(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 May 2014 (22.05.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/076146 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61K 31/5025* (2006.01)

(21) International Application Number:
PCT/EP2013/073758

(22) International Filing Date:
13 November 2013 (13.11.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12192452.6 13 November 2012 (13.11.2012) EP

(71) Applicant: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Strasse 173, 55216 Ingelheim Am Rhein (DE).

(72) Inventors: **ENGELHARDT, Harald**; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **SMETHURST, Christian**; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **STEFFEN, Andreas**; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **REISER, Ulrich**; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **KESSLER, Dirk**; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **GIANNI, Davide**; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE).

(74) Agents: **SIMON, Elke,** et al.; BOEHRINGER INGELHEIM GMBH;, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

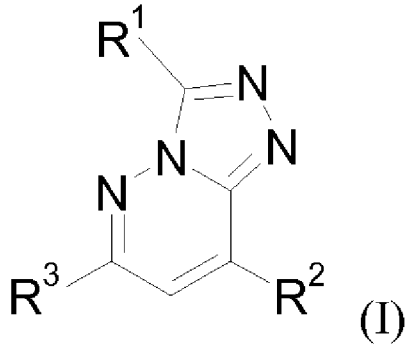
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: TRIAZOLOPYRIDAZINE



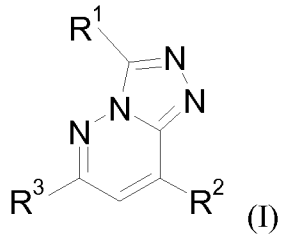
(I)

(57) Abstract: The present invention encompasses compounds of general formula (I), wherein the groups R^1 to R^3 have the meanings given in the claims and in the specification. The compounds of the invention are suitable for the treatment of diseases characterized by excessive or abnormal cell proliferation pharmaceutical preparations containing such compounds and their uses as a medicament.

WO 2014/076146 A1

TRIAZOLOPYRIDAZINE DERIVATIVES AS BROMODOMAIN INHIBITORS

This invention relates to compounds of the general formula (I)



(I)

wherein the groups **R**^{1} to **R**^{3} have the meanings given in the claims and in the specification. The compounds of the invention are suitable for the treatment of diseases characterized by excessive or abnormal cell proliferation, pharmaceutical preparations containing such compounds and their uses as a medicament. The compounds of the invention are BRD4 inhibitors.

Background of the invention

Histone acetylation is most usually associated with the activation of gene transcription, as the modification loosens the interaction of the DNA and the histone octomer by changing the electrostatics. In addition to this physical change, specific proteins bind to acetylated lysine residues within histones to read the epigenetic code. Bromodomains are small (about 110 amino acid) distinct domains within proteins that bind to acetylated lysine resides commonly but not exclusively in the context of histones. There is a family of around 50 proteins known to contain bromodomains, and they have a range of functions within the cell.

The BET family of bromodomain containing proteins comprises 4 proteins (BRD2, BRD3, BRD4 and BRD-T) which contain tandem bromodomains capable of binding to two acetylated lysine residues in close proximity, increasing the specificity of the interaction. Recent research has established a compelling rationale for targeting BRD4 in cancer. BRD4 remains bound to transcriptional start sites of genes expressed during the entry into the G1 phase of the cell cycle, and is functioning to recruit the positive transcription elongation factor complex

(P-TEFb), resulting in increased expression of growth promoting genes (Yang and Zhou, Mol. Cell. Biol. 28, 967, 2008). Importantly, BRD4 has been identified as a component of a recurrent t(15;19) chromosomal translocation in an aggressive form of human squamous carcinoma (French et al., Cancer Res. 63, 304, 2003). Such translocations express the tandem N-terminal bromodomains of BRD4 as an in-frame chimera with the NUT (nuclear protein in testis) protein, genetically defining the so-called NUT midline carcinoma (NMC). Functional studies in patient-derived NMC cell lines have validated the essential role of the BRD4-NUT oncoprotein in maintaining the proliferation and the differentiation block of these malignant cells. In addition, BRD4 has been identified as a critical sensitivity determinant in a genetically defined AML mouse model (Zuber et al., Nature 2011 478(7370):524-8). Suppression of BRD4 led to robust anti-leukemic effects in vitro and in vivo, accompanied by terminal myeloid differentiation. Interestingly, BRD4 inhibition triggered MYC down-regulation in a broad array of mouse and human leukemia cell lines examined, indicating that small molecule BRD4 inhibitors may provide a means to suppress the MYC pathway in a range of AML subtypes.

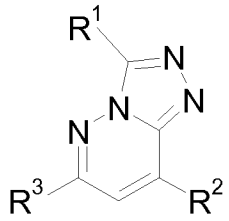
Finally, the other family members of the BET family have also been reported to have some function in controlling or executing aspects of the cell cycle, and have been shown to remain in complex with chromosomes during cell division - suggesting a role in the maintenance of epigenetic memory (Leroy et ai, Mol. Cell. 2008 30(1):51-60).

Examples of bromodomain inhibitors are benzodiazepine derivatives, disclosed in WO2011/054553, and imidazo [4,5] quinoline derivatives, disclosed in WO2011/054846.

Thus, there is the need to provide BRD4 inhibitors useful for the prevention and/or treatment of diseases characterized by excessive or abnormal cell proliferation, such as cancer.

Detailed description of the invention

The present invention relates to compounds of formula (**I**)



(I)

wherein,

R^1 is $-C_{1-3}$alkyl or $-C_{1-3}$haloalkyl;

R^2 is selected from $-NHR^4$, $-C_{1-5}$alkyl, $-C_{1-5}$haloalkyl, halogen and $-S-C_{1-3}$alkyl;

R^3 is selected from $-N(R^7, R^8)$ and 5-12 membered heteroaryl, wherein the heteroaryl group is substituted with $-X-R^{10}$ and optionally further substituted with one ore more groups independently selected from R^9;

R^4 is selected from $-C_{1-5}$alkyl and 5-12 memebered heterocycloalkyl, which can be optionally substituted with one or more groups independently selected from R^5;

R^5 is selected from $-C_{1-5}$alkyl, $-C_{1-5}$haloalkyl, $-C_{1-3}$alkylene-O-C_{1-3}alkyl, $-C(O)-C_{1-3}$alkyl, -C(O)-H and $-S(O)_2-R^6$;

R^6 is selected from $-C_{1-3}$alkylene-$N(C_{1-3}alkyl)_2$, $-C_{1-3}$alkylene-NH_2 and 5-12 membered heterocycloalkyl, wherein the heterocycloalkyl can be optionally substituted with $-C_{1-3}$alkyl;

R^7, R^8 can be the same or different and are independently selected from $-C_{1-3}$alkyl, $-C_{1-3}$alkylene-C_{6-10}aryl, $-C_{1-3}$alkylene-(5-12 membered heteroaryl), wherein the aryl and the heteroaryl groups can be optionally

substituted with one or more groups independently selected from halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, -C_{1-3}haloalkyl and -O-C_{1-3}haloalkyl;

R^9 is selected from-C_{1-5}alkyl, halogen, -C_{1-3}alkylene-O-C_{1-3}alkyl, -C_{1-5}alkylene-N(-C_{1-5}alkyl, -C_{1-5}alkyl), 5-12 memebered heterocycloalkyl,wherein the heterocycloalkyl group can be optionally substituted with -C_{1-3}alkyl, or

R^9 is selected from -C_{6-10}aryl and 5-12 memebered heteroaryl, wherein the aryl and heteroaryl groups can be optionally and independently substituted with one ore more groups selected from halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, -C_{1-3}haloalkyl, -O-C_{1-3}haloalkyl, -N(C_{1-5}alkyl, C_{1-5}alkyl) and -NH-C_{1-5}alkyl;

X is -C_{1-3}alkylene- or -O-;

R^{10} is-C_{6-10}aryl or 5-12 membered heteroaryl, each of which groups can be optionally substituted with one or more groups selected from halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, -C_{1-3}haloalkyl, -O-C_{1-3}haloalkyl;

wherein the compounds of formula (I) may be optionally be present in the form of salts.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^1 is -CH_3.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^2 is NHR^4.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^2 is NHR^4 and R^3 is as defined herein above and below.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^3 is 5-12 membered heteroaryl and R^2 is as defined herein above and below.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^2 is $-NHR^4$ and R^4 is a 5-6 membered heterocycloalkyl, optionally substituted as defined herein in the description and claims.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^2 is $-NHR^4$ and R^4 is piperidine substituted with one group selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$ and $-(CH_2)_2-O-CH_3$.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^2 is $-NHR^4$ and R^4 is $-C_{1-3}$alkyl.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^2 is $-NHR^4$ and R^4 is $-CH_3$ or $-CH(CH_3)_2$.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^2 is $-C_{1-3}$alkyl.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^3 is $-N(R^7,R^8)$, wherein R^7 is $-C_{1-3}$alkyl and R^8 $-C_{1-3}$alkylene-C_{6-10}aryl, wherein the aryl can be optionally substituted with halogen.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^3 is $-N(CH_3)-CH_2$-phenyl, wherein the phenyl can be optionally substituted with halogen.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^3 is a 5-9 membered heteroaryl substituted with $-X-R^{10}$ and optionally further substituted with one or more groups independently selected from R^9, wherein R^9, R^{10} and X are as defined herein in the description and the claims. Preferably, R^3 is optionally further substituted with one or two R^9.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein $-X-R^{10}$ is selected from $-CH_2$-phenyl, $-CH_2$-pyridyl, -O-pyridyl, -O-phenyl, each of which phenyl or pyridyl groups is optionally substituted with halogen or $-C_{1-3}$alkyl.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein-X-R^{10} is selected from -CH_2-phenyl, -CH_2-pyridyl, -O-phenyl, -O-pyridyl, each of which pyridyl or phenyl group is optionally substituted with –F or –CH_3.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein-X-R^{10} is selected from -CH_2-phenyl, -CH_2-pyridyl, -O-phenyl, -O-pyridyl, wherein the phenyl group is optionally substituted with -F.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^3 is pyrazolyl substituted with -X-R^{10} and optionally further substituted with one or more groups independently selected from R^9, wherein R^9, R^{10} and X are as defined herein in the description and the claims.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^3 is pyrazolyl substituted with -CH_2-pyridyl, -O-pyridyl, -CH_2-phenyl or -O-phenyl and optionally further substituted with -$C_{1\text{-}5}$alkyl.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein R^9 is selected from -CH_3 and –$CH(CH_3)_2$.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein the 5-9 membered heteroaryl in R^3 position is attached to the core of the structure via a carbon atom.

In a preferred embodiment, the invention relates to compounds of formula (I), wherein the pyridyl moiety in R^{10} position is bound to –X- in 2-position.

In a further embodiment, the invention relates to compounds of formula (I) for use in the treatment of cancer.

In a further embodiment, the invention relates to compound of general formula (I) according to anyone of the embodiments described herein in the description and the claims - or the pharmaceutically acceptable salts thereof - for use in the treatment and/or prevention of cancer.

In a further embodiment, the invention relates to pharmaceutical preparation comprising as active substance one or more compounds of general formula (I) according to anyone of the embodiments described herein in the description and the claims optionally in combination with conventional excipients and/or carriers.

In a further embodiment, the invention relates to pharmaceutical preparation comprising a compound of general formula (I) according to anyone of the embodiments described herein in the description and the claims - or one of the pharmaceutically acceptable salts thereof - and at least one other cytostatic or cytotoxic active substance, different from formula (I).

The present invention further relates to hydrates, solvates, polymorphs, metabolites, derivatives and prodrugs of compounds of general formula (I).

The present invention further relates to a pharmaceutically acceptable salt of a compound of general formula (I) with anorganic or organic acids or bases.

In another aspect the invention relates to compounds of general formula (I) – or the pharmaceutically acceptable salts thereof – as medicaments.

In another aspect the invention relates to compounds of general formula (I) – or the pharmaceutically acceptable salts thereof – for use in a method for treatment of the human or animal body.

In another aspect the invention relates to compounds of general formula (I) – or the pharmaceutically acceptable salts thereof – for use in the treatment and/or prevention of cancer, infections, inflammations and autoimmune diseases.

In another aspect the invention relates to compounds of general formula (I) – or the pharmaceutically acceptable salts thereof – for use in a method for treatment and/or prevention of cancer, infections, inflammations and autoimmune diseases in the human and animal body.

In another aspect the invention relates to compounds of general formula (I) – or the pharmaceutically acceptable salts thereof – for use in the treatment and/or prevention of cancer.

In another aspect the invention relates to the use of the compounds of general

formula (I) – or the pharmaceutically acceptable salts thereof –in the treatment and/or prevention of cancer.

In another aspect the invention relates to compounds of general formula (I) – or the pharmaceutically acceptable salts thereof – for use in a method for treatment and/or prevention of cancer in the human or animal body.

In another aspect the invention relates to compounds of general formula (I) – or the pharmaceutically acceptable salts thereof – for use in the treatment and/or prevention of hematopoietic malignancies, preferably AML, MM.

In another aspect the invention relates to compounds of general formula (I) – or the pharmaceutically acceptable salts thereof – for use in the treatment and/or prevention of solid tumors, preferably to lung, liver, colon, brain, thyroid, pancreas, breast, ovary and prostate cancer.

In another aspect the invention relates to a process for the treatment and/or prevention of cancer comprising administering a therapeutically effective amount of a compound of general formula (I) – or one of the pharmaceutically acceptable salts thereof – to a human being.

In another aspect the invention relates to a pharmaceutical preparation containing as active substance one or more compounds of general formula (I) – or the pharmaceutically acceptable salts thereof – optionally in combination with conventional excipients and/or carriers.

In another aspect the invention relates to a pharmaceutical preparation comprising a compound of general formula (I) – or one of the pharmaceutically acceptable salts thereof – and at least one other cytostatic or cytotoxic active substance, different from formula (I).

Definitions

Terms that are not specifically defined here have the meanings that are apparent to the skilled man in the light of the overall disclosure and the context as a whole.

As used herein, the following definitions apply, unless stated otherwise.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, -C_{1-5}alkyl means an alkyl group or radical having 1 to 5 carbon atoms. In general, for groups comprising two or more subgroups, the first named sub-group is the radical attachment point, for example the substitutent -C_{1-5}alkyl-C_{3-10}cylcoalkyl, means a C_{3-10}cylcoalkyl group which is bound to a C_{1-5}alkyl, the latter of which is bound to the core structure or to the group to which the substitutent is attached.

The indication of the number of members in groups that contain one or more heteroatom(s) (heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocycylalkyl) relates to the total atomic number of all the ring members or chain members or the total of all the ring and chain members.

The person skilled in the art will appreciate that substituent groups containing a nitrogen atom can also be indicated as **amine** or **amino**. Similarly, groups containing oxygen atom can also be indicated with **-oxy**, like for example **alkoxy**. Groups containing –C(O)- can also be indicated as **carboxy**; groups containing -NC(O)- can also be indicated as **amide**; groups containing –NC(O)N- can also be indicated as **urea**; groups containing –$NS(O)_2$- can also be indicated as **sulfonamide**.

Alkyl denotes monovalent, saturated hydrocarbon chains, which may be present in both linear and branched form. If an **alkyl** is substituted, the substitution may take place independently of one another, by mono- or polysubstitution in each case, on all the hydrogen-carrying carbon atoms.

The term "**C_{1-5}-alkyl**" includes for example methyl (Me; -CH_3), ethyl (Et; -CH_2CH_3), 1-propyl (*n*-propyl; *n*-Pr; -$CH_2CH_2CH_3$), 2-propyl (*i*-Pr; *iso*-propyl; -$CH(CH_3)_2$), 1-butyl (*n*-butyl; *n*-Bu; -$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (*iso*-butyl; *i*-Bu; -$CH_2CH(CH_3)_2$), 2-butyl (*sec*-butyl; *sec*-Bu; -$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (*tert*-butyl; *t*-Bu; -$C(CH_3)_3$), 1-pentyl (*n*-pentyl; -$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (-$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (-$CH(CH_2CH_3)_2$), 3-methyl-1-butyl (*iso*-pentyl; -$CH_2CH_2CH(CH_3)_2$), 2-methyl-2-

butyl (-C(CH_3)$_2$$CH_2$$CH_3$), 3-methyl-2-butyl (-CH(CH_3)CH(CH_3)$_2$), 2,2-dimethyl-1-propyl (*neo*-pentyl; -CH_2C(CH_3)$_3$), 2-methyl-1-butyl (-CH_2CH(CH_3)$CH_2$$CH_3$).

By the terms propyl, butyl, pentyl, etc. without any further definition are meant saturated hydrocarbon groups with the corresponding number of carbon atoms, wherein all isomeric forms are included.

The above definition for **alkyl** also applies if **alkyl** is a part of another group such as for example C_{x-y}-**alkyl**amino or C_{x-y}-**alkyl**oxy or C_{x-y}-**alk**oxy, wherein C_{x-y}-**alkyl**oxy and C_{x-y}-**alk**oxy indicate the same group.

