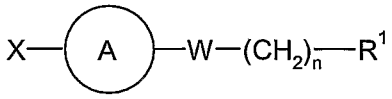
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New process for the preparation of diazine derivatives

The invention relates to a new process for the preparation of diazine derivatives of formula I:

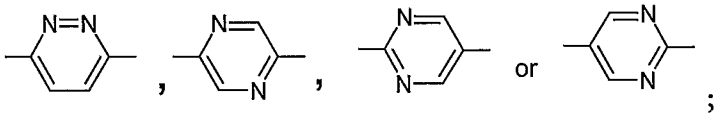


formula I,

wherein

X is fluorine, chlorine or bromine;

A is



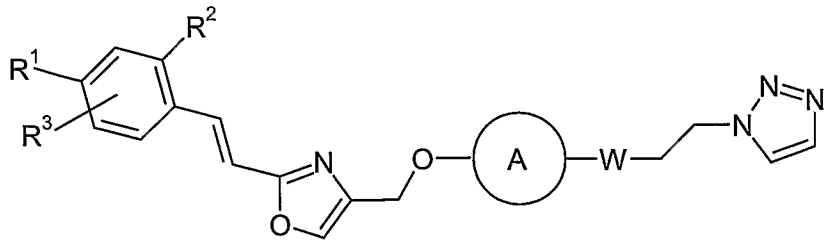
;

W is $-CH_2-CH_2-$ or -CH=CH-;

n is 1 to 10

R^1 is cycloalkyl, aryl, heterocyclyl or heteroaryl;

Compounds of formula I can be utilized as intermediates for the preparation of e.g. liquid crystalline media components as described in EP 0 606 090; or as intermediates of pharmaceutically active substances according to formula I-A,



formula II,

wherein

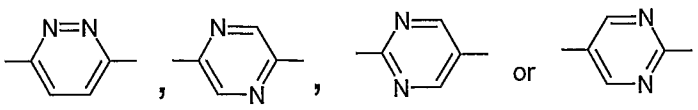
R^1 is halogen;
-O-alkyl;
-S-alkyl; -S(O)-alkyl; $-S(O)_2$-alkyl,
$-SF_5$,
-NH-alkyl; or
alkyl, all alkyl groups being optionally once or several times substituted with halogen; and

R^2 is hydrogen; or
halogen; and

R^3 is hydrogen; or alternatively

R^1 and R^3 are adjacent and together with the carbon atoms of the phenyl ring to which they are attached form a 5 or 6 membered heterocyclic ring; and

A is

 ; and

W is $-CH_2-CH_2-$ or -CH=CH- .

The term "cycloalkyl" means a monocyclic saturated hydrocarbon ring with 3 to 7, preferably 3 to 6, ring atoms. Examples of such saturated carbocyclic groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "heterocyclyl" means a saturated, monocyclic ring with 5 to 6 ring atoms which contains up to 3, preferably 1 or 2 heteroatoms selected independently from N, O or S and the remaining ring atoms being carbon atoms. Such saturated heterocyclic group can be optionally substituted one to three, preferably one or two times by alkyl, which is defined as above, preferably by methyl. Examples of such saturated heterocyclic groups are pyrrolidinyl, morpholinyl, piperazinyl, N-methyl-piperazinyl, piperidyl and the like.

The term "aryl" means a mono- or bicyclic aromatic ring with 6 to 10 ring carbon atoms. Examples of such aryl groups are phenyl and naphthyl, preferably phenyl. Such aryl groups are optionally substituted one to three, preferably one to two times by halogen, amino, hydroxy, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogenated (C_1-C_4)alkyl or halogenated (C_1-C_4)alkoxy.

The term "heteroaryl" means a mono- or bicyclic aromatic ring with 5 to 10, preferably 5 to 6, ring atoms, which contains up to 3, preferably 1 or 2 heteroatoms selected independently from N, O or S and the remaining ring atoms being carbon atoms. Examples of such heteroaryl groups are e.g. triazolyl, imidazolyl, pyrazolyl, tetrazolyl, thienyl, thiazolyl, oxazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, benzimidazolyl, indolyl, benzothiophenyl, benzofuranyl ,quinolyl, quinazolinyl and the like, preferably triazolyl and imidazolyl and especially triazolyl. Such heteroaryl groups are optionally substituted one to two times, preferably one time, by (C_1-C_4)alkyl.

The term "alkyl" as used herein means a saturated, straight-chain or branched-chain hydrocarbon containing from 1 to 6, preferably 1 to 4, carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, t-butyl, n-pentyl, n-hexyl.

