine	3-tBu-Ph
526	Me	H	H	/	/	/	C ₃	4-Tetrahydro-1,2,3,6-pyridine	2-Me,3-Me-Ph
527	Me	H	H	/	/	/	C ₃	4-Tetrahydro-1,2,3,6-pyridine	5-Tetralin
528	Me	H	H	/	/	/	C ₃	4-Tetrahydro-1,2,3,6-pyridine	4-Indan
529	Me	H	H	/	/	/	C ₃	4-Tetrahydro-1,2,3,6-pyridine	1-Naphthalene
530	Me	H	H	/	/	/	C ₃	4-Tetrahydro-1,2,3,6-pyridine	2-Me-1-Naphthalene
531	Me	H	H	/	/	/	C ₃	4-Tetrahydro-1,2,3,6-pyridine	2-Pyrimidine
532	Me	H	H	/	/	/	C ₃	4-Tetrahydro-1,2,3,6-pyridine	1-Phthalazine
533	Me	H	H	/	/	/	C ₃	Homopiperazine	2-Me-Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
534	Me	H	H	/	/	/	C ₃	Homopiperazine	2-Me, 3-Me-Ph
535	Me	H	H	/	/	/	C ₃	Homopiperazine	5-Tetralin
536	Me	H	H	/	/	/	C ₃	Homopiperazine	1-Naphthalene
537	Me	H	H	/	/	/	C ₃	Homopiperazine	2-Me-1-Naphthalene
538	Me	H	H	/	/	/	C ₃	Homopiperazine	2-Pyrimidine
539	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperazine	2-Me-Ph
540	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperazine	2-Me, 3-Me-Ph
541	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperazine	5-Tetralin
542	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperazine	1-Naphthalene
543	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperazine	2-OMe-1-Naphthalene
544	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperazine	2-Pyrimidine
545	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperazine	2-Quinoline
546	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperidine	2-Me-Ph
547	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperidine	2-Me, 3-Me-Ph
548	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperidine	5-Tetralin
549	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperidine	1-Naphthalene
550	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperidine	2-OMe-1-Naphthalene
551	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperidine	2-Pyrimidine
552	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Piperidine	2-Quinoline
553	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Tetrahydropyridine	2-Me-Ph

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
554	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Tetrahydropyridine	2-Me, 3-Me-Ph
555	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Tetrahydropyridine	5-Tetralin
556	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Tetrahydropyridine	1-Naphthalene
557	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Tetrahydropyridine	2-OMe-1-Naphthalene
558	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Tetrahydropyridine	2-Pyrimidine
559	Me	H	H				CH ₂ -C(CH ₂)-CH ₂	Tetrahydropyridine	2-Quinoline
560	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Homopiperazine	2-Me-Ph
561	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Homopiperazine	2-Me, 3-Me-Ph
562	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Homopiperazine	5-Tetralin
563	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Homopiperazine	1-Naphthalene
564	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Homopiperazine	2-OMe-1-Naphthalene
565	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Homopiperazine	2-Pyrimidine
566	Me	H	H	/	/	/	CH ₂ -C(CH ₂)-CH ₂	Homopiperazine	2-Quinoline
567	Me	H	H	/	/	/	CH ₂ -CH(OH)CH ₂	Piperazine	2-Me-Ph
568	Me	H	H	/	/	/	CH ₂ -CH(OH)CH ₂	Piperazine	2-Me, 3-Me-Ph
569	Me	H	H	/	/	/	CH ₂ -CH(OH)CH ₂	Piperazine	5-Tetralin
570	Me	H	H	/	/	/	CH ₂ -CH(OH)CH ₂	Piperazine	1-Naphthalene