The term **alkylene** can also be derived from **alkyl**. **Alkylene** is bivalent, unlike **alkyl,** and requires two binding partners. Formally, the second valency is produced by removing a hydrogen atom in an **alkyl**. Corresponding groups are for example -CH_3 and -CH_2, -$CH_2$$CH_3$ and -$CH_2$$CH_2$ or >$CHCH_3$ etc.

The term "**C_{1-4}-alkylene**" includes for example -(CH_2)-, -(CH_2-CH_2)-, -(CH(CH_3))-, -(CH_2-CH_2-CH_2)-, -(C(CH_3)$_2$)-, -(CH($CH_2$$CH_3$))-, -(CH($CH_3$)-$CH_2$)-, -($CH_2$-CH($CH_3$))-, -($CH_2$-$CH_2$-$CH_2$-$CH_2$)-, -($CH_2$-$CH_2$-CH($CH_3$))-, -(CH($CH_3$)-$CH_2$-$CH_2$)-, -($CH_2$-CH($CH_3$)-$CH_2$)-, -($CH_2$-C($CH_3$)$_2$)-, -(C ($CH_3$)$_2$-$CH_2$)-, -(CH($CH_3$)-CH($CH_3$))-, -($CH_2$-CH($CH_2$$CH_3$))-, -(CH($CH_2$$CH_3$)-$CH_2$)-, -(CH($CH_2$$CH_2$$CH_3$))-, -(CHCH($CH_3$)$_2$)- and -C($CH_3$)($CH_2$$CH_3$)-.

Other examples of **alkylene** are methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 1.1-dimethylethylene, 1,2-dimethylethylene, pentylene, 1,1-dimethylpropylene, 2,2-dimethylpropylene, 1,2-dimethylpropylene, 1,3-dimethylpropylene, etc.

By the generic terms propylene, butylene, pentylene, hexylene etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, i.e. propylene includes 1-methylethylene and butylene includes 1-methylpropylene, 2-methylpropylene, 1,1-dimethylethylene and 1,2-dimethylethylene.

The above definition for **alkylene** also applies if **alkylene** is part of another group such as for example in HO-C_{x-y}-**alkylen**amino or H_2N-C_{x-y}-**alkylen**oxy.

Unlike **alkyl, alkenyl** consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C double bond. If in an **alkyl** as hereinbefore defined having at least two carbon atoms, two hydrogen atoms on adjacent carbon atoms are formally removed and the free valencies are saturated to form a second bond, the corresponding **alkenyl** is formed.

Examples of **alkenyl** are vinyl (ethenyl), prop-1-enyl, allyl (prop-2-enyl), isopropenyl, but-1-enyl, but-2-enyl, but-3-enyl, 2-methyl-prop-2-enyl, 2-methyl-prop-1-enyl, 1-methyl-prop-2-enyl, 1-methyl-prop-1-enyl, 1-methylidenepropyl, pent-1-enyl, pent-2-enyl, pent-3-enyl, pent-4-enyl, 3-methyl-but-3-enyl, 3-methyl-but-2-enyl, 3-methyl-but-1-enyl, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, hex-5-enyl, 2,3-dimethyl-but-3-enyl, 2,3-dimethyl-but-2-enyl, 2-methylidene-3-methylbutyl, 2,3-dimethyl-but-1-enyl, hexa-1,3-dienyl, hexa-1,4-dienyl, penta-1,4-dienyl, penta-1,3-dienyl, buta-1,3-dienyl, 2,3-dimethylbuta-1,3-diene etc.

By the generic terms propenyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, heptadienyl, octadienyl, nonadienyl, decadienyl etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, i.e. propenyl includes prop-1-enyl and prop-2-enyl, butenyl includes but-1-enyl, but-2-enyl, but-3-enyl, 1-methyl-prop-1-enyl, 1-methyl-prop-2-enyl etc.

Alkenyl may optionally be present in the *cis* or *trans* or *E* or *Z* orientation with regard to the double bond(s).

The above definition for **alkenyl** also applies when **alkenyl** is part of another group such as for example in C_{x-y}-**alkenyl**amino or C_{x-y}-**alkenyl**oxy.

Unlike **alkylene, alkenylene** consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C double bond. If in an **alkylene** as hereinbefore defined having at least two carbon atoms, two hydrogen atoms at adjacent carbon atoms are formally removed and the free valencies are saturated to form a second bond, the corresponding **alkenylene** is formed.

Examples of **alkenylene** are ethenylene, propenylene, 1-methylethenylene, butenylene, 1-methylpropenylene, 1,1-dimethylethenylene,

1,2-dimethylethenylene, pentenylene, 1,1-dimethylpropenylene, 2,2-dimethylpropenylene, 1,2-dimethylpropenylene, 1,3-dimethylpropenylene, hexenylene etc.

By the generic terms propenylene, butenylene, pentenylene, hexenylene etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, i.e. propenylene includes 1-methylethenylene and butenylene includes 1-methylpropenylene, 2-methylpropenylene, 1,1-dimethylethenylene and 1,2-dimethylethenylene.

Alkenylene may optionally be present in the *cis* or *trans* or *E* or *Z* orientation with regard to the double bond(s).

The above definition for **alkenylene** also applies when **alkenylene** is a part of another group as in for example HO-C_{x-y}-**alkenylen**amino or H_2N-C_{x-y}-**alkenylen**oxy.

Unlike **alkyl, alkynyl** consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C triple bond. If in an **alkyl** as hereinbefore defined having at least two carbon atoms, two hydrogen atoms in each case at adjacent carbon atoms are formally removed and the free valencies are saturated to form two further bonds, the corresponding **alkynyl** is formed.

Examples of **alkynyl** are ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, 1-methyl-prop-2-ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, 3-methyl-but-1-ynyl.

By the generic terms propynyl, butynyl, pentynyl, etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, i.e. propynyl includes prop-1-ynyl and prop-2-ynyl, butynyl includes but-1-ynyl, but-2-ynyl, but-3-ynyl, 1-methyl-prop-1-ynyl, 1-methyl-prop-2-ynyl.

If a hydrocarbon chain carries both at least one double bond and also at least one triple bond, by definition it belongs to the **alkynyl** subgroup.

The above definition for **alkynyl** also applies if **alkynyl** is part of another group, as in C_{x-y}-**alkynyl**amino or C_{x-y}-**alkynyl**oxy, for example.

Unlike **alkylene, alkynylene** consists of at least two carbon atoms, wherein at least two adjacent carbon atoms are joined together by a C-C triple bond. If in an **alkylene** as hereinbefore defined having at least two carbon atoms, two hydrogen atoms in each case at adjacent carbon atoms are formally removed and the free valencies are saturated to form two further bonds, the corresponding **alkynylene** is formed.

Examples of **alkynylene** are ethynylene, propynylene, 1-methylethynylene, butynylene, 1-methylpropynylene, 1,1-dimethylethynylene, 1,2-dimethylethynylene, pentynylene, 1,1-dimethylpropynylene, 2,2-dimethylpropynylene, 1,2-dimethylpropynylene, 1,3-dimethylpropynylene, hexynylene etc.

By the generic terms propynylene, butynylene, pentynylene, etc. without any further definition are meant all the conceivable isomeric forms with the corresponding number of carbon atoms, i.e. propynylene includes 1-methylethynylene and butynylene includes 1-methylpropynylene, 2-methylpropynylene, 1,1-dimethylethynylene and 1,2-dimethylethynylene.

The above definition for **alkynylene** also applies if **alkynylene** is part of another group, as in HO-C_{x-y}-**alkynylene**amino or H_2N-C_{x-y}-**alkynylene**oxy, for example.

By **heteroatoms** are meant oxygen, nitrogen and sulphur atoms.

Haloalkyl (haloalkenyl, haloalkynyl) is derived from the previously defined **alkyl (alkenyl, alkynyl)** by replacing one or more hydrogen atoms of the hydrocarbon chain independently of one another by halogen atoms, which may be identical or different. If a **haloalkyl (haloalkenyl, haloalkynyl)** is to be further substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms.

Examples of **haloalkyl (haloalkenyl, haloalkynyl)** are $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, $-CHFCF_3$, $-CH_2CF_3$, $-CF_2CH_3$, $-CHFCH_3$, $-CF_2CF_2CF_3$, $-CF_2CH_2CH_3$,

-$CF=CF_2$, -$CCl=CH_2$, -$CBr=CH_2$, -$CI=CH_2$, -$C\equiv C-CF_3$, -$CHFCH_2CH_3$, -$CHFCH_2CF_3$ etc.

From the previously defined **haloalkyl (haloalkenyl, haloalkynyl)** are also derived the terms **haloalkylene (haloalkenylene, haloalkynylene)**. **Haloalkylene (haloalkenyl, haloalkynyl)**, unlike **haloalkyl**, is bivalent and requires two binding partners. Formally, the second valency is formed by removing a hydrogen atom from a **haloalkyl**.

Corresponding groups are for example -CH_2F and -CHF-, -$CHFCH_2F$ and -CHFCHF- or >$CFCH_2F$ etc.

The above definitions also apply if the corresponding halogen groups are part of another group.

Halogen relates to fluorine, chlorine, bromine and/or iodine atoms.

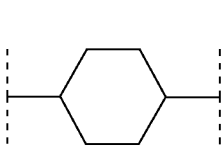
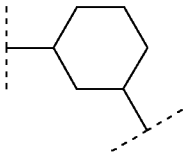
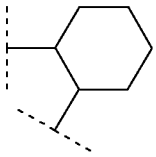
Cycloalkyl is made up of the subgroups **monocyclic hydrocarbon rings**, **bicyclic hydrocarbon rings** and **spiro-hydrocarbon rings**. The systems are saturated. In bicyclic hydrocarbon rings two rings are joined together so that they have at least two carbon atoms together. In spiro-hydrocarbon rings a carbon atom (spiroatom) belongs to two rings together. If a **cycloalkyl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. **Cycloalkyl** itself may be linked as a substituent to the molecule via every suitable position of the ring system.

Examples of **cycloalkyl** are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.0]hexyl, bicyclo[3.2.0]heptyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[4.3.0]nonyl (octahydroindenyl), bicyclo[4.4.0]decyl (decahydronaphthalene), bicyclo[2.2.1]heptyl (norbornyl), bicyclo[4.1.0]heptyl (norcaranyl), bicyclo-[3.1.1]heptyl (pinanyl), spiro[2.5]octyl, spiro[3.3]heptyl etc.

The above definition for **cycloalkyl** also applies if **cycloalkyl** is part of another group as in C_{x-y}-**cycloalkyl**amino or C_{x-y}-**cycloalkyl**oxy, for example.

If the free valency of a **cycloalkyl** is saturated, then an **alicyclic group** is obtained.

The term **cycloalkylene** can thus be derived from the previously defined **cycloalkyl**. **Cycloalkylene**, unlike **cycloalkyl**, is bivalent and requires two binding partners. Formally, the second valency is obtained by removing a hydrogen atom from a **cycloalkyl**. Corresponding groups are for example

cyclohexyl and  or  or  (cyclohexylene).

The above definition for **cycloalkylene** also applies if **cycloalkylene** is part of another group as in HO-C_{x-y}-**cycloalkylene**amino or H_2N-C_{x-y}-**cycloalkylene**oxy, for example.

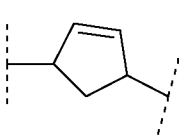
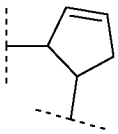
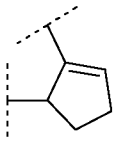
Cycloalkenyl is also made up of the subgroups **monocyclic hydrocarbon rings**, **bicyclic hydrocarbon rings** and **spiro-hydrocarbon rings**. However, the systems are unsaturated, i.e. there is at least one C-C double bond but no aromatic system. If in a **cycloalkyl** as hereinbefore defined two hydrogen atoms at adjacent cyclic carbon atoms are formally removed and the free valencies are saturated to form a second bond, the corresponding **cycloalkenyl** is obtained. If a **cycloalkenyl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. **Cycloalkenyl** itself may be linked as a substituent to the molecule via every suitable position of the ring system.

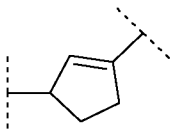
Examples of **cycloalkenyl** are cycloprop-1-enyl, cycloprop-2-enyl, cyclobut-1-enyl, cyclobut-2-enyl, cyclopent-1-enyl, cyclopent-2-enyl, cyclopent-3-enyl, cyclohex-1-enyl, cyclohex-2-enyl, cyclohex-3-enyl, cyclohept-1-enyl, cyclohept-2-enyl, cyclohept-3-enyl, cyclohept-4-enyl, cyclobuta-1,3-dienyl, cyclopenta-1,4-dienyl, cyclopenta-1,3-dienyl, cyclopenta-2,4-dienyl, cyclohexa-1,3-dienyl, cyclohexa-1,5-dienyl, cyclohexa-2,4-dienyl, cyclohexa-1,4-dienyl, cyclohexa-2,5-dienyl, bicyclo[2.2.1]hepta-2,5-dienyl (norborna-2,5-dienyl), bicyclo[2.2.1]hept-2-enyl (norbornenyl), spiro[4.5]dec-2-ene etc.

The above definition for **cycloalkenyl** also applies when **cycloalkenyl** is part of another group as in C_{x-y}-**cycloalkenyl**amino or C_{x-y}-**cycloalkenyl**oxy, for example.

If the free valency of a **cycloalkenyl** is saturated, then an **unsaturated alicyclic group** is obtained.

The term **cycloalkenylene** can thus be derived from the previously defined **cycloalkenyl**. **Cycloalkenylene**, unlike **cycloalkenyl**, is bivalent and requires two binding partners. Formally the second valency is obtained by removing a hydrogen atom from a **cycloalkenyl**. Corresponding groups are for example

cyclopentenyl and  or  or  or

 (cyclopentenylene) etc.

The above definition for **cycloalkenylene** also applies when **cycloalkenylene** is part of another group as in HO-C_{x-y}-**cycloalkenylene**amino or H_2N-C_{x-y}-**cycloalkenylene**oxy, for example.

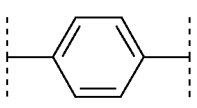
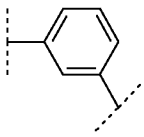
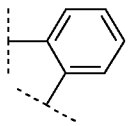
Aryl denotes a mono-, bi- or tricyclic group with at least one aromatic carbocycle. Preferably it denotes a a monocyclic group with six carbon atoms (phenyl) or a bicyclic group with nine or ten carbon atoms (two six-membered rings or one six-membered ring with a five-membered ring), wherein the second ring may also be aromatic or, however, may also be saturated or partially saturated. If an **aryl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. **Aryl** itself may be linked as a substituent to the molecule via every suitable position of the ring system.

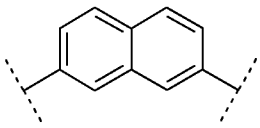
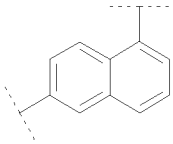
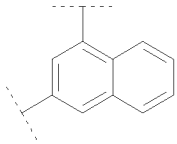
Examples of **aryl** are phenyl, naphthyl, indanyl (2,3-dihydroindenyl), indenyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl (1,2,3,4-tetrahydronaphthyl, tetralinyl), dihydronaphthyl (1,2- dihydronaphthyl), fluorenyl etc.

The above definition of **aryl** also applies when **aryl** is part of another group as in **aryl**amino or **aryl**oxy, for example.

If the free valency of an **aryl** is saturated, then an **aromatic group** is obtained.

The term **arylene** can also be derived from the previously defined **aryl**. **Arylene**, unlike **aryl**, is bivalent and requires two binding partners. Formally, the second valency is formed by removing a hydrogen atom from an **aryl**. Corresponding groups are e.g.

phenyl and  or  or  (*o*, *m*, *p*-phenylene),

naphthyl and  or  or  etc.

The above definition for **arylene** also applies when **arylene** is part of another group as in HO-**aryl**eneamino or H_2N-**aryl**eneoxy for example.