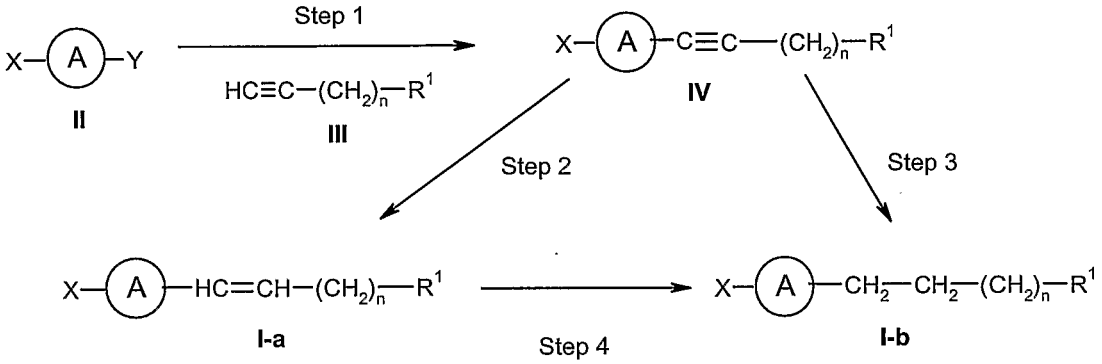
The term "alkoxy" as used herein means an alkyl-O- group wherein the alkyl is defined as above.

The term "halogenated alkyl" as used herein means an alkyl group as defined above which is substituted one or several times, preferably one to six and especially one to three times, by halogen, preferably by fluorine or chlorine, especially by fluorine. Examples are difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluorethyl, and the like, especially trifluoromethyl.

The term "halogenated alkoxy" as used herein means an alkoxy group as defined above which is substituted one or several times by halogen, preferably by fluorine or chlorine, especially fluorine. Examples are difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy and the like, especially trifluoromethoxy.

The term "halogen" means fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine or bromine and especially fluorine and chlorine.

The invention is thus concerned with a new process for the preparation of compounds of formula I according to Scheme 1



In scheme 1, X, ring A, W and R^1 have the significance given above and Y is iodine or bromine and not both X and Y are bromine. The synthesis of the compounds of formula I starts from the corresponding dihalodiazines of formula III. The preparation of these dihalodiazines of formula III is described in the accompanying examples or in e.g. WO 2004/000811, Pieterse, K., et al., Chemistry-A European Journal 9 (2003) 5597-5604 and Sato, N., J. Heterocyclic Chem., 19 (1982) 673-674, Draper, T. L., et al., J. Org. Chem. 60 (1995) 748-50; Goodman, A. J., Tetrahedron 55 (1999) 15067-15070; WO 2004/006922; Vlad, G., et al., J. Org. Chem. 67 (2002) 6550-6552; Zhang, Y., et al., J. Med. Chem, 47 (2004) 2453-2465; EP 0 742 212 and Gacek, M., et al., Acta Chem. Scand. B39 (1985) 691-696.

In Step 1, scheme 1 the dihalodiazines of formula III are reacted with alkyne derivatives of formula IV in a Sonogashira cross-coupling reaction in the presence of catalytic amounts of copper iodide and a palladium complex, e.g. $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$ or the like. The reaction is carried out in the presence of a base like triethyl amine, diisopropyl amine, isopropyl amine, piperidine, morpholine or pyrrolidine and in solvents like tetrahydrofuran, *N,N*-dimethylformamide or mixtures thereof at temperatures varying from 20°C to 120°C yielding derivatives of formula V.

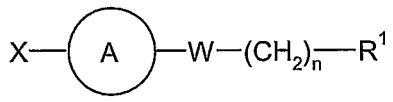
When the synthesis is proceeded by the reduction Step 2 the compounds of formula I wherein W is –HC=CH- are obtained. Such compounds are named I-a. Preferably, as reduction reaction a catalytic hydrogenation is performed. The catalysts are usually used as finely dispersed solids or adsorbed on to an inert support such as charcoal (C), calcium carbonate ($CaCO_3$), barium sulfate ($BaSO_4$) or alumina (Al). Typical catalyst are e.g. $Pd/Pb/CaCO_3$ (Pd-$CaCO_3$-PbO system wherein the PbO acts as catalytic poison and tempers the reactivity), $Pd/CaCO_3$, $Pd/BaSO_4$ or$Pt/BaSO_4$ eventually poisoned with quinoline, especially $Pd/CaCO_3$ or $Pd/Pb/CaCO_3$. Alternatively nickel boride(Ni_2B) can be used as catalyst. The mol% of catalyst added can vary between 1 mol% and 50 mol%, preferably between 5 and 25 mol%. Eventually, a catalytic poison like can be used to slow down the reaction and to prevent further hydrogenation according to Step 3. The reaction is typically carried out at temperatures between 0°C and 50°C, at hydrogen pressures between $1x10^3$ and $4x10^5$ Pa, preferably between $2x10^3$ and 15 $x10^4$ Pa, in solvents like ethyl acetate, hexane, tetrahydrofuran or mixtures thereof. Alternatively sodium or lithium metal in liquid ammonia (or some pure primary amines like e.g. ethylamine) can be used to hydrogenate the alkyne group (–C≡C-) to an alkene group (W is –HC=CH-).