No	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
571	Me	H	H	/	/	/	CH ₂ -CH(OH)CH ₂	Piperidine	2-OMe-1-Naphthalene
572	Me	H	H	/	/	/	CH ₂ -CH(OH)CH ₂	Tetrahydropyridine	2-Pyrimidine
573	Me	H	H	/	/	/	CH ₂ -CH(OH)CH ₂	Homopiperazine	2-Quinoline
574	Me	H	H	/	/	/	C ₂ -N(Me)-C ₂	Piperazine	2-Me-Ph
575	Me	H	H	/	/	/	C ₂ -N(Me)-C ₂	Piperazine	2-Me, 3-Me-Ph
576	Me	H	H	/	/	/	C ₂ -N(Me)-C ₂	Piperazine	5-Tetralin
577	Me	H	H	/	/	/	C ₂ -N(Me)-C ₂	Piperazine	1-Naphthalene
578	Me	H	H	/	/	/	C ₂ -N(Me)-C ₂	Piperidine	2-OMe-1-Naphthalene
579	Me	H	H	/	/	/	C ₂ -N(Me)-C ₂	Tetrahydropyridine	2-Pyrimidine
580	Me	H	H	/	/	/	C ₂ -N(Me)-C ₂	Homopiperazine	2-Quinoline
581	Me	H	H	/	/	/	CH ₂ -CH(CH ₃)-C H ₂	Piperazine	5-Tetralin
582	Me	H	H	/	/	/	CH ₂ -CH(CH ₃)-C H ₂	Piperazine	1-Naphthalene
583	Me	H	H	/	/	/	CH ₂ -CH(CH ₃)-C H ₂	Piperidine	2-Me, 3-Me-Ph
584	Me	H	H	/	/	/	CH ₂ -CH(CH ₃)-C H ₂	Tetrahydropyridine	2-Pyrimidine
585	Me	H	H	/	/	/	CH ₂ -CH(CH ₃)-C H ₂	Homopiperazine	2-OMe-Naphthalene
586	Me	H	H	/	/	/	C ₈	Piperazine	5-Tetralin

NO	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
587	Me	H	H	/	/	/	C ₈	Piperazine	1-Naphthalene
588	Me	H	H	/	/	/	C ₈	Piperidine	2-Me, 3-Me-Ph
589	Me	H	H	/	/	/	C ₈	Tetrahydropyridine	2-Pyrimidine
590	Me	H	H	/	/	/	C ₈	Homopiperazine	2-OMe-Naphthalene
591	Me	5-Me	H	/	/	/	C ₂	Piperazine	5-Tetralin
592	Me	5-Me	H	/	/	/	C ₂	Piperazine	1-Naphthalene
593	Me	5-Me	H	/	/	/	C ₂	Piperazine	2-OMe-Ph
594	Me	5-Me	H	/	/	/	C ₂	Piperazine	2-Pyrimidine
595	Me	5-Me	H	/	/	/	C ₂	Piperazine	2-OMe-Naphthalene
596	Me	5-Me	H	/	/	/	C ₂	Piperidine	2-Me, 3-Me-Ph
597	Me	5-Me	H	/	/	/	C ₂	Tetrahydropyridine	2-Quinoline
598	Me	5-Me	H	/	/	/	C ₂	Homopiperazine	2-Cl-Ph
599	Me	5-Me	H	/	/	/	C ₃	Piperazine	5-Tetralin
600	Me	5-Me	H	/	/	/	C ₃	Piperazine	1-Naphthalene
601	Me	5-Me	H	/	/	/	C ₃	Piperidine	2-Pyrimidine
602	Me	5-Me	H	/	/	/	C ₃	Tetrahydropyridine	2-Me, 3-Me Ph
603	Me	5-Me	H	/	/	/	C ₃	Homopiperazine	2-OMe-Naphthalene
604	Me	4-Cl	H	/	/	/	C ₂	Piperazine	1-Naphthalene
605	Me	5-OH	H	/	/	/	C ₂	Piperazine	1-Naphthalene