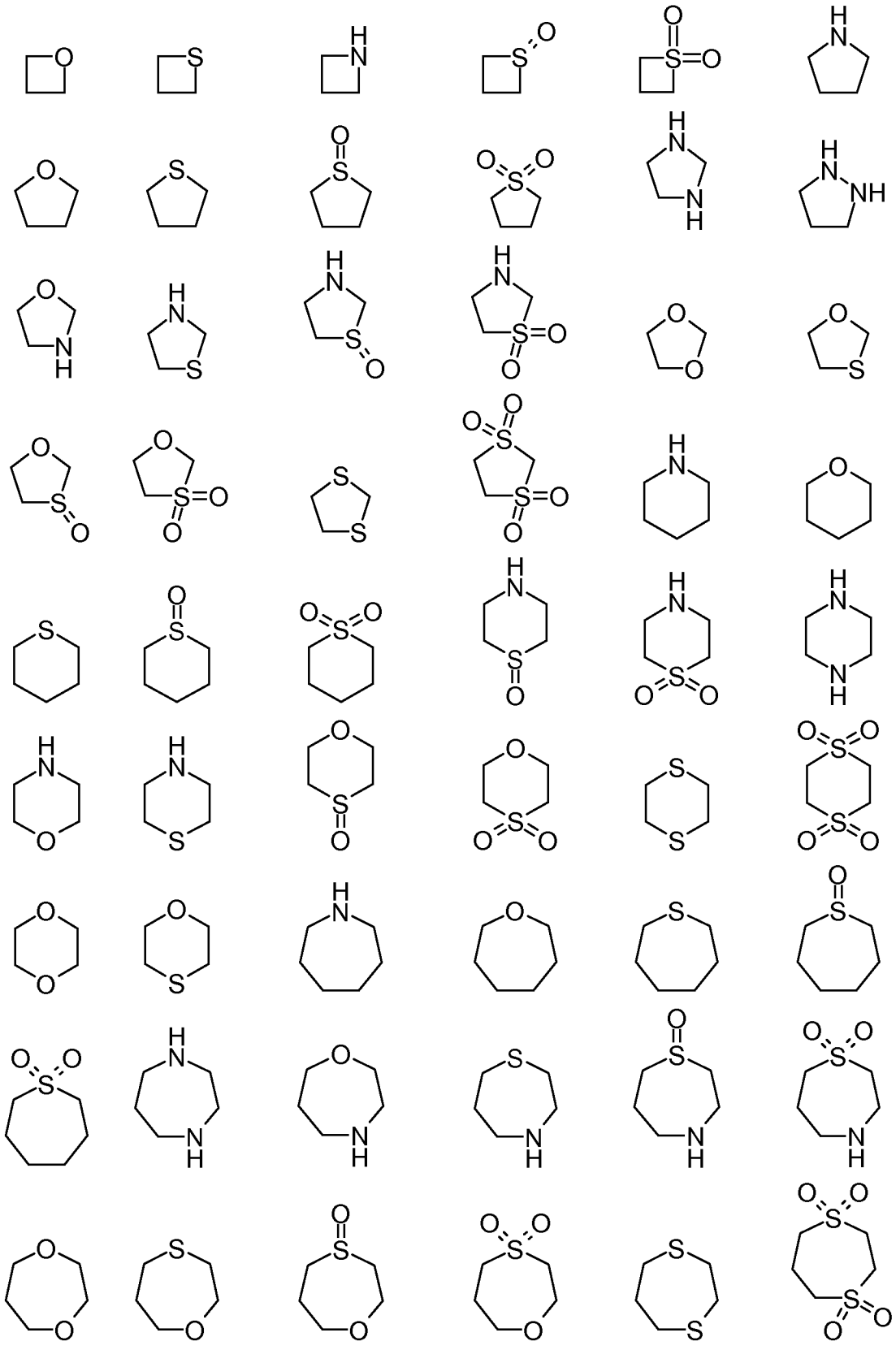
Heterocyclyl denotes ring systems, which are derived from the previously defined **cycloalkyl**, **cycloalkenyl** and **aryl** by replacing one or more of the groups -CH_2- independently of one another in the hydrocarbon rings by the groups -O-, -S- or -NH- or by replacing one or more of the groups =CH- by the group =N-, wherein a total of not more than five heteroatoms may be present, at least one carbon atom may be present between two oxygen atoms and between two sulphur atoms or between one oxygen and one sulphur atom and the ring as a whole must have chemical stability. Heteroatoms may optionally be present in all the possible oxidation stages (sulphur → sulphoxide -SO, sulphone -SO_2-; nitrogen → N-oxide).

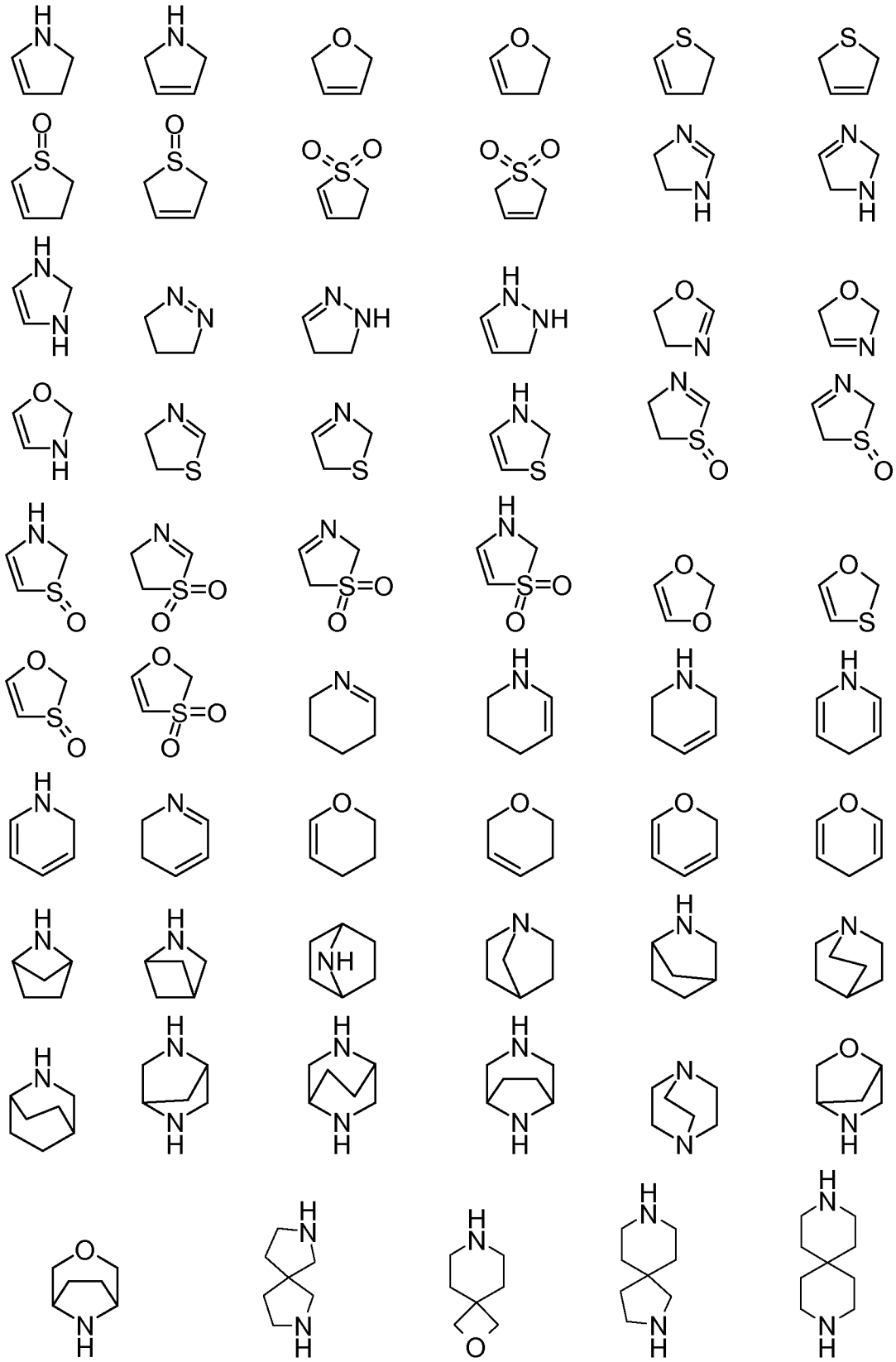
A direct result of the derivation from **cycloalkyl**, **cycloalkenyl** and **aryl** is that **heterocyclyl** is made up of the subgroups **monocyclic heterorings**, **bicyclic heterorings**, **tricyclic heterorings** and **spiro-heterorings**, which may be present in saturated or unsaturated form. Saturated and unsaturated, non aromatic, **heterocyclyl** are also defined as **heterocycloalkyl**. By unsaturated is meant that

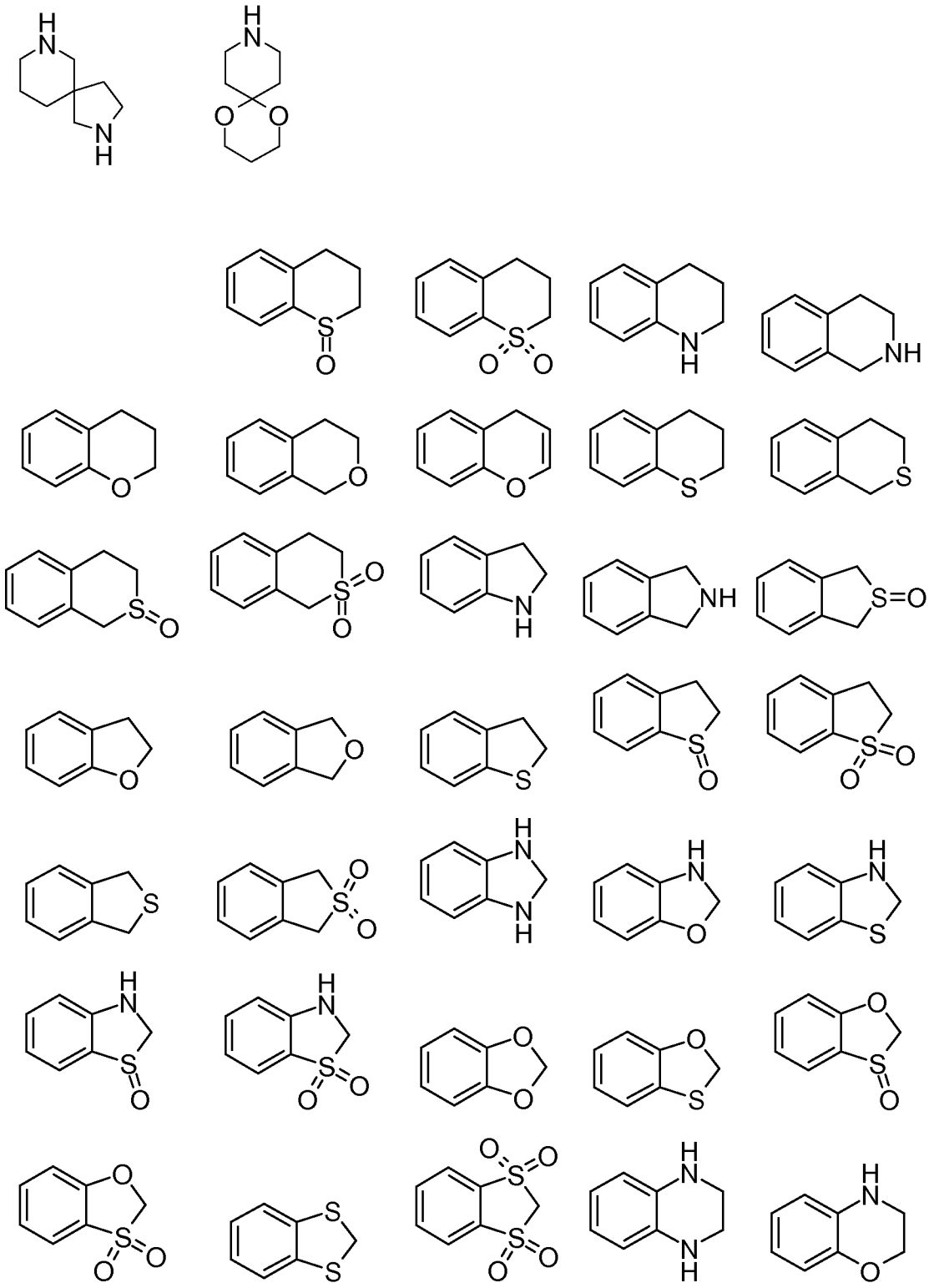
there is at least one double bond in the ring system in question, but no heteroaromatic system is formed. In bicyclic heterorings two rings are linked together so that they have at least two (hetero)atoms in common. In spiro-heterorings a carbon atom (spiroatom) belongs to two rings together. If a **heterocyclyl** is substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon and/or nitrogen atoms. **Heterocyclyl** itself may be linked as a substituent to the molecule via every suitable position of the ring system. When the heterocyclyl has a nitrogen atom, the preferred position to bind the heterocyclyl substituent to the molecule is the nitrogen atom.

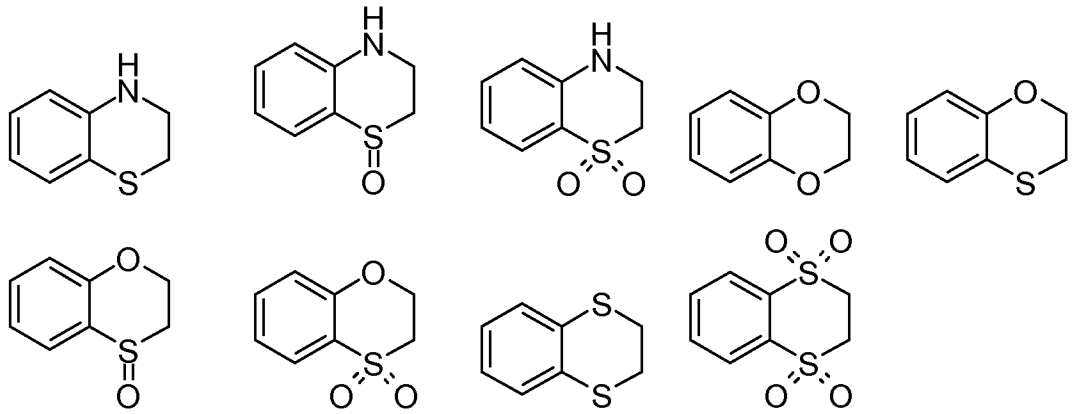
Examples of **heterocyclyl** are tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, thiazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, oxiranyl, aziridinyl, azetidinyl, 1,4-dioxanyl, azepanyl, diazepanyl, morpholinyl, thiomorpholinyl, homomorpholinyl, homopiperidinyl, homopiperazinyl, homothiomorpholinyl, thiomorpholinyl-*S*-oxide, thiomorpholinyl-*S,S*-dioxide, 1,3-dioxolanyl, tetrahydropyranyl, tetrahydrothiopyranyl, [1.4]-oxazepanyl, tetrahydrothienyl, homothiomorpholinyl-*S,S*-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridyl, dihydro-pyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl-*S*-oxide, tetrahydrothienyl-*S,S*-dioxide, homothiomorpholinyl-*S*-oxide, 2,3-dihydroazet, 2*H*-pyrrolyl, 4*H*-pyranyl, 1,4-dihydropyridinyl, 8-azabicyclo[3.2.1]octyl, 8-azabicyclo[5.1.0]octyl, 2-oxa-5-azabicyclo[2.2.1]heptyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 3,8-diaza-bicyclo[3.2.1]octyl, 2,5-diaza-bicyclo-[2.2.1]heptyl, 1-aza-bicyclo[2.2.2]octyl, 3,8-diaza-bicyclo[3.2.1]octyl, 3,9-diaza-bicyclo[4.2.1]nonyl, 2,6-diaza-bicyclo[3.2.2]nonyl, 1,4-dioxa-spiro[4.5]decyl, 1-oxa-3.8-diaza-spiro[4.5]decyl, 2,6-diaza-spiro[3.3]heptyl, 2,7-diaza-spiro[4.4]-nonyl, 2,6-diaza-spiro[3.4]octyl, 3,9-diaza-spiro[5.5]undecyl, 2.8-diaza-spiro[4.5]-decyl etc.

Further examples are the structures illustrated below, which may be attached via each hydrogen-carrying atom (exchanged for hydrogen):





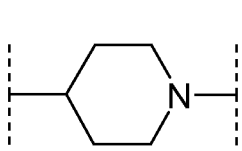
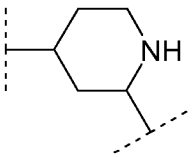
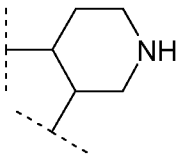


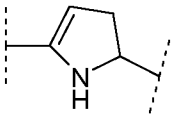
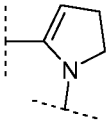
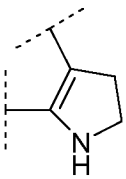
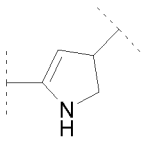


The above definition of **heterocyclyl** also applies if **heterocyclyl** is part of another group as in **heterocyclyl**amino or **heterocyclyl**oxy for example.

If the free valency of a **heteroyclyl** is saturated, then a **heterocyclic group** is obtained.