When the synthesis is proceeded by the reduction step 3 the compounds of formula I wherein W is $-CH_2-CH_2-$ are obtained. Such compounds are named I-b. Preferably, as reduction reaction a catalytic hydrogenation is performed. Typical catalysts are e.g. Pt, PtO_2, Pd, Rh, Ru and Ni (late transition metals)- usually used as finely dispersed solids or adsorbed on to an inert support such as charcoal (C), calcium carbonate ($CaCO_3$) or alumina (Al). Preferably Pd/C, $Pd/CaCO_3$ or PtO_2 is used. The mol% of catalyst added can vary between 1 mol% and 50 mol%, preferably between 5 and 25 mol%. The reaction is typically carried out at

temperatures between 0°C and 50°C, at hydrogen pressures between $1x10^3$ and $4x10^5$ Pa, preferably between $2x10^3$ and 15 $x10^4$ Pa, in solvents like methanol, ethanol, tetrahydrofuran, acetone, ethyl acetate or mixtures thereof. Alternatively a variety of homogeneous catalysts are also effective *e.g.* Wilkinson's catalyst $[(PPh_3)_3RhCl]$.

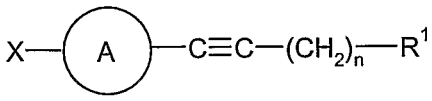
In step 4 of scheme 1 the compounds of formula I-a are converted to the compounds of formula I-b by obtained by a reduction reaction. Preferably, as reduction reaction a catalytic hydrogenation is performed. Typical catalysts are e.g. Pt, PtO_2, Pd, Rh, Ru and Ni (late transition metals)- usually used as finely dispersed solids or adsorbed on to an inert support such as charcoal (C), calcium carbonate ($CaCO_3$) or alumina (Al). Preferably Pd/C, $Pd/CaCO_3$ or PtO_2 is used. The mol% of catalyst added can vary between 1 mol% and 50 mol%, preferably between 5 and 25 mol%. The reaction is typically carried out at temperatures between 0°C and 50°C, at hydrogen pressures between $1x10^3$ and $4x10^5$ Pa, preferably between $2x10^3$ and 15 $x10^4$ Pa, in solvents like methanol, ethanol, tetrahydrofuran, acetone, ethyl acetate or mixtures thereof. Alternatively a variety of homogeneous catalysts are also effective *e.g.* Wilkinson's catalyst $[(PPh_3)_3RhCl]$.

An embodiment of the invention is a process according to Step 2 or Step 3 of Scheme 1 , for the preparation of diazine derivatives of formula I



formula I,

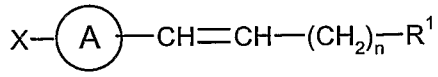
comprising the step of hydrogenating the compounds of formula V



formula V,

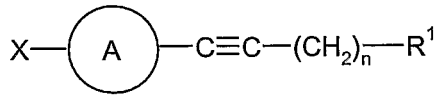
with hydrogen in the presence of a catalyst, to obtain a compound of formula I.

Another embodiment of the invention is a process according to Step 2 of Scheme 1 , for the preparation of diazine derivatives of formula I-a



formula I-a,

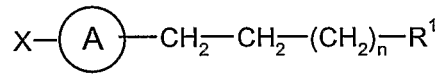
comprising the step of hydrogenating the compounds of formula V



formula V,

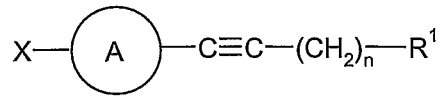
with hydrogen in the presence of a catalyst, to obtain a compound of formula I-a.

Another embodiment of the invention is a process according to Step 3 of Scheme 1 , for the preparation of diazine derivatives of formula I-b



formula I-b,

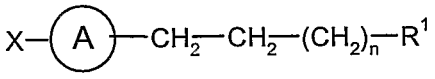
comprising the step of hydrogenating the compounds of formula V



formula V,

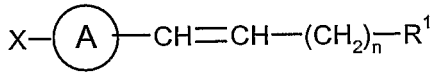
with hydrogen in the presence of a catalyst, to obtain a compound of formula I-b.

Another embodiment of the invention is a process according to Step 4 of Scheme 1 , for the preparation of diazine derivatives of formula I-b



formula I-b,

comprising the step of hydrogenating the compounds of formula I-a



formula I-a,

with hydrogen in the presence of a catalyst, to obtain a compound of formula I-b.

Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

X is chlorine or bromine.

n is 1 to 4

Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

X is chlorine or bromine.

n is 1 to 4

R^1 is heteroaryl.

Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

R^1 is heteroaryl.

Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

W is $-CH_2-CH_2-$.

Another embodiment of the invention is a process according to Step 2b of Scheme 1, for the preparation of diazine derivatives of formula I, wherein

W is $-CH_2-CH_2-$.

Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

W is -CH=CH-.

Another embodiment of the invention is a process according to Step 2a of Scheme 1, for the preparation of diazine derivatives of formula I, wherein

W is -CH=CH-.

Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

W is $-CH_2-CH_2-$; and

the catalyst in the hydrogenation step 2 is Pd/C or PtO_2.

Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

W is $-CH_2-CH_2-$; and

the catalyst in the hydrogenation step 2 is PtO_2.

Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

W is -CH_2-CH_2- or -CH=CH-; and

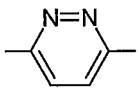
the catalyst in the hydrogenation step 2 is Pd/$CaCO_3$.

Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

W is -CH=CH-; and

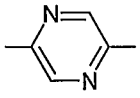
the catalyst in the hydrogenation step is Pd/$CaCO_3$ or Pd/Pb/$CaCO_3$.

Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

ring A is 

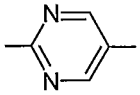
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Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

ring A is 

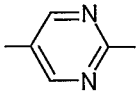
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Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

ring A is 

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Another embodiment of the invention is a process according to Scheme 1 , for the preparation of diazine derivatives of formula I, wherein

ring A is 

.

The following examples and references are provided to aid the understanding of the present invention, the true scope of which is set forth in the appended claims. It is understood that modifications can be made in the procedures set forth without departing from the spirit of the invention.

Examples:

A: starting materials

Preparation of 3-Chloro-6-iodo-pyridazine

To a suspension of 3, 6-dichloro-pyridazine (1.0 g, 6.71 mmol) and NaI (1.35 g, 9.0 mmol) in chloroform (2.5 ml) a Hydroiodic acid (57 wt. %) (2.85 g, 25.6 mmol) is added at 0°C. The mixture is stirred for 20 hours (h) at room temperature (r.t.) and then poured into a mixture of 100 ml ice water and 20 ml 10N sodium hydroxide (NaOH). Chloroform (50 ml) is added and the mixture is stirred for 10 minutes (min). The organic phase is separated, the aqueous layer is extracted with chloroform (1 x 50 ml) and the combined organic phases dried over magnesium sulfate ($MgSO_4$) and concentrated in vacuo to yield 3-chloro-6-iodo-pyridazine as an off-white solid. Yield 1.16 g (72%)

MS: M = 340.6 (ESI+)

^{1}H-NMR (300 MHz, CDCl3): 7.22 (d, J = 8.9 Hz, 1H), 7.83 (d, J = 8.9 Hz, 1H)

Preparation of 5-Bromo-2-chloro-pyrimidine

2-Pyrimidinol hydrochloride (13.26 g, 100 mmol) is dissolved in 2N NaOH (50 ml) and bromine (17.98 g, 112.5 mmol) is added over 15 min. The mixture is stirred for 45 min at r.t. and then concentrated in vacuo to yield a brownish solid.

The solid is suspended in phosphorus oxychloride (125 ml), N,N-dimethylaniline (9.35 g, 77mmol) added and the mixture is heated to reflux for 3 h. After cooling the reaction mixture is poured slowly under stirring onto 1 L ice water and the resulting mixture is extracted with diethyl ether (3 x 200 ml). The extract is washed with brine, dried over $MgSO_4$ and concentrated in vacuo yielding 5-bromo-2-chloro-pyrimidine as a pale yellow solid. Yield 10.85 g (56 %)

^{1}H-NMR (300 MHz, CDCl3): 8.70 (s, 2H)

Preparation of 5-Bromo-2-iodo-pyrimidine

To a suspension of 5-bromo-2-chloro-pyrimidine (5.80 g, 30 mmol) and sodium iodide (7.5 g, 50 mmol) in chloroform (20 ml) a Hydroiodic acid (57 wt. %) (2.85 g, 25.6 mmol) is added at 0°C. After removing the cooling the reaction mixture is stirred for 20 h at r.t. and then poured into a mixture of 200 ml ice water and 30 ml 10N NaOH. Chloroform (150 ml) is added and the mixture is stirred for 10 min. The organic phase is separated, the aqueous layer is extracted with chloroform (2 x 100 ml) and the combined organic phases dried over $MgSO_4$ and concentrated in vacuo to yielding 5-bromo-2-iodo-pyrimidine as a pale yellow solid. Yield 6.29 g (84%)

MS: M = 284.8 (ESI+)
^{1}H-NMR (300 MHz, CDCl3): 8.54 (s, 2H)
7.56(d, J = 16.4 Hz, 1H), 7.59-7.66(m, 4H).

Preparation of 1-But-3-ynyl-1H-[1,2,3]triazole

But-3-yn-1-ol (49.57 g, 707.2 mmol) and triethylamine (107.7 mL, 777 mmol, dried over KOH) are dissolved in dry dichloromethane (500 mL) under a nitrogen atmosphere and cooled to 0°C. Methanesulfonyl chloride (54.8 mL, 708 mmol), dissolved in 500 mL of dry dichloromethane is added within 90 min while keeping the temperature below 5 °C. The mixture is stirred for 3.5 hours at room temperature, then poured onto 2.5 L of ice water. The organic phase is separated and washed with 2 x 500 mL of water and 1 x 250 mL of brine and dried over sodium sulfate. The volatiles are removed to yield 94.18 g of the methane sulfonate (631.2 mmol, 89.2 %) as a yellow liquid.

A suspension of NaOH (37.86 g, 946.5 mmol), sodium iodide (94.65 g, 631.5 mmol) and 1H-[1,2,3]triazole (61.03 g, 883.6 mmol) in 2-methyl-2-butanol (750 mL) is refluxed for 1 h under an inert atmosphere. After cooling to room temperature the methane sulfonate (94.18 g, 631.2 mmol) is added within 5 minutes. The resulting suspension is then heated to reflux for 3 h, cooled to room temperature and concentrated in vacuo at 45 °C.