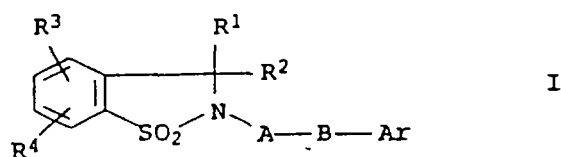
NO	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
606	Me	6-OMe	H	/	/	/	C ₂	Piperazine	1-Naphthalene
607	Me	4-F	H	/	/	/	C ₂	Piperazine	1-Naphthalene
608	Me	6-OMe	H	/	/	/	C ₂	Piperazine	1-Naphthalene
609	Me	4-CF ₃	H	/	/	/	C ₂	Piperazine	1-Naphthalene
610	Me	6-CO ₂ R ⁷	H	/	/	H	C ₂	Piperazine	1-Naphthalene
611	Me	6-CO ₂ R ⁷	H	/	/	Me	C ₂	Piperazine	1-Naphthalene
612	Me	6-NO ₂	H	/	/	/	C ₂	Piperazine	1-Naphthalene
613	Me	4-CN	H	/	/	/	C ₂	Piperazine	1-Naphthalene
614	Me	6-Pyrrol	H	/	/	/	C ₂	Piperazine	1-Naphthalene
615	Me	4(-C ₂ -Ph)	H	/	/	/	C ₂	Piperazine	1-Naphthalene
616	Me	4[-C ₄ -(4-Cl)Ph]	H	/	/	/	C ₂	Piperazine	1-Naphthalene
617	Me	4[-C ₂ -(2-OMe)Ph]	H	/	/	/	C ₂	Piperazine	1-Naphthalene
618	Me	4[C ₂ -(3-CF ₃)Ph]	H	/	/	/	C ₂	Piperazine	1-Naphthalene
619	Me	4[C ₂ -(2-Me)Ph]	H	/	/	/	C ₂	Piperazine	1-Naphthalene
620	Me	4[C ₂ -(2-NH ₂)Ph]	H	/	/	/	C ₂	Piperazine	1-Naphthalene
621	Me	4[C ₂ -(4-NO ₂)Ph]	H	/	/	/	C ₂	Piperazine	1-Naphthalene
622	Me	4[C ₂ -(4-OH)Ph]	H	/	/	/	C ₂	Piperazine	1-Naphthalene
623	Me	6-NR ⁵ R ⁶	H	Me	H	/	C ₂	Piperazine	1-Naphthalene
624	Me	6-NR ⁵ R ⁶	H	CO Ph	H	/	C ₂	Piperazine	1-Naphthalene
625	Me	6-NR ⁵ R ⁶	H	CO Me	H	/	C ₂	Piperazine	1-Naphthalene
626	Me	6-NR ⁵ R ⁶	H	CO ₂ tBu	H	/	C ₂	Piperazine	1-Naphthalene

NO	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	A	B	Ar
627	Me	6-NR ⁵ R ⁶	H	H	H	/	C ₂	Piperazine	1-Naphthalene
628	Me	6-NR ⁵ R ⁶	H	Piperazine		/	C ₂	Piperazine	1-Naphthalene
629	Me	6-NR ⁵ R ⁶	H	Me	H	/	C ₃	Piperidine	5-Tetralin
630	Me	6-NR ⁵ R ⁶	H	CO Ph	H	/	C ₃	Piperidine	5-Tetralin
631	Me	6-NR ⁵ R ⁶	H	CO Me	H	/	C ₃	Piperidine	5-Tetralin
632	Me	6-NR ⁵ R ⁶	H	/	/	/	C ₃	Piperidine	5-Tetralin
633	Me	6-Pyrrol	H	/	/	/	C ₃	Piperidine	5-Tetralin
634	Me	6-NO ₂	H	/	/	/	C ₃	Piperidine	5-Tetralin
635	Et	H	H	/	/	/	C ₂	Piperazine	1-Naphthalene
636	Et	H	H	/	/	/	C ₂	Piperazine	2-OMe-Ph
637	Et	H	H	/	/	/	C ₂	Piperazine	2-Pyrimidine
638	Et	H	H	/	/	/	C ₂	Piperazine	2-OMe-1-Naphthalene
639	Et	H	H	/	/	/	C ₂	Piperazine	2-Me, 3-Me-Ph

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CLAIMS:

1. A 2-substituted 1,2-benzisothiazole derivative of the formula I



where

R^1 and R^2 are, independently of one another, (C_{1-6}) alkyl,

R^3 , R^4 are, independently of one another, hydrogen, (C_{1-6}) alkyl branched or unbranched, OH, O- (C_{1-6}) -alkyl branched or unbranched, F, Cl, Br, I, trifluoromethyl, NR^5R^6 , CO_2R^7 , nitro, cyano, pyrrole, a phenylalkyl C_1 - C_4 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, amino, cyano or nitro,

R^5 and R^6 are, independently of one another, hydrogen, (C_{1-6}) alkyl branched or unbranched, CPh, CO_2tBu , CO- (C_{1-4}) -alkyl or together are a 5- or 6-membered ring which may contain a second nitrogen,

R^7 is hydrogen or (C_{1-6}) alkyl branched or unbranched,

A is branched or unbranched (C_{1-10}) -alkylene or straight-chain or branched

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(C₂₋₁₀)-alkylene which contains one or more groups Z selected from O, S, NR⁷, cyclopropyl, CHOH, a double or a triple bond,