The term **heterocyclylene** is also derived from the previously defined **heterocyclyl**. **Heterocyclylene**, unlike **heterocyclyl**, is bivalent and requires two binding partners. Formally, the second valency is obtained by removing a hydrogen atom from a **heterocyclyl**. Corresponding groups are for example

piperidinyl and  or  or  ,

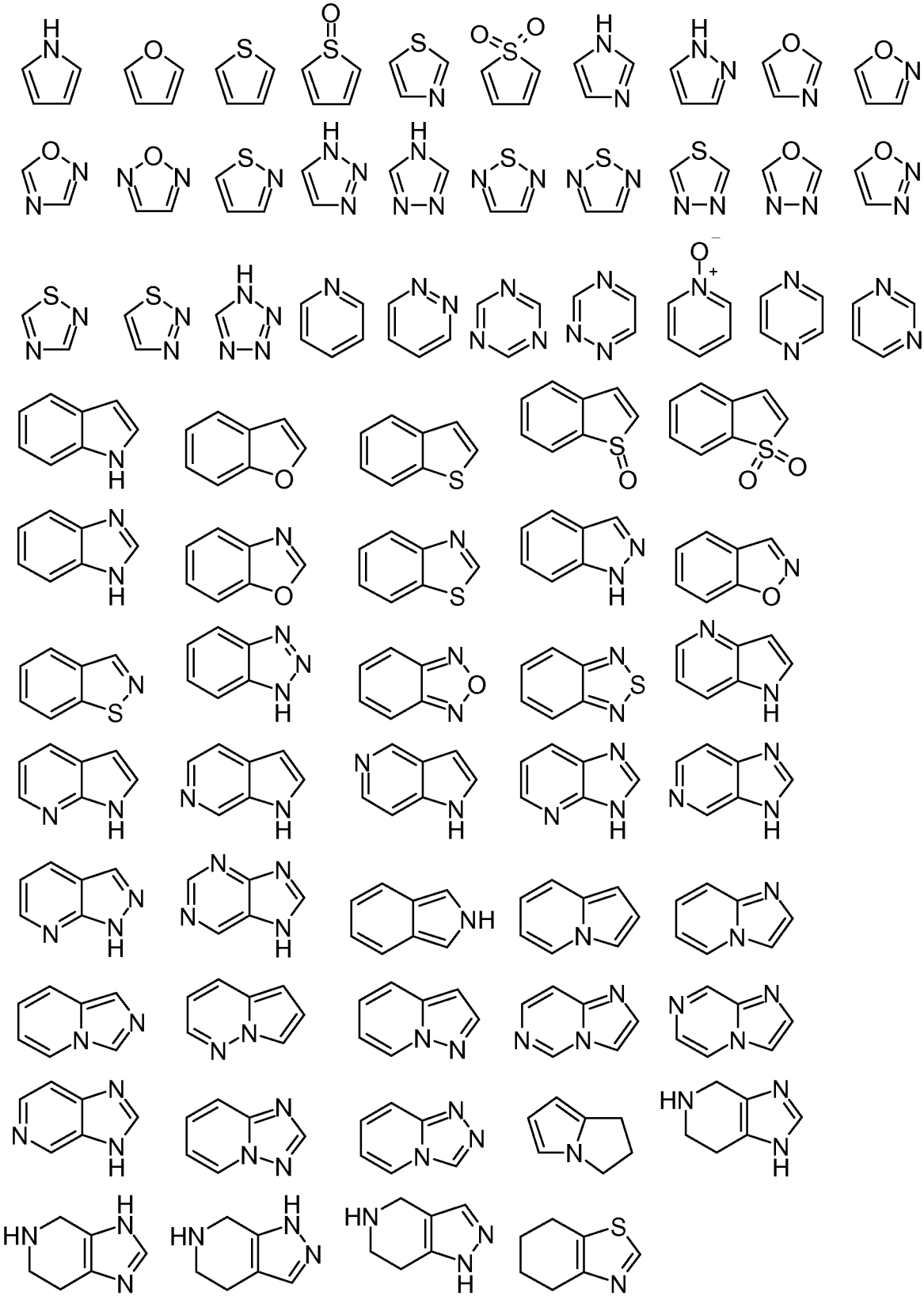
2,3-dihydro-1*H*-pyrrolyl and  or  or  or  etc.

The above definition of **heterocyclylene** also applies if **heterocyclylene** is part of another group as in HO-**heterocyclylene**amino or H_2N-**heterocyclylene**oxy for example.

Heteroaryl denotes monocyclic heteroaromatic rings or polycyclic rings with at least one heteroaromatic ring, which compared with the corresponding **aryl** or **cycloalkyl (cycloalkenyl)** contain, instead of one or more carbon atoms, one or more identical or different heteroatoms, selected independently of one another from among nitrogen, sulphur and oxygen, wherein the resulting group must be chemically stable. The prerequisite for the presence of **heteroaryl** is a heteroatom and a heteroaromatic system. If a **heteroaryl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon and/or nitrogen atoms. **Heteroaryl** itself may be linked as a substituent to the molecule via every suitable position of the ring system, both carbon and nitrogen.

Examples of **heteroaryl** are furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, pyridyl-*N*-oxide, pyrrolyl-*N*-oxide, pyrimidinyl-*N*-oxide, pyridazinyl-*N*-oxide, pyrazinyl-*N*-oxide, imidazolyl-*N*-oxide, isoxazolyl-*N*-oxide, oxazolyl-*N*-oxide, thiazolyl-*N*-oxide, oxadiazolyl-*N*-oxide, thiadiazolyl-*N*-oxide, triazolyl-*N*-oxide, tetrazolyl-*N*-oxide, indolyl, isoindolyl, benzofuryl, benzothienyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, indazolyl, isoquinolinyl, quinolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinazolinyl, benzotriazinyl, indolizinyl, oxazolopyridyl, imidazopyridyl, naphthyridinyl, benzoxazolyl, pyridopyridyl, purinyl, pteridinyl, benzothiazolyl, imidazopyridyl, imidazothiazolyl, quinolinyl-*N*-oxide, indolyl-*N*-oxide, isoquinolyl-*N*-oxide, quinazolinyl-*N*-oxide, quinoxalinyl-*N*-oxide, phthalazinyl-*N*-oxide, indolizinyl-*N*-oxide, indazolyl-*N*-oxide, benzothiazolyl-*N*-oxide, benzimidazolyl-*N*-oxide etc.

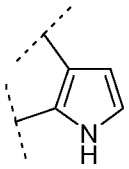
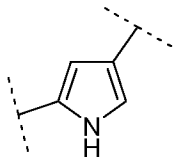
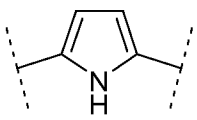
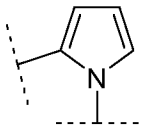
Further examples are the structures illustrated below, which may be attached via each hydrogen-carrying atom (exchanged for hydrogen):



The above definition of **heteroaryl** also applies when **heteroaryl** is part of another group as in **heteroaryl**amino or **heteroaryl**oxy, for example.

If the free valency of a **heteroaryl** is saturated, a **heteroaromatic group** is obtained.

The term **heteroarylene** can therefore be derived from the previously defined **heteroaryl**. **Heteroarylene**, unlike **heteroaryl**, is bivalent and requires two binding partners. Formally, the second valency is obtained by removing a hydrogen atom from a **heteroaryl**. Corresponding groups are for example

pyrrolyl and  or  or  or  etc.

The above definition of **heteroarylene** also applies when **heteroarylene** is part of another group as in HO-**heteroarylene**amino or H_2N-**heteroarylene**oxy, for example.

The bivalent groups mentioned above (alkylene, alkenylene, alkynylene etc.) may also be part of composite groups (e.g. H_2N-C_{1-4}alkylene- or HO-C_{1-4}alkylene-). In this case one of the valencies is saturated by the attached group (here: $-NH_2$, -OH), so that a composite group of this kind written in this way is only a monovalent substituent over all.

By **substituted** is meant that a hydrogen atom which is bound directly to the atom under consideration, is replaced by another atom or another group of atoms (**substituent**). Depending on the starting conditions (number of hydrogen atoms) mono- or polysubstitution may take place on one atom. Substitution with a particular substituent is only possible if the permitted valencies of the substituent and of the atom that is to be substituted correspond to one another and the substitution leads to a stable compound (i.e. to a compound which is not converted spontaneously, e.g. by rearrangement, cyclisation or elimination).

Bivalent substituents such as =S, =NR, =NOR, =NNRR, =NN(R)C(O)NRR, $=N_2$ or the like, may only be substituted at carbon atoms, wherein the bivalent substituent =O may also be a substituent at sulphur. Generally, substitution may be carried out by a bivalent substituent only at ring systems and requires replacement by two geminal hydrogen atoms, i.e. hydrogen atoms that are bound to the same carbon atom that is saturated prior to the substitution. Substitution by a bivalent substituent is therefore only possible at the group $-CH_2-$ or sulphur atoms of a ring system.

Stereochemistry/Solvates/Hydrates: Unless stated otherwise a structural formula given in the description or in the claims or a chemical name refers to the corresponding compound itself, but also encompasses the tautomers, stereoisomers, optical and geometric isomers (e.g. enantiomers, diastereomers, *E*/*Z* isomers, etc.), racemates, mixtures of separate enantiomers in any desired combinations, mixtures of diastereomers, mixtures of the forms mentioned hereinbefore (if such forms exist) as well as salts, particularly pharmaceutically acceptable salts thereof. The compounds and salts according to the invention may be present in solvated form (e.g. with pharmaceutically acceptable solvents such as e.g. water, ethanol etc.) or in unsolvated form. Generally, for the purposes of the present invention the solvated forms, e.g. hydrates, are to be regarded as of equal value to the unsolvated forms.

Salts: The term "**pharmaceutically acceptable**" is used herein to denote compounds, materials, compositions and/or formulations which are suitable, according to generally recognised medical opinion, for use in conjunction with human and/or animal tissue and do not have or give rise to any excessive toxicity, irritation or immune response or lead to other problems or complications, i.e. correspond overall to an acceptable risk/benefit ratio.

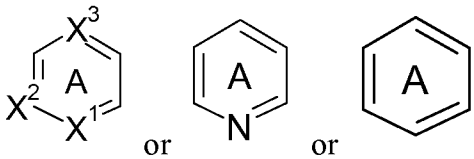
The term "**pharmaceutically acceptable salts**" relates to derivatives of the chemical compounds disclosed in which the parent compound is modified by the addition of acid or base. Examples of pharmaceutically acceptable salts include (without being restricted thereto) salts of mineral or organic acids in relation to basic functional groups such as for example amines, alkali metal or organic salts of acid functional groups such as for example carboxylic acids, etc. These salts

include in particular acetate, ascorbate, benzenesulphonate, benzoate, besylate, bicarbonate, bitartrate, bromide/hydrobromide, Ca-edetate/edetate, camsylate, carbonate, chloride/hydrochloride, citrate, edisylate, ethane disulphonate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycollylarsnilate, hexylresorcinate, hydrabamine, hydroxymaleate, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, malate, maleate, mandelate, methanesulphonate, mesylate, methylbromide, methylnitrate, methylsulphate, mucate, napsylate, nitrate, oxalate, pamoate, pantothenate, phenyl acetate, phosphate/diphosphate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, sulphamide, sulphate, tannate, tartrate, teoclate, toluenesulphonate, triethiodide, ammonium, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumin and procaine. Other pharmaceutically acceptable salts may be formed with cations of metals such as aluminium, calcium, lithium, magnesium, potassium, sodium, zinc, etc. (cf. also Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention may be prepared starting from the parent compound which carries a basic or acidic functionality, by conventional chemical methods. Generally, such salts may be synthesised by reacting the free acid or base form of these compounds with a sufficient amount of the corresponding base or acid in water or an organic solvent such as for example ether, ethyl acetate, ethanol, isopropanol, acetonitrile (or mixtures thereof).

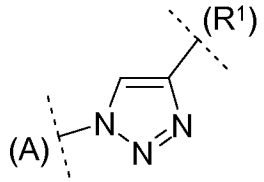
Salts of acids other than those mentioned above, which are useful for example for purifying or isolating the compounds from the reaction mixtures (e.g. trifluoroacetates), are also to be regarded as part of the invention.

In a representation such as for example



the letter A has the function of a ring designation in order to make it easier, for example, to indicate the attachment of the ring in question to other rings.

For bivalent groups in which it is crucial to determine which adjacent groups they bind and with which valency, the corresponding binding partners are indicated in brackets, where necessary for clarification purposes, as in the following representations:



or (R^2)-C(O)NH- or (R^2)-NHC(O)-;

Groups or substituents are frequently selected from among a number of alternative groups/ substituents with a corresponding group designation (e.g. **R^a**, **R^b** etc). If such a group is used repeatedly to define a compound according to the invention in different molecular parts, it must always be borne in mind that the various uses are to be regarded as totally independent of one another.

By a **therapeutically effective amount** for the purposes of this invention is meant a quantity of substance that is capable of obviating symptoms of illness or of preventing or alleviating these symptoms, or which prolong the survival of a treated patient.

List of abbreviations

ACN, CH_3CN	acetonitrile
Boc	*tert*.butoxy carbonyl
DCM	dichloromethane
DIPEA	diisopropylethyl amine
DMAP	dimethyl-pyridin-4-yl-amine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulphoxide
EDTA	ethylenediaminetetraacetic acid
EtOAc or EA	ethyl acetate
FCS	Fetal calf serum

h	hour(s)
HATU	*N*-[(dimethylamino)-(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)-methylene]-*N*-methylmethan-aminium hexafluorophosphate *N*-oxide
HPLC	high performance liquid chromatography
KOAc	potassium acetate
LiHMDS	lithium hexamethyl disilazide
M	Molar
Min	minute(s)
mL	Millilitre
MS	mass spectrometry
N	Normal
NMR	nuclear resonance spectroscopy
PE	petrol ether
PPh3	triphenylphosphine
DIBAL	diisobutylaluminium hydride
RP	reversed phase
Rpm	rounds per minute
RT or rt	room temperature
STAB	Sodium triacetoxy borohydride
TBME	*tert*.butyl methyl ether
TEA	triethylamine
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tR	retention time [min]
TRIS	tris(hydroxymethyl)aminomethane
wt%	weight percent
sat.	Saturated

Other features and advantages of the present invention will become apparent from the following more detailed Examples which illustrate the principles of the invention without restricting its scope.

General

Unless stated otherwise, all the reactions are carried out in commercially obtainable apparatus using methods that are commonly used in chemical laboratories. Starting materials that are sensitive to air and/or moisture are stored under protective gas and corresponding reactions and manipulations therewith are carried out under protective gas (nitrogen or argon).

The compounds are named according to the Beilstein rules using the Autonom software (Beilstein). If a compound is to be represented both by a structural formula and by its nomenclature, in the event of a conflict the structural formula is decisive.

Chromatography

Thin layer chromatography is carried out on ready-made TLC plates of silica gel 60 on glass (with fluorescence indicator F-254) made by Merck.

The **preparative high pressure chromatography (HPLC)** of the example compounds according to the invention is carried out with columns made by Waters (names: Sunfire C18 OBD, 10 µm, 30 x 100 mm Part. No. 186003971; X-Bridge C18 OBD, 10 µm, 30 x 100 mm Part. No. 186003930). The compounds are eluted using different gradients of H_2O/ACN wherein 0.2 % HCOOH is added to the water (acid conditions). For chromatography under basic conditions the water is made basic according to the following recipe: 5 mL of ammonium hydrogen carbonate solution (158 g to 1 L H_2O) and 2 ml 32 % ammonia $_{(aq)}$ are made up to 1 L with H_2O.

The **analytical HPLC (reaction monitoring)** of intermediate compounds is carried out with columns made by Waters and Phenomenex. The analytical

equipment is also provided with a mass detector in each case.

HPLC mass spectroscopy/UV spectrometry

The retention times/MS-ESI$^+$ for characterising the example compounds according to the invention are produced using an HPLC-MS apparatus (high performance liquid chromatography with mass detector) made by Agilent. Compounds that elute at the injection peak are given the retention time $t_{Ret.} = 0$.