Water (500 mL) and dichloro methane (1 L) are added and the organic phase is separated, dried over sodium sulfate and the volatiles removed at 30 °C .The residue is distilled at 1 mmHg . A forerun is collected at 20-70 °C . The main fraction distilled at 123-129 °C as a colourless, turbid liquid. After filtration over Celite 1-but-3-ynyl-1H-[1,2,3]triazole is obtained as a colourless liquid (29.77 g, 38.9 %).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.05 (t, 1H), 2.75 (dt, 2H), 4.5 (t, 2H), 7.65 (s, 1H), 7.7 (s, 1H)

Example1:

3-chloro-6-(4-[1,2,3]triazol-1-yl-butyl)-pyridazine

3-Chloro-6-iodo-pyridazine (11.56 g, 48.1 mmol), 1-but-3-ynyl-1H-[1,2,3]triazole (6.99 g, 57.7 mmol) and triethyl amine (NEt_3) (94 ml) are dissolved in DMF (188 ml) and copper iodide (CuI) (0.981 g, 5.15 mmol) is added under stirring. After passing a stream of argon through the mixture for 10 min tetrakis(triphenylphosphine)palladium(0) (2.836 g, 2.43 mmol) is added and stirring is continued for 6 h at r.t.. Dichloromethane (300 ml) is added, the mixture is washed with 0.5N hydrochloric acid (HCl) and brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product is purified by flash column chromatography (ethyl acetate) yielding 3-chloro-6-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyridazine as a colorless solid. Yield 9.52 g (85 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.12 (t, 2H, CH_2-C≡), 4.67 (t, 2H, CH_2-N), 7.39 (d, 1H, pyridazine), 7.45 (d, 1H, pyridazine), 7.70 (s, 1H, triazole), 7.73 (s, 1H, triazole).

3-Chloro-6-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyridazine (2.50 g, 10.7 mmol) is dissolved in ethyl acetate (450 ml) and hydrogenated at 3x 10^3 Pa H_2-pressure for 3.5 h at r.t. in the presence of palladium on charcoal (10 %, 2.50 g). The reaction mixture is filtered and concentrated in vacuo. The residue was dissolved in THF (10 ml) and added to a solution of benzyl alcohol (0.94 ml, 9.0 mmol) and sodium tert-butoxide (NaOtBu) (0.842 g, 8.76 mmol) in THF (80 ml). After stirring for 2 h ethyl acetate (100 ml) is added, the mixture is washed with saturated ammonium chloride (NH_4Cl), dried over Na_2SO_4 and concentrated in vacuo. After flash

column chromatography (ethyl acetate) 3-chloro-6-(4-[1,2,3]triazol-1-yl-butyl)-pyridazine is obtained as a colorless solid. Yield 1.14 g (45 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.76-1.84 (m, 2H, C*H*$_2$-CH_2-C=), 1.97-2.05 (m, 2H, C*H*$_2$-CH_2-N), 2.98 (t, 2H, CH_2-C=), 4.43 (t, 2H, CH_2-N), 7.25 (d, 1H, pyridazine), 7.40 (d, 1H, pyridazine), 7.52 (s, 1H, triazole), 7.68 (s, 1H, triazole).

Example 2:

3-chloro-6-(4-[1,2,3]triazol-1-yl-butyl)-pyridazine starting from 3-chloro-6-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyridazine

3-Chloro-6-(4-[1,2,3]triazol-1-yl-butyl)-pyridazine

3-Chloro-6-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyridazine (0.100 mg, 0.43 mmol) is dissolved in methanol (10 ml) and hydrogenated at 3x 10^3 Pa H_2-pressure for 4.5 h at r.t. in the presence of platinum(IV) oxide x H_2O (0.044 mg, 0.18 mmol). The reaction mixture is filtered and concentrated in vacuo to yield 3-chloro-6-(4-[1,2,3]triazol-1-yl-butyl)-pyridazine as a colorless solid. Yield 0.059 g (58 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.76-1.84 (m, 2H, C*H*$_2$-CH_2-C=), 1.97-2.05 (m, 2H, C*H*$_2$-CH_2-N), 2.98 (t, 2H, CH_2-C=), 4.43 (t, 2H, CH_2-N), 7.25 (d, 1H, pyridazine), 7.40 (d, 1H, pyridazine), 7.52 (s, 1H, triazole), 7.68 (s, 1H, triazole).

Example 3:

2-bromo-5-(4-[1,2,3]triazol-1-yl-but-1-enyl)-pyrazine

2-bromo-5-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyrazine

2-Bromo-5-iodo-pyrazine (13.69 g, 48.0 mmol), 1-but-3-ynyl-1H-[1,2,3]triazole (7.01 g, 57.9 mmol) and triethyl amine (NEt_3) (94 ml) are dissolved in DMF (188 ml) and copper iodide (CuI) (0.984 g, 5.17 mmol) is added under stirring. After passing a stream of argon through the mixture for 10 min tetrakis(triphenylphosphine)palladium(0) (2.844 g, 2.46 mmol) is added and stirring is continued for 5 h at r.t.. Dichloromethane (300 ml) is added; the mixture is washed with 0.5N hydrochloric acid (HCl) and brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product is purified by flash column

chromatography (ethyl acetate/hexanes 7:3) yielding 2-bromo-5-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyrazine as a colorless solid. Yield 9.99 g (75 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.10 (t, 2H, CH_2-C≡), 4.66 (t, 2H, CH_2-N), 7.70 (s, 1H, triazole), 7.72 (s, 1H, triazole), 8.31 (d, 1H, pyrazine), 8.60 (d, 1H, pyrazine).