B is 4-piperidine, 4-tetrahydro-1,2,3,6-pyridine, 4-piperazine and homopiperazine, the linkage to A taking place by one nitrogen atom of B, and

Ar is phenyl which is unsubstituted or substituted by (C₁₋₆) alkyl branched or unbranched, O-(C₁₋₆)-alkyl branched or unbranched, OH, F, Cl, Br, I, trifluoromethyl, NR⁵R⁶, CO₂R⁷, cyano or phenyl or is tetralin, indan, a fused aromatic system selected from the group consisting of naphthyl which is unsubstituted or substituted by (C₁₋₄) alkyl or O(C₁₋₄) alkyl, anthracene and 5- or 6-membered aromatic heterocycles having 1 or 2 nitrogen atoms which may be substituted by methyl and/or trifluoromethyl and which may also be fused to other aromatic radicals, its possible enantiomers and diastereomers, tautomeric forms and its salts with physiologically tolerated acids.

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

R¹ and R² are (C₁₋₂) alkyl,

R³ and R⁴ are, independently of one another, hydrogen,

O-(C₁₋₄)-alkyl branched or unbranched, F, Cl, Br, trifluoromethyl, NR⁵R⁶, nitro, cyano and phenyl,

R⁵ and R⁶ are, independently of one another, hydrogen, CPh, CO₂tBu, (C₁₋₆) alkyl

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branched or unbranched and CO-(C₁₋₄)-alkyl,

A is branched or unbranched (C₂₋₅) alkylene or straight-chain or branched (C₂₋₅)

alkylene which contains a group Z which is selected from CHOH, cyclopropyl, a double or a triple bond,

B is 4-piperidin-1-yl, 4-tetrahydro-1,2,3,6-pyridin-1-yl, 4-piperazin-1-yl or 4-(1,4-diazepin-1-yl), and

Ar is phenyl which is unsubstituted or substituted by (C₁₋₆) alkyl branched or unbranched, O-(C₁₋₆)-alkyl branched or unbranched, F, Cl, trifluoromethyl, NR⁵R⁶, CO₂R⁷, cyano and phenyl, or tetralin, indan, naphthyl which is unsubstituted or substituted by (C₁₋₄) alkyl or O(C₁₋₄) alkyl, or 6-membered aromatic heterocycles having 1 or 2 nitrogen atoms and which may also be fused to other aromatic radicals.

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

R¹ and R² are methyl,

R³ and R⁴ are, independently of one another, hydrogen, nitro, Cl or NR⁵R⁶,

R⁵ and R⁶ are, independently of one another, hydrogen, CPh and CO-(C₁₋₂)-alkyl,

A is (C₂₋₃) alkylene,

B is selected from the group consisting of 4-piperidin-1-yl, 4-piperazin-1-yl and 4-tetrahydro-1,2,3,6-pyridin-1-yl, and

Ar is phenyl which is unsubstituted or substituted by (C₁₋₂) alkyl or O(C₁₋₂)alkyl in

position 2 and 3, or tetralin, indan or naphthalene which is unsubstituted or substituted by (C₁₋₂)alkyl or O(C₁₋₂) alkyl, or pyridine, pyrimidine and isoquinoline.

4. A pharmaceutical composition which is a selective 5HT_{1B} and 5HT_{1A} antagonist comprising as active ingredient a compound as claimed in claim 1.

5. A method of treating depression in a subject requiring such treatment which comprises administering an effective amount of the composition of claim 4.

6. A method of treating depression and related disorders in a subject requiring such treatment which comprises administering an effective amount of the composition of claim 4.

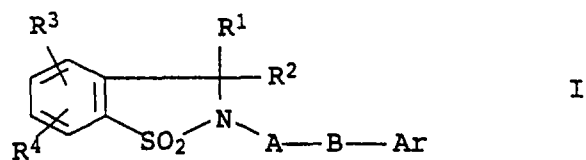
7. The 2-substituted 1,2-benzothiazole derivative of claim 1, wherein A is branched or unbranched (C₂₋₅)-alkylene or straight-chain or branched (C₂₋₅)-alkylene which contains one or more groups Z selected from cyclopropyl, CHOH and a double or triple bond.

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2-Substituted 1,2-benzisothiazole derivatives of the formula I

Abstract [sic]

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where

the substituents have the meanings indicated in the description,
15 their preparation and use as serotonin antagonists.

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