HPLC-Methods preperative

prep. HPLC1

HPLC:	333 and 334 Pumps	
Column:	Waters X-Bridge C18 OBD, 10 µm, 30 x 100 mm, Part.No. 186003930	
Solvent:	A: 10 mM NH_4HCO_3 in H_2O; B: Acetonitril (HPLC grade)	
Detection:	UV/Vis-155	
Flow:	50 ml/min	
Gradient:	0.00 – 1.50 min:	1.5 % B
	1.50 – 7.50 min:	varying
	7.50 – 9.00 min:	100 % B

prep. HPLC2

HPLC:	333 and 334 Pumps	
Column:	Waters Sunfire C18 OBD, 10 µm, 30 x 100 mm, Part.No. 186003971	
Solvent:	A: H_2O + 0.2 % HCOOH; B: Acetonitril (HPLC grade) + 0.2 % HCOOH	
Detection:	UV/Vis-155	
Flow:	50 ml/min	
Gradient:	0.00 – 1.50 min:	1.5 % B
	1.50 – 7.50 min:	varying
	7.50 – 9.00 min:	100 % B

HPLC-Methods analytic

LCMSBAS1

HPLC:	Agilent 1100 Series	
MS:	Agilent LC/MSD SL	
Column:	Phenomenex Mercury Gemini C18, 3 µm, 2 x 20 mm, Part.No. 00M-4439-B0-CE	
Solvent:	A: 5 mM NH_4HCO_3/20 mM NH_3 in H_2O; B: Acetonitril (HPLC grade)	
Detection:	MS:Positive and negative mode	
Mass range:	120 – 900 m/z	
Flow:	1.00 ml/min	
Column temperature:	40 °C	
Gradient:	0.00 – 2.50 min:	5 % → 95 % B
	2.50 – 2.80 min:	95 % B
	2.81 – 3.10 min:	95 % → 5 % B

FECB5

HPLC:	Agilent 1100/1200 Series	
MS:	Agilent LC/MSD SL	
Column:	Waters X-Bridge C18 OBD, 5 µm, 2.1 x 50 mm	
Solvent:	A: 5 mM NH_4HCO_3/19 mM NH_3 in H_2O; B: Acetonitril (HPLC grade)	
Detection:	MS:Positive and negative mode	
Mass range:	105 – 1200 m/z	
Flow:	1.20 ml/min	
Column temperature:		35 °C
Gradient:	0.00 – 1.25 min:	5 % → 95 % B
	1.25 – 2.00 min:	95 % B
	2.00 – 2.01 min:	95 % → 5 % B

FECBM3ESI

HPLC:	Agilent 1100/1200 Series	
MS:	Agilent LC/MSD SL	
Column:	Waters X-Bridge C18 OBD, 5 µm, 2.1 x 50 mm	
Solvent:	A: 5 mM NH_4HCO_3/19 mM NH_3 in H_2O; B: Acetonitril (HPLC grade)	
Detection:	MS:Multimode ESI Positive and negative mode	
Mass range:	105 – 1200 m/z	
Flow:	1.20 ml/min	
Column temperature:		35 °C
Gradient:	0.00 – 1.25 min:	5 % → 100 % B
	1.25 – 2.00 min:	100 % B
	2.00 – 2.01 min:	100 % → 5 % B

VAB

HPLC:	Agilent 1100/1200 Series	
MS:	Agilent LC/MSD SL	
Column:	Waters X-Bridge BEH C18, 2.5 µm, 2.1 x 30 mm XP	
Solvent:	A: 5 mM NH_4HCO_3/19 mM NH_3 in H_2O; B: Acetonitril (HPLC grade)	
Detection:	MS:Positive and negative mode	
Mass range:	100 – 1200 m/z	
Flow:	1.40 ml/min	
Column temperature:		45 °C
Gradient:	0.00 – 1.00 min:	5 % → 100 % B
	1.00 – 1.37 min:	100 % B
	1.37 – 1.40 min:	100 % → 5 % B

FA-1

HPLC-MS:	Waters UPLC- micromass Triple quad
Column:	Aquity UPLC BEH C18 1.7µm 2.1x50mm
Solvent:	A: H_2O + 0.1% formic acid; B: Acetonitril + 0.1% formic acid;
Detection:	MS:Positive and negative mode

Mass range:	100 – 1200 m/z	
Flow:	0.4 ml/min	
Column temperature:		45 °C
Gradient:	0.0 – 2.0 min:	5% B
	2.0 – 4.5 min:	5 → 95 % B
	4.5 – 6.0 min:	80% → 20 % B

FA-8

HPLC-MS:	Waters – Alliance 2996	
Column:	Symmetryshield C18, 5 µm, 4.6 x 250 mm	
Solvent:	A: H_2O + 0.1% TFA; B: Acetonitril (HPLC grade)	
Detection:	MS:Positive and negative mode	
Mass range:	100 – 1200 m/z	
Flow:	1.00 ml/min	
Column temperature:		25 °C
Gradient:	2.00 - 8.00 min:	20 % → 80 % B
	8.00 - 19.00 min:	80 % B
	19.00 – 20.00 min:	80% → 20 % B

FSUN2

HPLC:	Agilent 1100/1200 Series	
MS:	Agilent LC/MSD SL	
Column:	Waters Sunfire C18, 5 µm, 2.1 x 50 mm	
Solvent:	A: H_2O + 0.2% formic acid; B: Acetonitril (HPLC grade)	
Detection:	MS:Positive and negative mode	
Mass range:	105 – 1200 m/z	
Flow:	1.20 ml/min	
Column temperature:		35 °C
Gradient:	0.0 min:	5 % B
	0.0 – 1.50 min:	5 % → 95 % B
	1.50 – 2.00 min:	95 % B
	2.00 – 2.01 min:	95 % → 5 % B

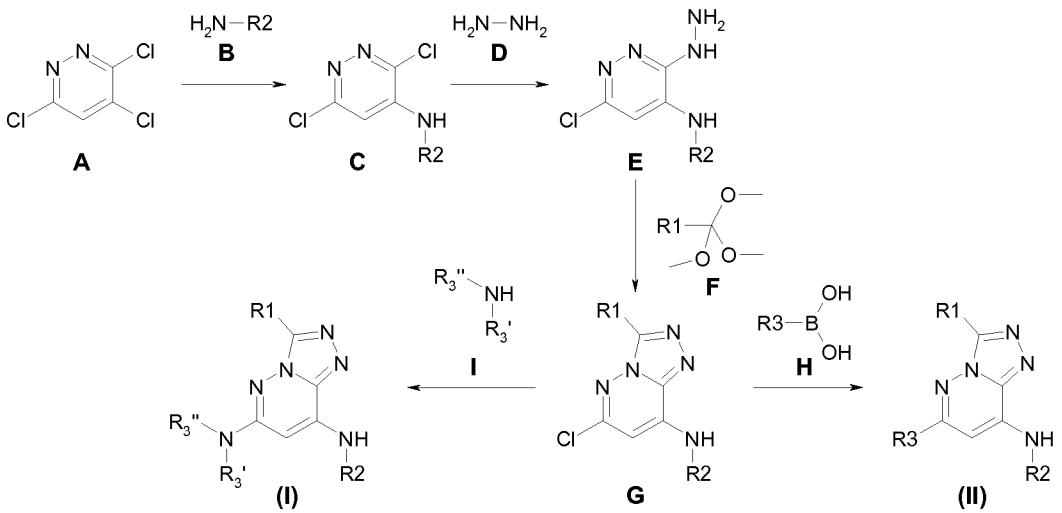
Preparation of the compounds according to the invention

The compounds according to the invention are prepared by the methods of synthesis described hereinafter, in which the substituents of the general formulae have the meanings given hereinbefore. These methods are intended as an illustration of the invention, without restricting its subject matter and the scope of the compounds claimed to these examples. Where the preparation of starting compounds is not described, they are commercially obtainable or may be prepared analogously to known compounds or methods described herein. Substances described in the literature are prepared according to the published methods of synthesis.

Unless otherwise specified, the substituents **R1** through **R3** of the following reaction schemes are as defined in the description and claims.

The synthesis of compounds of formula **I** and **II** from intermediate A is illustrated in Scheme 1.

Scheme 1

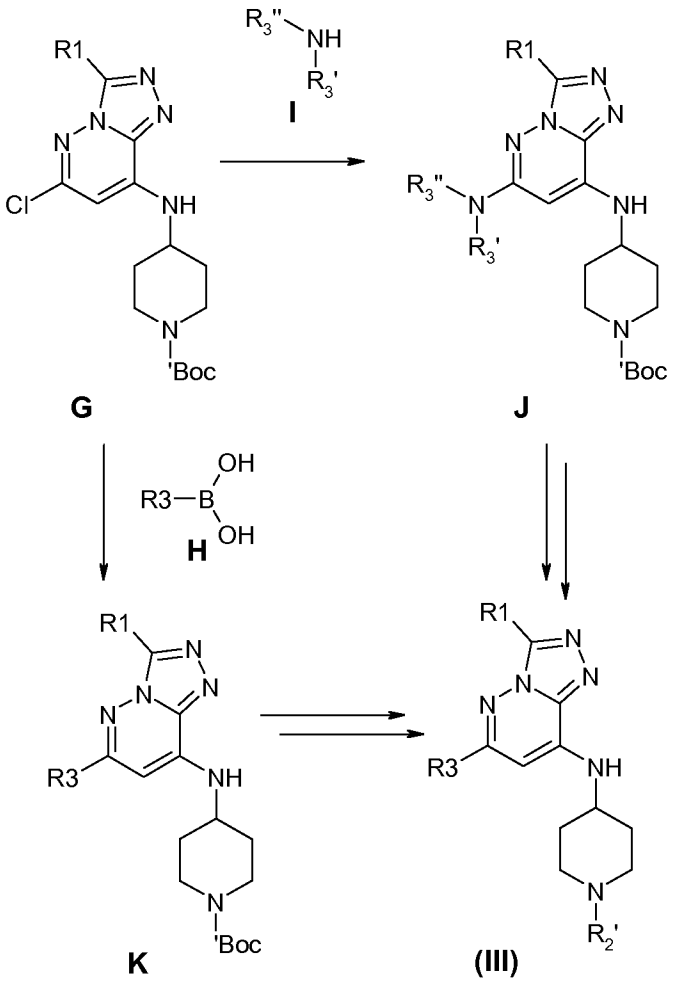


Starting from A, a nucleophilic aromatic substitution reaction can be used to introduce amine B, which leads to C. A reaction of the same type with hydrazine lead to compound E, which can be transformed with orthoester derivatives F or the

corresponding acidanhydrides to the bicyclic compound G. Performing a further nucleophilic aromatic substitution reaction with I lead to final compounds (I). Final compounds (II) can be synthesized applying a Suzuki reaction with boronic acids H.

The synthesis of compounds of formula **III** from intermediate G is illustrated in Scheme 2.

Scheme 2

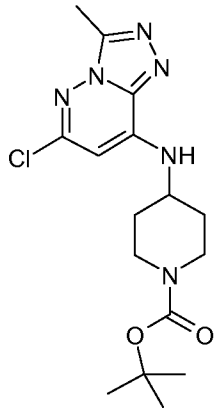


Starting from G a nucleophilic aromatic substitution reaction with amines I lead to intermediate J, which can be transformed to the final compounds (III) through boc de-protection and installing of R2' using a reductive amination, an amide coupling

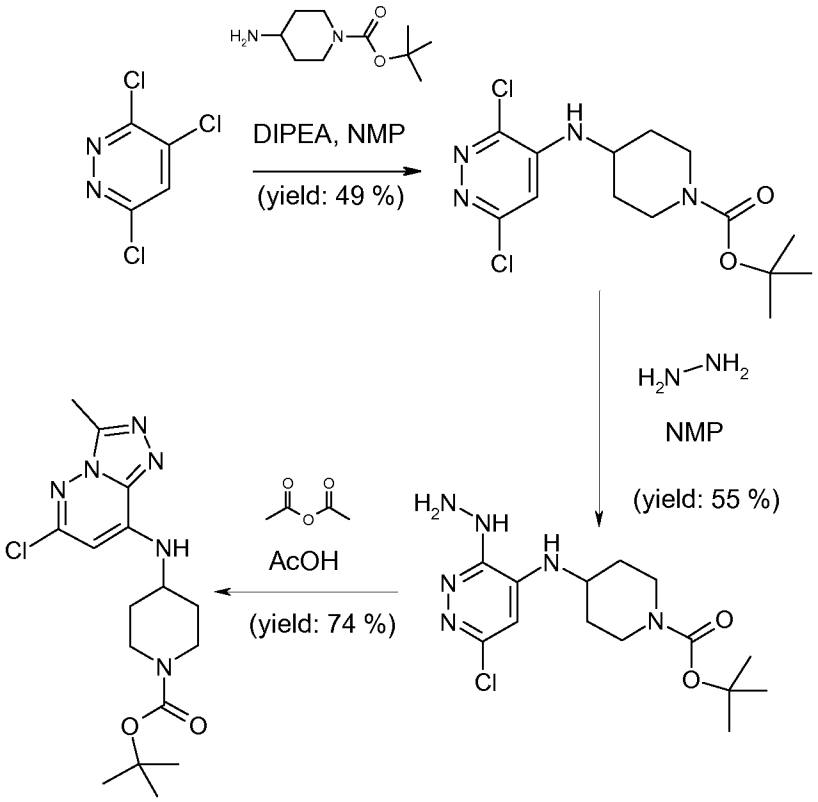
or a sulfonamide formation. Final compounds (III) can be also synthesized applying a Suzuki reaction with boronic acids H leading to intermediate K, followed by a reductive amination, an amide coupling or a sulfonamide formation.

Preparation of intermediate G-1

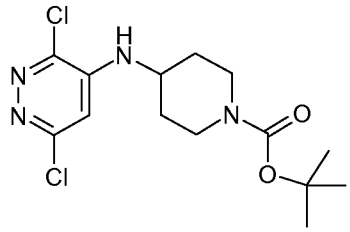
4-(6-Chloro-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-ylamino)-piperidine-1-carboxylic acid tert-butyl ester:



Reaction scheme:



4-(3,6-Dichloro-pyridazin-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester

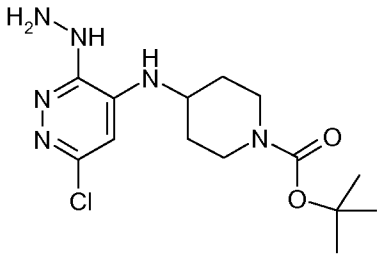


3,4,6-Trichloropyridazin (10.5 g; 57.25 mmol) was dissolved in 10 ml of dry NMP. Afterwards were added DIPEA (28.4 ml; 171.73 mmol) and 4- amino-piperidine-1-carboxylic acid tert-butyl ester (12.04 g; 60.11 mmol) and all let stir at ambient temperature for 16 hours and 3 hours at 50 °C. The reaction mixture was purified by using reversed phase chromatography under basic conditions.

Yield: 49 % (9.73 g; 28.03 mmol)

HPLC-MS: $(M+H)^+$ = 347/349; t_{Ret} = 1.82 min; method FECBM3ESI

4-(6-Chloro-3-hydrazino-pyridazin-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester

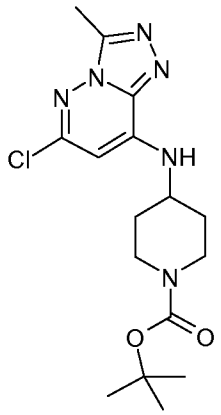


4-(3,6-Dichloro-pyridazin-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester (9.73 g; 28.03 mmol) was dissolved in 20 ml EtOH and treated with Hydrazine Hydrate (14.03 g; 280.33 mmol). It was stirred at 70 °C for 16 hours. Two peaks with product mass detected via HPLC-MS. The reaction mixture was extracted with aqueous $NaHCO_3$ solution and DCM. The organic phase was dried and evaporated to dryness. The crude product was purified by using reversed phase chromatography under acid conditions.

Yield: 55 % (5.33 g; 15.55 mmol)

HPLC-MS: $(M+H)^+$ = 343/345; t_{Ret} = 1.65 min; method FECBM3ESI

4-(6-Chloro-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-ylamino)-piperidine-1-carboxylic acid tert-butyl ester:



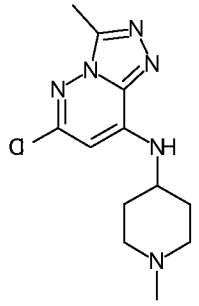
4-(6-Chloro-3-hydrazino-pyridazin-4-ylamino)-piperidine-1-carboxylic acid tert-butyl ester (5.33 g; 15.55 mmol) was treated with 20.0 ml AcOH and then with Ac_2O (18.80 ml; 198.89 mmol). It was stirred at ambient temperature for 2 hours. The reaction mixture was diluted with half saturated $NaHCO_3$ solution and extracted with DCM. The organic layer was dried over $MgSO_4$ and purified by using reversed phase chromatography under basic conditions.