2-Bromo-5-(4-[1,2,3]triazol-1-yl-but-1-enyl)-pyrazine

2-Bromo-5-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyrazine (0.501 mg, 1.80 mmol) is dissolved in ethyl acetate (115 ml) and hydrogenated at 3x 10^3 Pa H_2-pressure for 4.5 h at r.t. in the presence of palladium on calcium carbonate (10 %, 0.454 g). The reaction mixture is filtered and concentrated in vacuo to yield 2-bromo-5-(4-[1,2,3]triazol-1-yl-but-1-enyl)-pyrazine as a colorless solid. Yield 0.386 g (77 %).

MS: M = 280.1, 282.2 (ESI+)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.33 (dq, 2H, CH_2-C=), 4.59 (t, 2H, CH_2-N), 6.04 (dt, 1H, =CH-CH_2), 6.47 (d, 1H, =CH-C=), 7.57 (s, 1H, triazole), 7.69 (s, 1H, triazole), 8.19 (d, 1H, pyrazine), 8.64 (d, 1H, pyrazine).

Example 4:

2-bromo-5-(4-[1,2,3]triazol-1-yl-butyl)-pyrazine starting from 2-Bromo-5-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyrazine

2-Bromo-5-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyrazine (2.50 g, 9.0 mmol) is dissolved in methanol (700 ml) and hydrogenated at 3x 10^3 Pa H_2-pressure for 2 h at r.t. in the presence of platinum(IV) oxide x H_2O (0.840 g, 3.40 mmol). The reaction mixture is filtered and concentrated in vacuo to yield 2-bromo-5-(4-[1,2,3]triazol-1-yl-butyl)-pyrazine as a colorless solid. Yield 1.63 g (64 %)

MS: M = 282.1, 284.2 (ESI+)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.72-1.80 (m, 2H, C*H*$_2$-CH_2-C=), 1.94-2.01 (m, 2H, C*H*$_2$-CH_2-N), 2.79 (t, 2H, CH_2-C=), 4.42 (t, 2H, CH_2-N), 7.51 (s, 1H, triazole), 7.69 (s, 1H, triazole), 8.17 (d, 1H, pyrazine), 8.57 (d, 1H, pyrazine).

Example 5:

2-bromo-5-(4-[1,2,3]triazol-1-yl-butyl)-pyrazine starting from 2-bromo-5-(4-[1,2,3]triazol-1-yl-but-1-enyl)-pyrazine

2-Bromo-5-(4-[1,2,3]triazol-1-yl-butyl)-pyrazine

2-Bromo-5-(4-[1,2,3]triazol-1-yl-but-1-enyl)-pyrazine (0.020 mg, 0.07 mmol) is dissolved in methanol (4 ml) and hydrogenated at 3x 10^3 Pa H_2-pressure for 1 h at r.t. in the presence of platinum(IV) oxide x H_2O (0.007 mg, 0.03 mmol). The reaction mixture is filtered and concentrated in vacuo to yield 2-bromo-5-(4-[1,2,3]triazol-1-yl-butyl)-pyrazine and 2-bromo-5-(4-[1,2,3]triazol-1-yl-butyl)-pyrazine at the ratio of 80:20.

MS: M = 282.1, 284.2 (ESI+)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.72-1.80 (m, 2H, C*H*$_2$-CH$_2$-C=), 1.94-2.01 (m, 2H, C*H*$_2$-CH$_2$-N), 2.79 (t, 2H, CH$_2$-C=), 4.42 (t, 2H, CH$_2$-N), 7.51 (s, 1H, triazole), 7.69 (s, 1H, triazole), 8.17 (d, 1H, pyrazine), 8.57 (d, 1H, pyrazine).

Example 6:

5-(4-[1,2,3]Triazol-1-yl-butyl)-2-{2-[2-(4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-pyrimidine

5-Bromo-2-chloro-pyrimidine (0.500 g, 2.53 mmol), 1-but-3-ynyl-1H-[1,2,3]triazole (0.368 g, 3.03 mmol) and triethyl amine (NEt_3) (5.0 ml) are dissolved in DMF (10 ml) and copper iodide (CuI) (0.052 g, 0.27 mmol) is added under stirring. After passing a stream of argon through the mixture for 10 min tetrakis(triphenylphosphine)palladium(0) (0.149 g, 0.13 mmol) is added and stirring is continued for 4 h at 80°C. Dichloromethane (125 ml) is added, the mixture is washed with 0.5N hydrochloric acid (HCl) and brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product is purified by flash column chromatography (ethyl acetate/hexanes 4:1) yielding 2-chloro-5-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyrimidine as a colorless solid. Yield 373 mg (63 %).

MS: M = 234 (API+)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.10 (t, 2H, CH_2-C≡), 4.63 (t, 2H, CH_2-N), 7.64 (s, 1H, triazole), 7.72 (s, 1H, triazole) 8.54 (s, 2H, pyrimidine).