Yield: 74 % (4.24 g; 11.56 mmol)

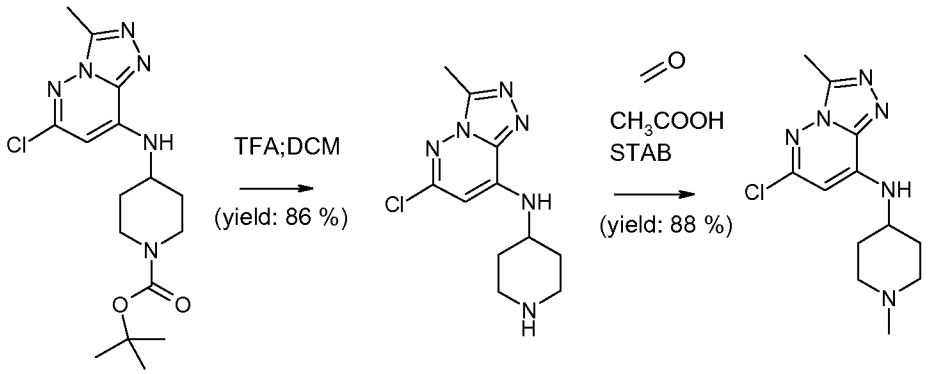
HPLC-MS: $(M+H)^+$ = 367/369; t_{Ret} = 1.81 min; method FECBM3ESI

Preparation of intermediate G-2

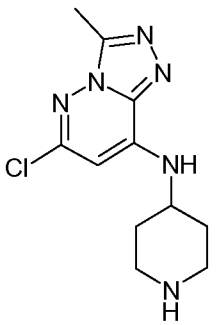
(6-Chloro-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-yl)-(1-methyl-piperidin-4-yl)-amine



Reaction scheme:



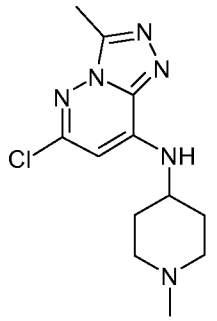
(6-Chloro-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-yl)-piperidin-4-yl-amine



Intermediate **G-1** (7.10 g; 18.84 mmol) was dissolved in 42.0 ml of DCM and treated with 14.0 ml TFA. It was stirred at ambient temperature for 2 hours. The solution was concentrated under reduced pressure and the residue taken up in DCM and purified by using reversed phase chromatography under basic conditions.
Yield: 86 % (4.31 g; 16.16 mmol)

HPLC-MS: $(M+H)^+$ = 267/269; t_{Ret} = 1.39 min; method FECB5

(6-Chloro-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-yl)-(1-methyl-piperidin-4-yl)-amine

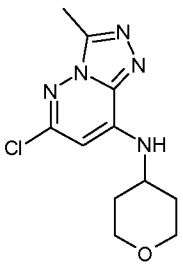


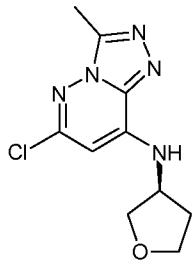
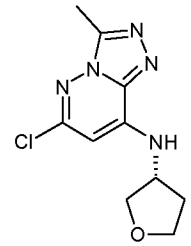
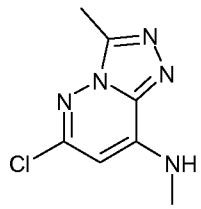
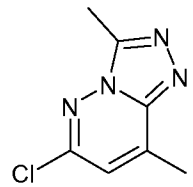
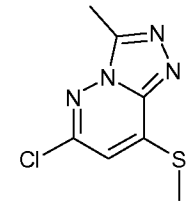
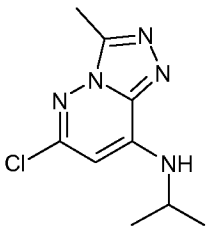
(6-Chloro-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-yl)-piperidin-4-yl-amine (0.26 g; 0.97 mmol) was dissolved in 5.0 ml THF. Acetic acid (0.11 ml; 1.94 mmol), formaldehyde 37 % in water (0.29 ml; 3.89 mmol) and STAB (0.27 g; 1.27 mmol) were added and stirred at ambient temperature for 1 hour. The crude material was purified by using reversed phase chromatography under basic conditions.

Yield: 88 % (0.24 g; 0.86 mmol)

HPLC-MS: $(M+H)^+$ = 281/283; t_{Ret} = 1.46 min; method FECBM3ESI

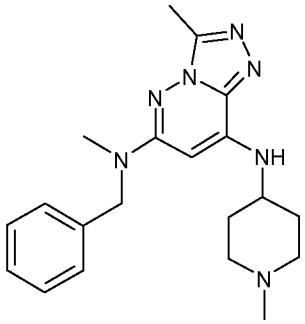
According to the procedures of **G-1** and **G-2** the intermediates **G-3** – **G-9** were synthesized.

#	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
G-3		M+H=268; $t_{Ret.}$= 1.43	FECBM3ESI

#	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
G-4		M+H=254; $t_{Ret.}$= 0.76	LCMSBAS1
G-5		M+H=254; $t_{Ret.}$= 0.76	LCMSBAS1
G-6		M+H=198; $t_{Ret.}$= 0.63	VAB
G-7		M+H=183; $t_{Ret.}$= 0.57	LCMSBAS1
G-8		M+H=215; $t_{Ret.}$= 0.69	LCMSBAS1
G-9		M+H=226; $t_{Ret.}$= 3.02	FA-1

General method for preparation of compounds of formula I

N6-Benzyl-3,N6-dimethyl-N8-(1-methyl-piperidin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazine-6,8-diamine I-1

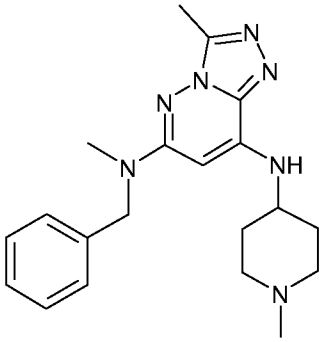


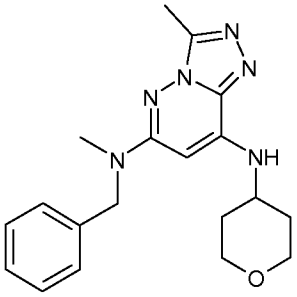
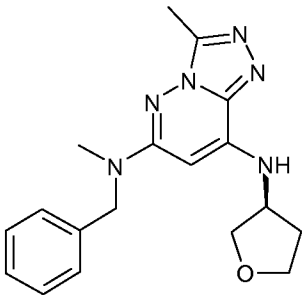
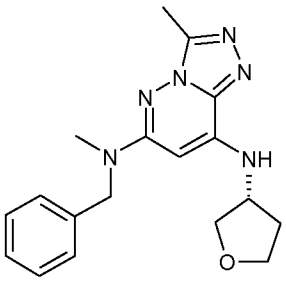
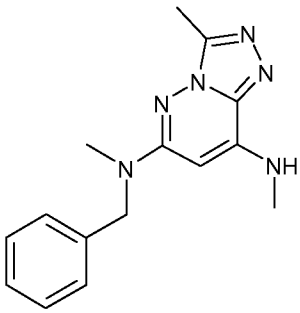
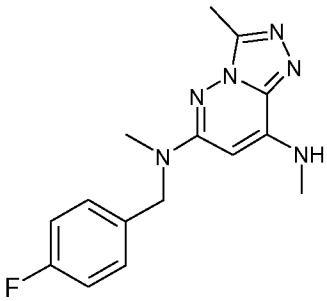
Intermediate **G-2** (0.07 g; 0.25 mmol) and N-methylbenzylamine (0.08 ml; 0.62 mmol) were weight in a reaction vessel and dissolved with 0.01 ml NMP and DIPEA (0.05 ml; 0.33 mmol). It was stirred at 130 °C for 2 days. The crude reaction mixture was purified by using reversed phase chromatography under basic conditions.

Yield: 27 % (0.02 g; 0.07 mmol)

HPLC-MS: $(M+H)^+$ = 366; t_{Ret} = 1.19 min; method LCMSBAS1

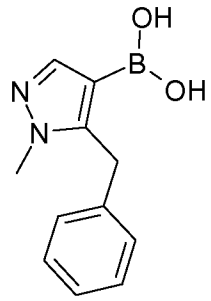
According to **I-1** the following examples were synthesized.

EX #	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
I-1		M+H=366; $t_{Ret.}$= 1.19	LCMSBAS1

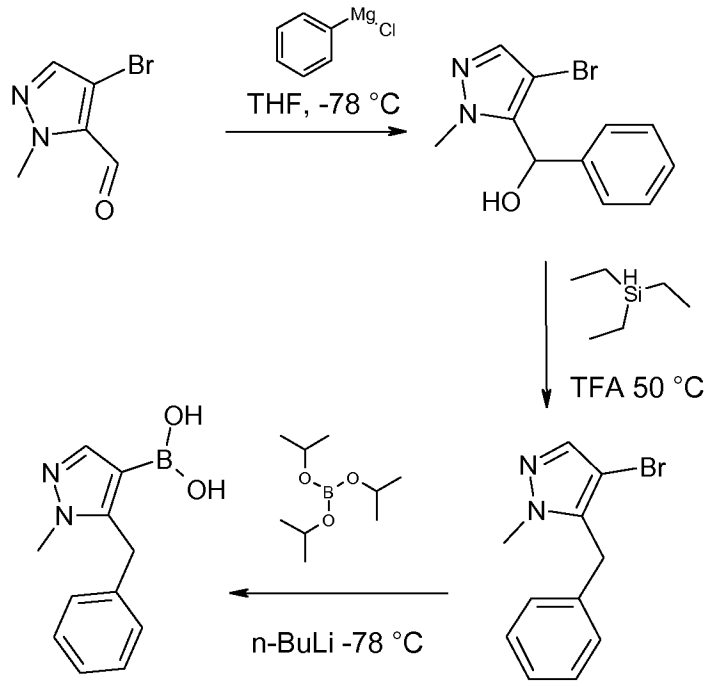
EX #	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
I-2		M+H=353; $t_{Ret.}$= 1.14	LCMSBAS1
I-3		M+H=339; $t_{Ret.}$= 1.11	LCMSBAS1
I-4		M+H=339; $t_{Ret.}$= 1.11	LCMSBAS1
I-5		M+H=283; $t_{Ret.}$= 1.13	LCMSBAS1
I-6		M+H=301; $t_{Ret.}$= 1.14	LCMSBAS1

Preparation of intermediate H-1

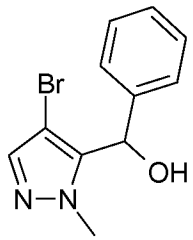
(5-benzyl-1-methyl-1H-pyrazol-4-yl)boronic acid H-1



Reaction scheme:



(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl-methanol

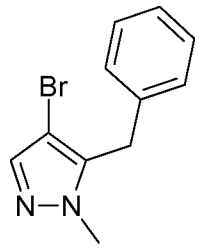


4-Bromo-2-methyl-2H-pyrazole-3-carbaldehyde (1.00 g; 5.29 mmol) was dissolved in 5.0 ml of anhydrous THF and cooled down to – 78 °C. Phenylmagnesium chloride 2 mol/l (6.61 ml; 13.23 mmol) was dropped and stirred for 1 hour. It was warmed up to 0 °C and quenched carefully with water, then extracted with DCM. The organic layers were pooled, dried over $MgSO_4$ and purified purified by using reversed phase chromatography under basic conditions.

Yield: 82 % (1.16 g; 4.35 mmol)

HPLC-MS: $(M+H)^+$ = 267; t_{Ret} = 1.59 min; method FECBM3ESI

5-Benzyl-4-bromo-1-methyl-1H-pyrazole

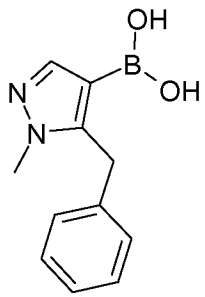


(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl-methanol (0.50 g; 1.87 mmol) was treated with 3.0 ml TFA and Triethylsilane (1.49 ml; 9.36 mmol) and heated to 50 °C for 16 hours. The product was purified via reversed phase chromatography under acid conditions.

Yield: 56 % (0.26 g; 1.06 mmol)

HPLC-MS: $(M+H)^+$ = 251/253; t_{Ret} = 1.71 min; method FECBM3ESI

(5-benzyl-1-methyl-1H-pyrazol-4-yl)boronic acid



5-Benzyl-4-bromo-1-methyl-1H-pyrazole (0.27 g; 1.06 mmol) was dissolved in 5.0 ml anhydrous THF and cooled down to – 78 °C. Afterwards was added

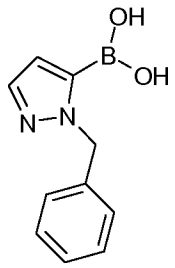
Triisopropyl borate (0.46 ml; 2.01 mmol) and n-BuLi; 1,6 mol/l in Hexane; (0.69 ml; 1.11 mmol). It was stirred for 1 hour within the desired product was formed. It was warmed to 25 °C and quenched with water. It was purified with reverse phase chromatography by using basic conditions.

Yield: 39 % (0.08 g; 0.41 mmol)

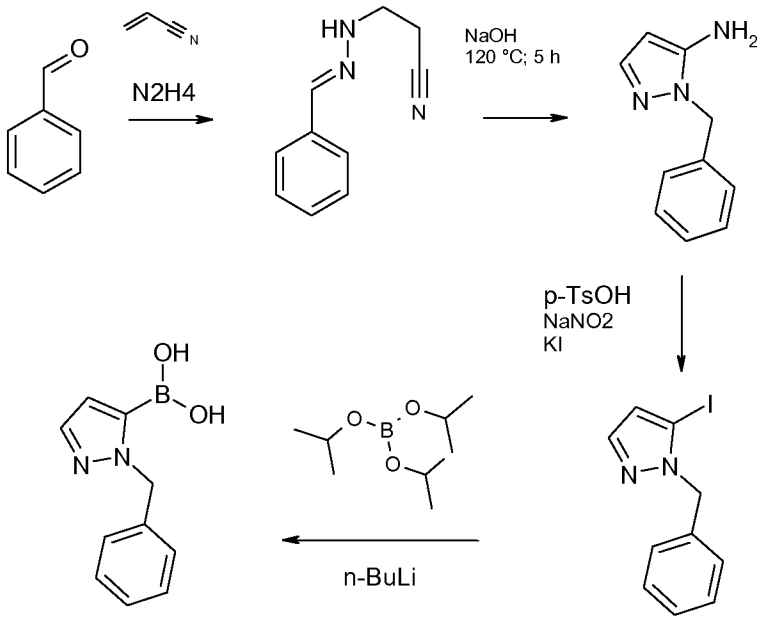
HPLC-MS: $(M+H)^+$ = 217; t_{Ret} = 1.41 min; method FECBM3ESI

Preparation of intermediate H-2

1-benzyl-5-[(hydroxyboranyl)-λ^1 - oxidanyl]pyrazol-3-yl

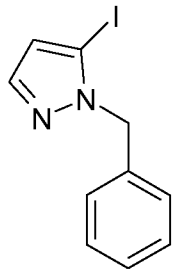


Reaction scheme:



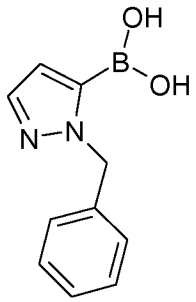
Step 1 and 2 were prepared according to the procedure described in *Tetrahydron Letters 44 (2003) 41-43*

1-Benzyl-5-iodo-1H-pyrazole



p-Toluenesulfonic acid (29.82 g; 0.17 mol) was stirred in 150 ml ACN. 2-Benzyl-2H-pyrazol-3-ylamine (10.0 g; 0.06 mol) was added and cooled down to 10-15 °C. Sodium nitrite (7.97 g; 0.12 mol) was dissolved in 15.0 ml water and added. The resulting mixture was stirred for 1 hour at 0 °C. In 30 ml of water was dissolved potassium iodide (23.96 g; 0.14 mol) and added at 0 °C. The reaction mixture was stirred at ambient temperature for 6 hours. It was diluted with 100 ml water and neutralized with $NaHCO_3$ solution, then extracted with DCM. The organic layers were pooled and washed with sodium thiosulfate, dried and evaporated. The crude material was purified with normal phase chromatography (2 % EtOAc/Hexane). Yield: 24 % (4.00 g; 0.01 mol)

1-benzyl-5-[(hydroxyboranyl)-λ^1 - oxidanyl]pyrazol-3-yl

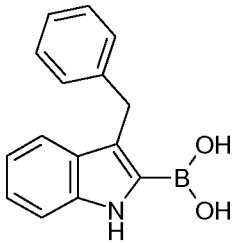


1-Benzyl-5-iodo-1H-pyrazole (4.00 g; 0.01 mol) was dissolved in 50 ml of anhydrous THF under argon and cooled to – 78 °C. Afterwards was added n-BuLi; 1.6 mol/l in Hexane; (1.35 g; 0.02 mol) drop wise within 20 minutes. Stirring and cooling was continued for 1 hour, Triisopropyl borate (10.59 g; 0.06 mol) was added drop wise during 30 minutes and then the temperature was brought to ambient temperature within 16 hours. The pH of the mixture was adjusted to 5 with

1 M HCl. Most of the THF was evaporated and the residue extracted with EtOAc that followed brine. The organic phase was dried and evaporated to dryness.
Yield: 42 % (1.20 g; 5.94 mmol)

Preparation of intermediate H-3

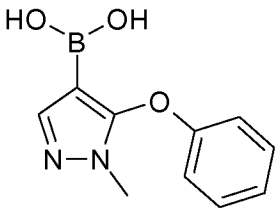
3-benzyl-2-[(hydroxyboranyl)-λ^1-oxidanyl]- 1λ^2-indol-4-yl



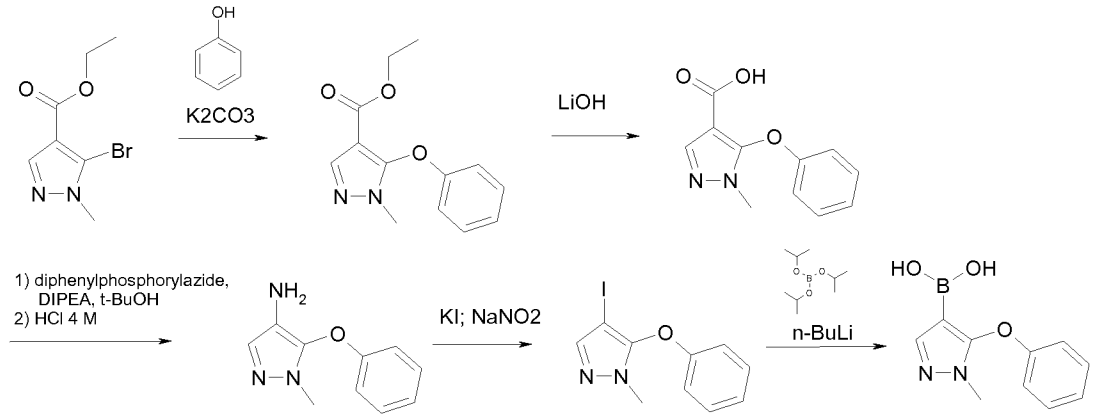
2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-indole (250.0 mg; 1.03 mmol) was suspended in 1 ml THF and treated with Cs_2CO_3 (512.67 mg; 1.57 mmol). After 10 minutes was added Benzylbromide (128.17 µl; 1.08 mmol) and stirred for 16 hours. It was purified by using reversed phase chromatography under basic conditions.
Yield: 30 % (102.0 mg; 0.31 mmol; purity 75 %)
HPLC-MS: $(M+H)^+$ = 247; t_{Ret} = 3.50 min; method LCMS FA-8

Preparation of intermediate H-5

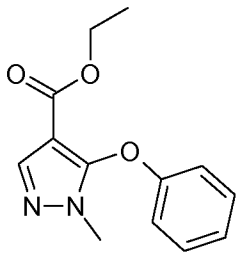
(1-methyl-5-phenoxy-1H-pyrazol-4-yl)boronic acid



Reaction scheme:



1-Methyl-5-phenoxy-1H-pyrazole-4-carboxylic acid ethyl ester

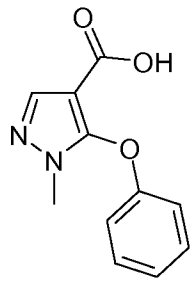


Phenol (30.29 g; 321.80 mmol) was dissolved in DMA and K_2CO_3 (88.95 g; 643.60 mmol) was added portion wise. It was stirred for 10 minutes, then 5-Bromo-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (50.0 g; 214.53 mmol) was dropped to the reaction mixture and heated up to 140 °C for 16 hours. A 10 % citric acid solution was added and extracted with DCM. The organic layer was washed with sodium bicarbonate and brine, then dried and purified through column chromatography.

Yield: 43 % (22.5 g; 91.37 mmol)

HPLC-MS: $(M+H)^+$ = 247; t_{Ret} = 3.50 min; method LCMS FA-8

1-Methyl-5-phenoxy-1H-pyrazole-4-carboxylic acid

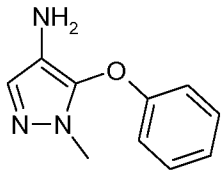


1-Methyl-5-phenoxy-1H-pyrazole-4-carboxylic acid ethyl ester (22.55 g; 91.37 mmol) was dissolved in THF/MeOH (1/1) and LiOH in water (7.67 g; 182.73 mmol) was added. After 16 hours at ambient temperature the reaction mixture was washed with EtOAc. The aqueous layer was acidified with 1 N HCl and extracted with EtOAc which was dried and evaporated afterwards.

Yield: 80 % (16.00 g; 73.32 mmol)

HPLC-MS: $(M+H)^+$ = 219; t_{Ret} = 2.88 min; method LCMS FA-8

1-Methyl-5-phenoxy-1H-pyrazol-4-ylamine

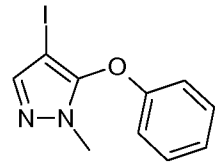


To a stirred mixture of 1-Methyl-5-phenoxy-1H-pyrazole-4-carboxylic acid (16.00 g; 73.32 mmol), t- BuOH (51.20 g; 690.77 mmol) in 1,4-dioxane under argon was added DIPEA (37.44 g ; 289.69 mmol) and Diphenylphosphoryl azide (41.60 g; 151.16 mmol). After 10 minutes at ambient temperature it was heated up to 110 °C and stirred there for 3 hours. The solvent was evaporated and the crude material purified by column chromatography. This compound was dissolved in DCM and treated with 4 M HCl in 1,4-dioxane. It was stirred for 2 days at ambient temperature. The solvent was evaporated and the residue dissolved in water and washed with EtOAc. The aqueous layer was basified with $NaHCO_3$ solution and extracted with EtOAc. The organic layer was dried and concentrated to dryness.

Yield: 32 % (16.00 g; 73.32 mmol)

HPLC-MS: $(M+H)^+$ = 190; t_{Ret} = 2.32 min; method LCMS FA-8

4-Iodo-1-methyl-5-phenoxy-1H-pyrazole

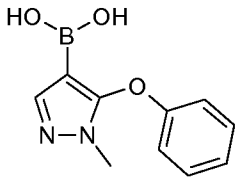


1-Methyl-5-phenoxy-1H-pyrazol-4-ylamine (4.50 g; 23.78 mmol) was dissolved in H_2SO_4 and cooled to 0 °C. $NaNO_2$ (1.64 g; 23.78 mmol) was dissolved in water and added to the reaction mixture. It was stirred for 1 hour at 0 °C then was added KI (15.79 g; 95.13 mmol) whilst vigorous stirring and warming up to ambient temperature within 30 minutes. It was treated with water and neutralized with saturated $NaHCO_3$ solution. The water layer was extracted with DCM, dried and purified by column chromatography.

Yield: 38 % (2.70 g; 8.99 mmol)

HPLC-MS: $(M+H)^+$ = 301; t_{Ret} = 3.74 min; method LCMS FA-8

(1-methyl-5-phenoxy-1H-pyrazol-4-yl)boronic acid

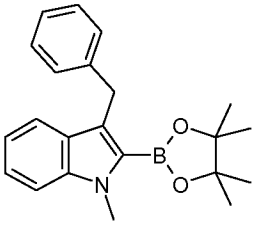
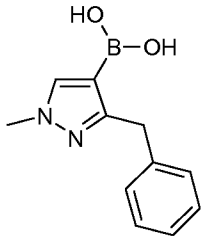
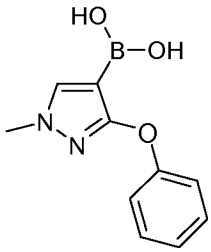
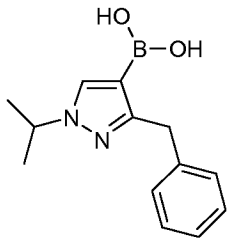
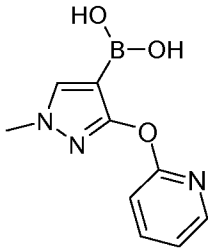


4-Iodo-1-methyl-5-phenoxy-1H-pyrazole (862.00 mg; 2.75 mmol) was dissolved in 15 ml THF extra dry and cooled down to -78 °C. Afterwards was added n-BuLi (1.80 ml; 2.88 mmol; 1.6 mol/l in Hexane) and Triisopropyl borate (982.28 mg; 5.22 mmol). It was stirred for 1 hour. The reaction mixture was quenched with 1 ml water and purified with reversed phase chromatography under basic conditions.

Yield: 67 % (400.00 mg; 1.84 mmol)

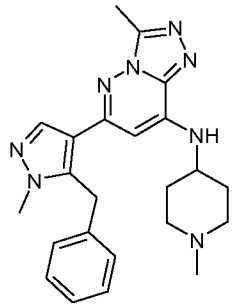
HPLC-MS: $(M+H)^+$ = 219; t_{Ret} = 1.34 min; method FECB5

According to the procedures of **H-1**, **H2**, **H3** and **H-5** the intermediates **H-4 - H-9** were synthesized.

#	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
H-4		M+H=348; $t_{Ret.}$= 2.24	FECB5
H-6		M+H=217; $t_{Ret.}$= 0.60	VAB
H-7		M+H=219; tRet.= 0.68	VAB
H-8		M+H=245; $t_{Ret.}$= 0.71	VAB
H-9		M+H=220; tRet.= 0.14	VAB

General method for preparation of compounds of formula II

[6-(5-Benzyl-1-methyl-1H-pyrazol-4-yl)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-yl]-(1-methyl-piperidin-4-yl)-amine II-1

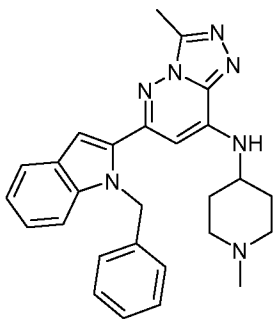


Intermediate **G-2** (0.04 g; 0.13 mmol), (5-benzyl-1-methyl-1H-pyrazol-4-yl)boronic acid (0.03 g; 0.13 mmol), Cs_2CO_3 70 % solution in water (0.05 ml; 0.25 mmol) and $Pd[P(t\text{-}Bu)_3]_2$ (5 mg; 0.01 mmol) were weight in a reaction vessel, diluted with THF/NMP = 2/1 (0.3 ml) and flushed with argon. It was stirred at 90 °C for 1 hour. The crude reaction mixture was purified by using reversed phase chromatography under acid conditions.

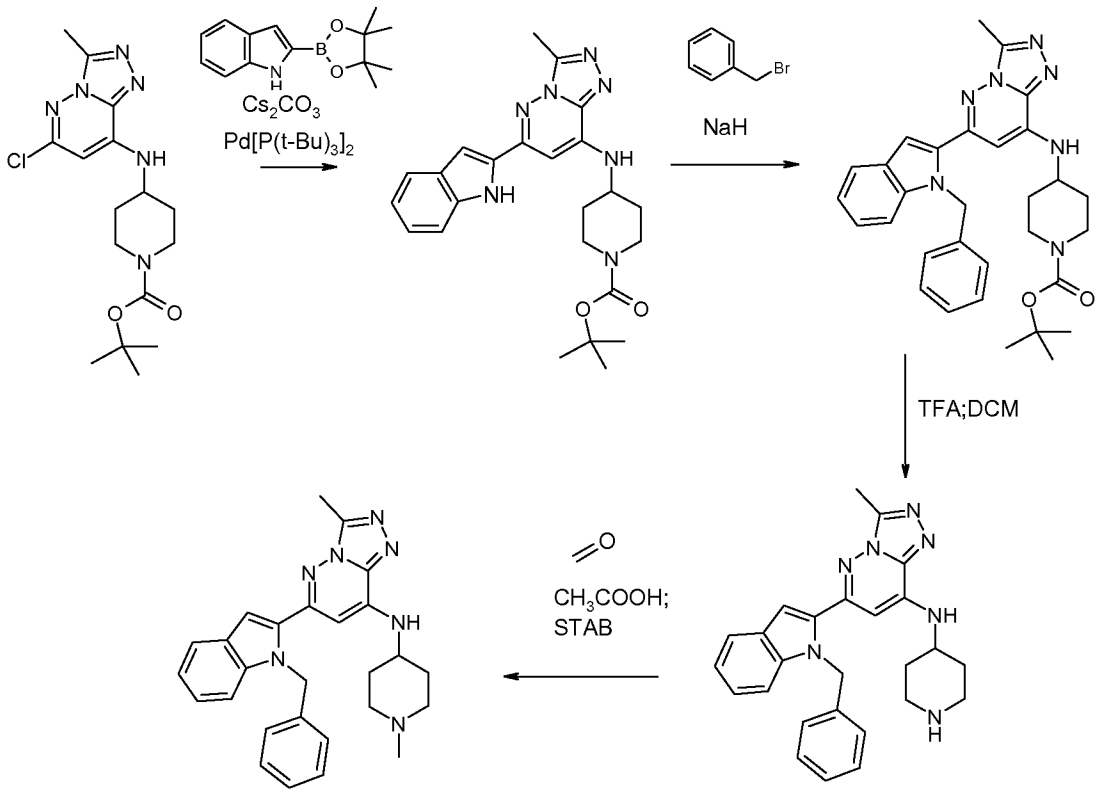
Yield: 33 % (0.02 g; 0.04 mmol)

HPLC-MS: $(M+H)^+ = 417$; $t_{Ret} = 1.05$ min; method LCMSBAS1

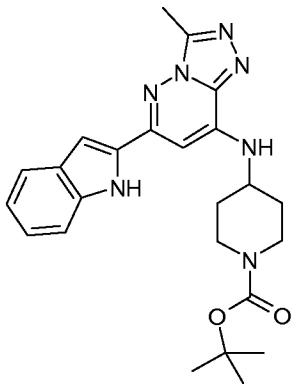
[6-(1-Benzyl-1H-indol-2-yl)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-yl]-(1-methyl-piperidin-4-yl)-amine II-5



Reaction scheme:



4-[6-(1H-Indol-2-yl)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-ylamino]-piperidine-1-carboxylic acid tert-butyl ester



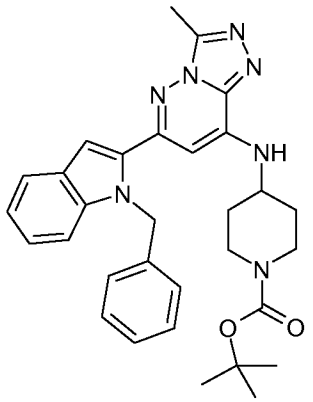
Intermediate **G-1** (100 mg; 0.27 mmol), 2-(Pinacolateboryl)indole (80 mg; 0.33 mmol), Cs_2CO_3 70 % solution in water (110 µl; 0.55 mmol) and $Pd[P(t\text{-}Bu)_3]_2$ (30 mg; 0.06 mmol) were weight in a reaction vessel, diluted with THF/NMP = 2/1 (0.5 ml) and flushed with argon. It was stirred at 90 °C for 1 hour. The crude

reaction mixture was purified by using reversed phase chromatography under basic conditions.

Yield: 58 % (71.00 mg; 0.16 mmol)

HPLC-MS: $(M+H)^+$ = 448; t_{Ret} = 2.09 min; method FSUN2

4-[6-(1-Benzyl-1H-indol-2-yl)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-ylamino]-piperidine-1-carboxylic acid tert-butyl ester

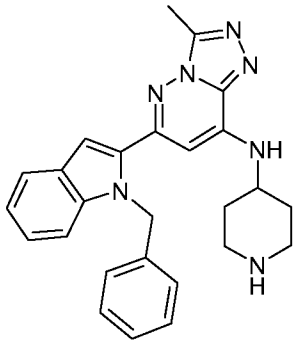


4-[6-(1H-Indol-2-yl)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-ylamino]-piperidine-1-carboxylic acid tert-butyl ester (71.00 mg; 0.16 mmol) was suspended in 300 µl THF and treated with NaH (10.19 mg; 0.26 mmol; 60 % in mineral oil). After 10 minutes of stirring, Benzyl bromide (19.17 µl; 0.16 mmol) was added and stirred for 16 hours. The crude material was purified via flash chromatography and afterwards with reversed phase chromatography under basic conditions.

Yield: 15 % (13 mg; 0.02 mmol)

HPLC-MS: $(M+H)^+$ = 538; t_{Ret} = 1.57 min; method LCMSBAS1

[6-(1-Benzyl-1H-indol-2-yl)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-yl]-piperidin-4-yl-amine

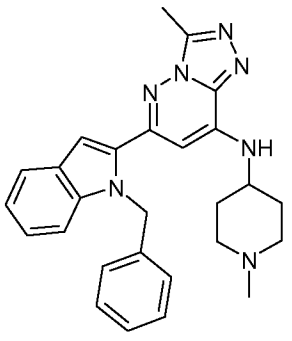


4-[6-(1-Benzyl-1H-indol-2-yl)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-ylamino]-piperidine-1-carboxylic acid tert-butyl ester (13 mg; 0.02 mmol) was dissolved in 1 ml DCM and treated with 300 µl TFA. It was stirred for 1 hour. The solvent was evaporated and the residue taken up in DCM and extracted with aqueous $NaHCO_3$. The organic layer was dried and evaporated to dryness.

Yield: 95 % (10 mg; 0.02 mmol)

HPLC-MS: $(M+H)^+$ = 438; t_{Ret} = 1.83 min; method FECB5

[6-(1-Benzyl-1H-indol-2-yl)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-yl]-(1-methyl-piperidin-4-yl)-amine

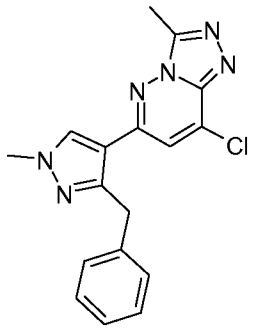


[6-(1-Benzyl-1H-indol-2-yl)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-yl]-piperidin-4-yl-amine (10 mg; 0.02 mmol) was dissolved in 300 µl THF, treated with glacial acetic acid (3 µl 0.05 mmol) and formaldehyde (7 µl; 0.09 mmol). At least was added STAB (6 mg; 0.03 mmol) and all stirred for 2 hours. The crude reaction mixture was purified by reversed phase under basic conditions.

Yield: 19 % (2.00 mg; 4.43 µmol)

HPLC-MS: $(M+H)^+$ = 452; t_{Ret} = 1.38 min; method LCMSBAS1

3-benzyl-4-{8-chloro-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-6-yl}-1-methyl-1H-pyrazole II-12



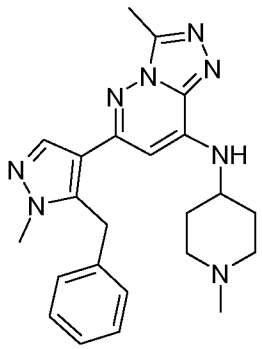
3-benzyl-1-methyl-4-[3-methyl-8-(methylsulfanyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1H-pyrazole (32 mg; 0.09 mmol) was dissolved in 1 ml chloroform and was treated with sulfurylchlorid (44 µl ; 0.54 mmol). The reaction mixture is stirred for 18 h at 25 °C.