2-Chloro-5-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyrimidine (2.52 g, 10.8 mmol) is dissolved in ethyl acetate (210 ml) and hydrogenated at 3x 10^3 Pa H_2-pressure for 2.5 h at r.t. in the presence of palladium on calcium carbonate (10 %, 2.55 g). The reaction mixture is filtered and concentrated in vacuo to yield 2-chloro-5-(4-[1,2,3]triazol-1-yl-butyl)-pyrimidine as a colorless solid. Yield 2.15 g (84 %)

MS: M = 236.2, 238.2 (ESI+)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.60-1.68 (m, 2H, C*H*$_2$-CH_2-C=), 1.94-2.02 (m, 2H, C*H*$_2$-CH_2-N), 2.62 (t, 2H, CH_2-C=), 4.42 (t, 2H, CH_2-N), 7.50 (s, 1H, triazole), 7.70 (s, 1H, triazole), 8.41 (s, 2H, pyrimidine).

Example 7:

5-Bromo-2-(4-[1,2,3]triazol-1-yl-butyl)-pyrimidine

5-Bromo-2-iodo-pyrimidine (1.14 g, 4.0 mmol), 1-but-3-ynyl-1H-[1,2,3]triazole (0.533 g, 4.4 mmol) and triethyl amine (NEt_3) (2 ml) are dissolved in DMF (1 ml) and copper iodide (CuI) (0.38 g, 0.2 mmol) is added under stirring. After passing a stream of argon through the mixture for 10 min bis(triphenylphosphine) palladium(II) dichloride (0.140 g, 0.2 mmol) is added and stirring is continued for 3 h at r.t.. Chloroform (300 ml) is added; the mixture is washed with 1N HCl and water, dried over $MgSO_4$ and concentrated in vacuo. The residue is purified by flash column chromatography (chloroform (100%) -> ethyl acetate (100%)) yielding 5-bromo-2-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyrimidine as a beige solid. Yield 0.96 g (86 %).

MS: M = 277.9 (ESI+)

5-Bromo-2-(4-[1,2,3]triazol-1-yl-butyl)-pyrimidine

5-Bromo-2-(4-[1,2,3]triazol-1-yl-but-1-ynyl)-pyrimidine (1.50 g, 5.4 mmol) is dissolved in THF (400 ml) and hydrogenated at 3x 10^3 Pa H_2-pressure for 8 h at r.t. in the presence of palladium on calcium carbonate (10 %, 1.20 g). The reaction

mixture is filtered and concentrated in vacuo to yield 5-bromo-2-(4-[1,2,3]triazol-1-yl-butyl)-pyrimidine as a colorless solid. Yield 1.34 g (88 %).

MS: M = 282.1, 284.2 (ESI+)

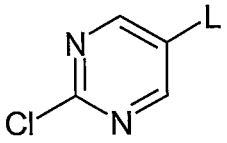
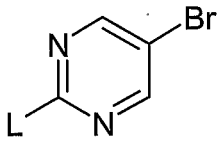
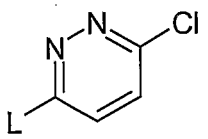
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.83-1.90 (m, 2H, C*H*$_2$-CH$_2$-C=), 1.95-2.04 (m, 2H, C*H*$_2$-CH$_2$-N), 2.97 (t, 2H, CH$_2$-C=), 4.44 (t, 2H, CH$_2$-N), 7.54 (s, 1H, triazole), 7.75 (s, 1H, triazole), 8.70 (s, 2H, pyrimidine).

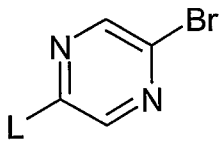
Example 8:

Hydrogenation of halogen-diazine-alkyne-derivatives with different catalysts

The different halogen-diazine-alkyne derivatives were dissolved in the appropriate solvent and hydrogenated in the presence of a catalyst. The reaction mixture is filtered and concentrated in vacuo to yield 5-bromo-2-(4-[1,2,3]triazol-1-yl-butyl)-pyrimidine as a colorless solid. The used catalysts and reaction conditions (mol% catalyst, solvent, reaction temperature, reaction time) are listed in Table 1. The ratios of the obtained alkenes (A) and alkanes (B) were detected by ^{1}H-NMR (400 MHz, $CDCl_3$). Where the main products were isolated the yield is given.

Table 1:

Educt: halogen-alkynyl-diazine L= -C≡C-$(CH_2)_2$- 1-[1,2,3]triazole	Main Product: halogen-alkenyl-diazine = A		Main Product: halogen-alkyl-diazine = B	
	Catalyst and Conditions	Ratios/ Yields	Catalyst and Conditions	Ratios/ Yields
	9 mol% Pd/Pb on $CaCO_3$(5%(w/w) Pd)/ 8%(w/w)Pb) $3x10^3$ Pa, ethyl acetate (EtOAc), 0.75h, r.t.	A :B [I] 92 :8	22 mol% Pd/$CaCO_3$, $3x10^3$ Pa, EtOAc, 2h, r.t.	A :B [I] 0:100 (NMR) (isolated Yield 84%)
			13 mol% Pd/C (10%(w/w)Pd), ~$1x10^5$ Pa, EtOAc, 2h, r.t.	A :B 0:100 (isolated Yield 82%)
	22 mol% Pd/$CaCO_3$, $3x10^3$ Pa, EtOAc, 2h, r.t.	A :B [II] 75:25	21 mol% Pd/$CaCO_3$, $3x10^3$ Pa, tetrahydrofuran (THF), 8h, r.t.	A :B [II] 0: 100 (isolated Yield 88%)
			22 mol% Pd/C (10%(w/w)Pd), $3x10^3$ Pa, EtOAc, 5h, r.t.	A :B [III] 13:87 (isolated Yield 45%)
	22 mol% Pd/$CaCO_3$, $3x10^3$ Pa, EtOAc, 2h, r.t.	A :B [III] 94: 6	42 mol% PtO_2, $3x10^3$ Pa, methanol (MeOH), 4.5h, r.t.	A :B [III] 0:100 (isolated Yield 58%)

	22 mol% Pd/C (10% Pd), $3x10^3$ Pa, EtOAc, 6.5h, r.t.	A :B [III] 65:35	22 mol% Pd/C (10% Pd), $3x10^3$ Pa, EtOAc, 17h, r.t.	A :B [III] 61:39 (isolated Yield 45%)
	22 mol% $Pd/CaCO_3$, $3x10^3$ Pa, EtOAc, 4.5h, r.t.	A :B [IV] 86:14 (isolated Yield 77%)	38 mol% PtO_2, $3x10^3$ Pa, MeOH, 1.5h, r.t.	A :B [IV] 0:100 (isolated Yield 64%)

The ratios of the obtained alkenes (A) and alkanes (B) were detected by ^{1}H-NMR (400 MHz, $CDCl_3$) according to the integrals of the following ^{1}H-NMR-signals (underlined):

I) -C<u>H$_2$</u>-CH$_2$-triazole

II) -CH$_2$-C<u>H$_2$</u>-triazole

III) -CH$_2$-C<u>H$_2$</u>-triazole;

IV) -CH$_2$-C<u>H$_2$</u>-triazole;

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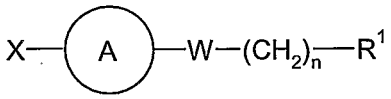
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Patent Claims

1. A process for the preparation of diazine derivatives of formula I

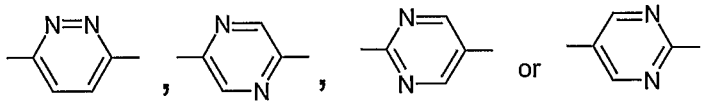


formula I,

wherein

X is fluorine, chlorine or bromine;

ring A is



;

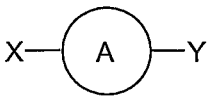
W is $-CH_2-CH_2-$ or -CH=CH-;

n is 1 to 10

R^1 is cycloalkyl, aryl, heterocyclcl or heteroaryl;

comprising the steps of

a) coupling a diazine of formula II

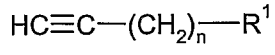


formula II,

wherein

Y is iodine or bromine;
X and ring A are as defined above;
and not both X and Y are bromine;

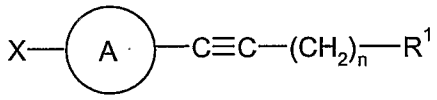
with a compound of formula IV,



formula IV,

wherein R^1 is as defined above;

to obtain the compounds of formula V,



formula V,

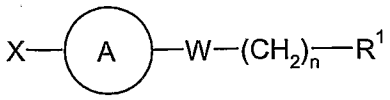
wherein

X, ring A and R^1 are as defined above;

and
b) hydrogenating the compounds of formula V with hydrogen in the presence of a catalyst;

to obtain a compound of formula I.

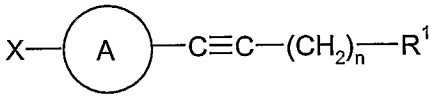
2. A process according to claim 1 , for the preparation of diazine derivatives of formula I



formula I,

wherein X, ring A, W and R^1 have significance given in claim 1,

comprising the step of hydrogenating the compounds of formula IV



formula IV,

wherein X, ring A and R^1 have significance given in claim 1,

with hydrogen in the presence of a catalyst;

to obtain a compound of formula I.

3. A process according to any one of claims 1 to 4, wherein

X is		chlorine or bromine;
n is		1 to 4; and
R^1 is		cycloalkyl, aryl, heterocyclcl or heteroaryl.

4. A process according to any one of claims 1 to 5, wherein
R^1 is heteroaryl.

5. A process according to any one of claims 1 to 4, wherein
W is -CH-CH-.

6. A process according to any one of claims 1 to 4, wherein W is -CH=CH-.

7. A process according to claim 5, wherein the catalyst in the hydrogenation step is Pd/C or PtO_2

8. A process according to claim 5, wherein the catalyst in the hydrogenation step is PtO_2.

9. A process according to any one of claims 5 to 6, wherein the catalyst in the hydrogenation step is $Pd/CaCO_3$.

10. A process according to claim 6, wherein the catalyst in the hydrogenation step is $Pd/CaCO_3$ or $Pd/Pb/CaCO_3$.