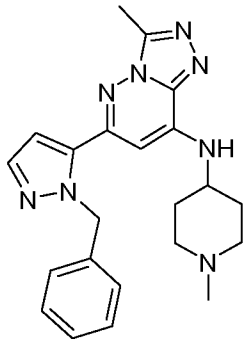
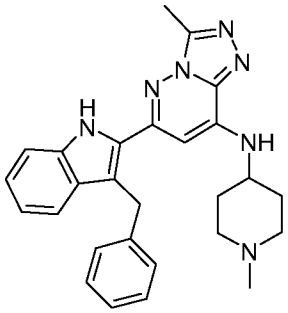
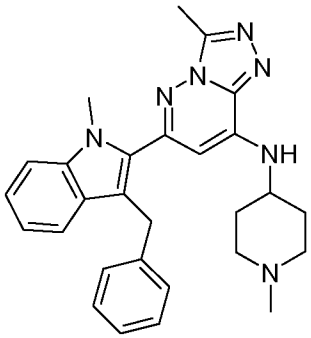
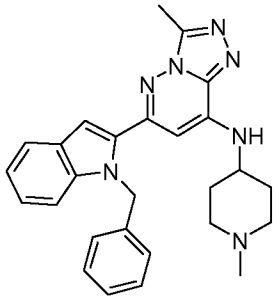
The solvent was evaporated and the residue taken up in DCM and extracted with aqueous $NaHCO_3$. The organic layer was dried and evaporated to dryness. The crude product was purified using reversed phase chromatography (prep. HPLC1)

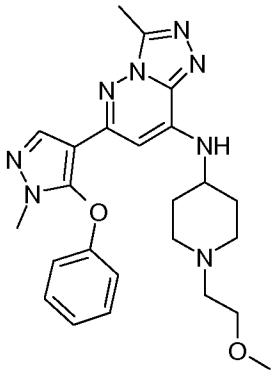
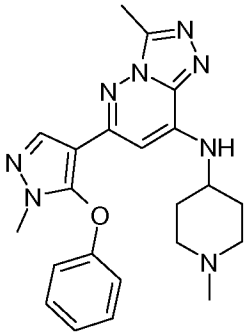
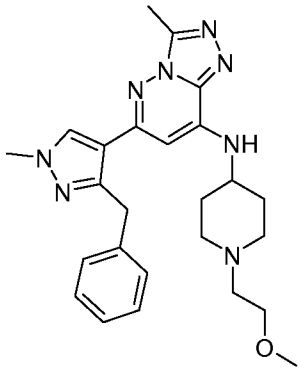
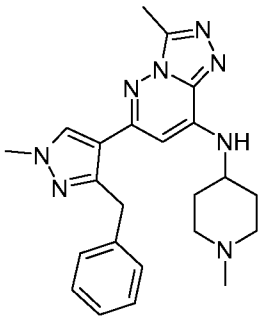
Yield: 36 % (11 mg; 0.03 mmol)

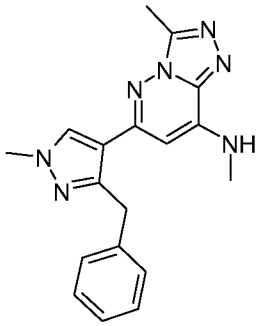
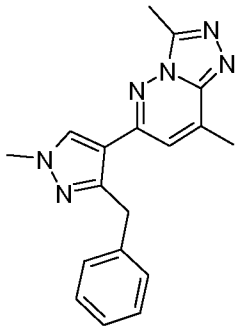
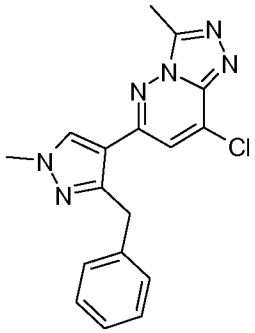
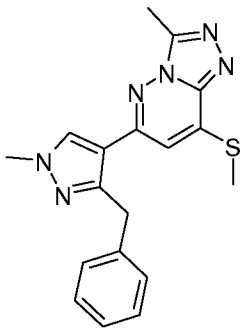
HPLC-MS: $(M+H)^+$ = 339/341; t_{Ret} = 1.31 min; method FECB5

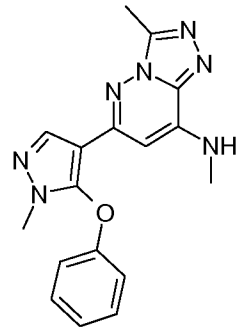
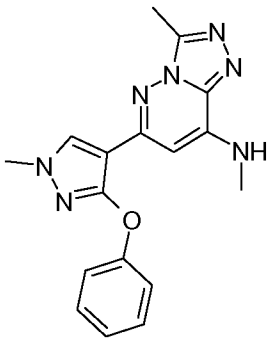
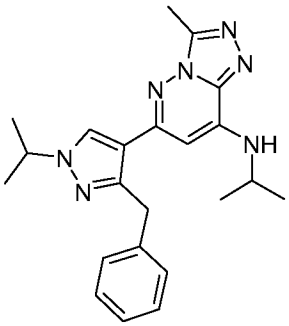
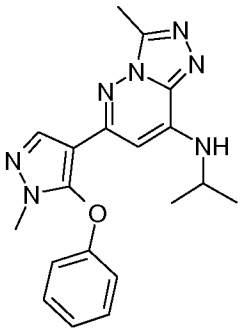
According to **II-1**, **II-5** or **II-12** the following examples were synthesized.

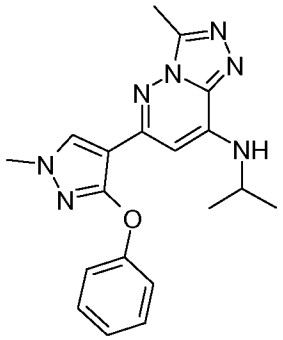
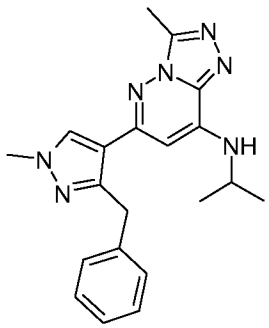
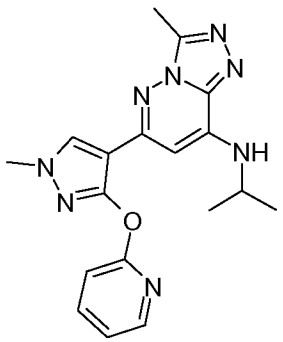
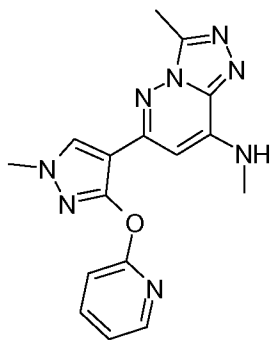
#	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
II-1		M+H=417; $t_{Ret.}$= 1.05	LCMSBAS1

#	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
II-2		M+H=403; $t_{Ret.}$= 1.05	LCMSBAS1
II-3		M+H=452; $t_{Ret.}$= 1.36	LCMSBAS1
II-4		M+H=466; $t_{Ret.}$= 1.42	LCMSBAS1
II-5		M+H=452; $t_{Ret.}$= 1.38	LCMSBAS1

#	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
II-6		M+H=463; $t_{Ret.}$= 1.07	LCMSBAS1
II-7		M+H=419; $t_{Ret.}$= 1.06	LCMSBAS1
II-8		M+H=461; $t_{Ret.}$= 1.06	LCMSBAS1
II-9		M+H=417; $t_{Ret.}$= 1.08	LCMSBAS1

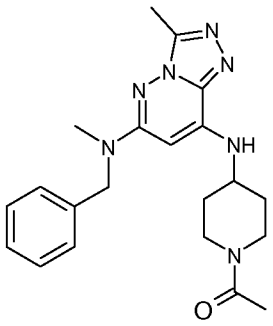
#	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
II-10		M+H=334; $t_{Ret.}$= 0.98	LCMSBAS1
II-11		M+H=319; $t_{Ret.}$= 0.97	LCMSBAS1
II-12		M+H=339/341; $t_{Ret.}$= 0.99	LCMSBAS1
II-13		M+H=351; $t_{Ret.}$= 1.01	LCMSBAS1

#	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
II-14		M+H=336; tRet.= 1.00	LCMSBAS1
II-15		M+H=336; tRet.= 1.01	LCMSBAS1
II-16		M+H=390; $t_{Ret.}$= 1.27	LCMSBAS1
II-17		M+H=364; tRet.= 1.23	LCMSBAS1

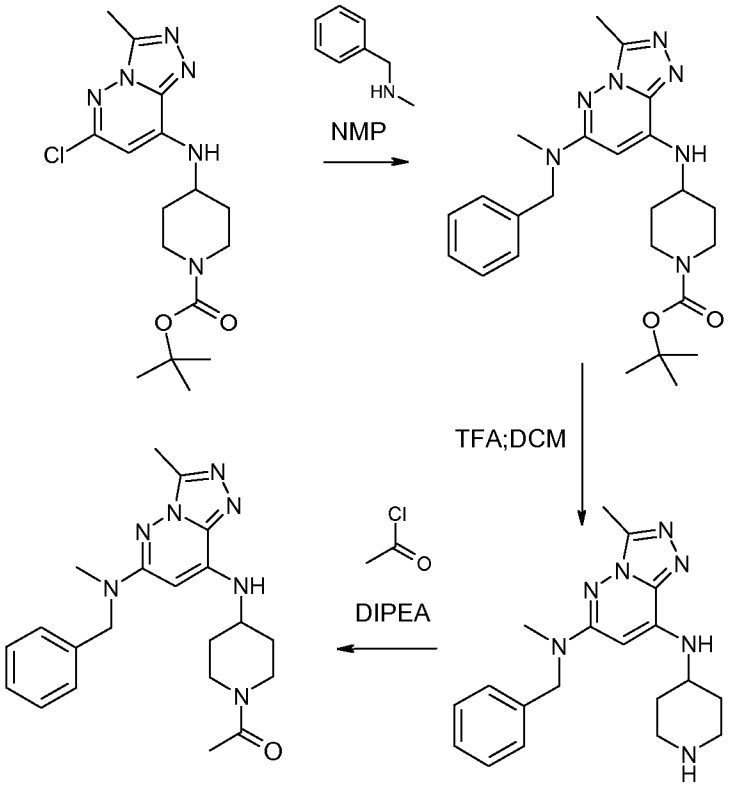
#	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
II-18		M+H=364; tRet.= 1.20	LCMSBAS1
II-19		M+H=362; $t_{Ret.}$= 1.11	LCMSBAS1
II-20		M+H=365; $t_{Ret.}$= 0.90	LCMSBAS1
II-21		M+H=337; $t_{Ret.}$= 0.75	LCMSBAS1

General method for preparation of compounds of formula III

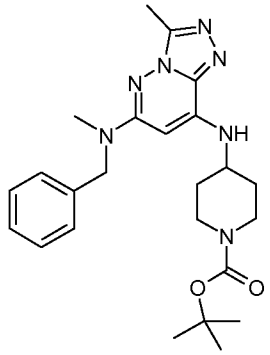
1-{4-[6-(Benzyl-methyl-amino)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-ylamino]-piperidin-1-yl}-ethanone III-1



Reaction scheme:



4-[6-(Benzyl-methyl-amino)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-ylamino]-piperidine-1-carboxylic acid tert-butyl ester

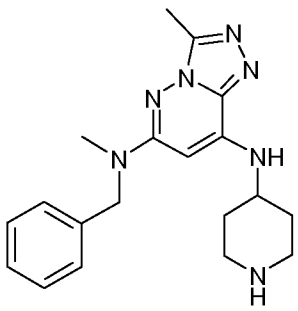


Intermediate **G-1** (4.24 g; 11.56 mmol) and N-methylbenzylamine (7.46 ml; 57.78 mmol) were weight in a reaction vessel and dissolved with 3.0 ml NMP. It was stirred at 130 °C for 5 days. The crude reaction mixture was purified by using reversed phase chromatography under basic conditions.

Yield: 78 % (4.08 g; 9.04 mmol)

HPLC-MS: $(M+H)^+$ = 452; t_{Ret} = 1.99 min; method FECBM3ESI

N6-Benzyl-3,N6-dimethyl-N8-piperidin-4-yl-[1,2,4]triazolo[4,3-b]pyridazine-6,8-diamine



4-[6-(Benzyl-methyl-amino)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-ylamino]-piperidine-1-carboxylic acid tert-butyl ester (4.08 g; 9.04 mmol) was dissolved in 20.0 ml of DCM and treated with 5.0 ml TFA. It was stirred at ambient temperature for 1 hour. The solution was concentrated under reduced pressure and the residue

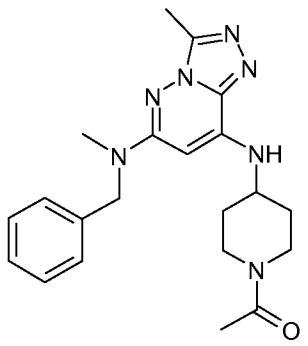
taken up in DCM and washed with half concentrated $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$ and concentrated.

The crude material was purified by using reversed phase chromatography under basic conditions.

Yield: 97 %; purity 80 % (3.84 g; 8.74 mmol)

HPLC-MS: $(M+H)^+ = 352$; $t_{Ret} = 1.55$ min; method FECBM3ESI

1-{4-[6-(Benzyl-methyl-amino)-3-methyl-[1,2,4]triazolo[4,3-b]pyridazin-8-ylamino]-piperidin-1-yl}-ethanone

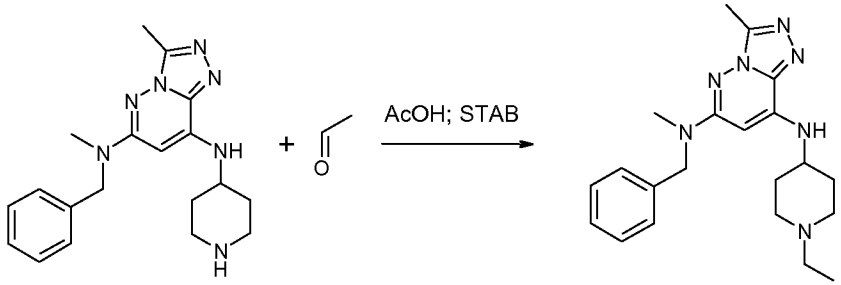


N6-Benzyl-3,N6-dimethyl-N8-piperidin-4-yl-[1,2,4]triazolo[4,3-b]pyridazine-6,8-diamine (0.05 g; 0.11 mmol) was placed in 1 ml DCM and treated with DIPEA (0.04 ml; 0.23 mmol) and acetyl chloride (0.04 ml; 0.57 mmol). It was stirred at ambient temperature for 4 hours. The crude reaction mixture was purified by using reversed phase chromatography under acid conditions.

Yield: 71 % (0.03 g; 0.08 mmol)

HPLC-MS: $(M+H)^+ = 394$; $t_{Ret} = 1.03$ min; method LCMSBAS1

N6-Benzyl-N8-(1-ethyl-piperidin-4-yl)-3,N6-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine-6,8-diamine III-2

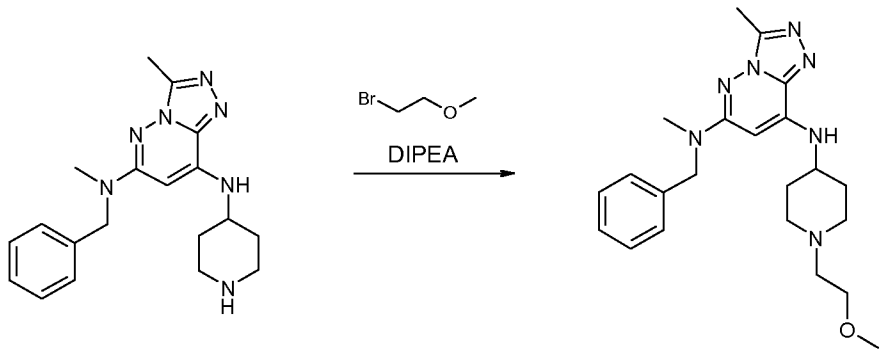


N6-Benzyl-3,N6-dimethyl-N8-piperidin-4-yl-[1,2,4]triazolo[4,3-b]pyridazine-6,8-diamine (0.05 g; 0.11 mmol) was dissolved in 0.5 ml THF. Acetic acid (0.01 ml; 0.23 mmol), acetaldehyde (0.03 ml; 0.46 mmol) and STAB (0.03 g; 0.15 mmol) were added and stirred at ambient temperature for 3 hours. The crude material was purified by using reversed phase chromatography under basic conditions and afterwards by TLC.

Yield: 7 % (3 mg; 0.008 mmol)

HPLC-MS: $(M+H)^+$ = 380; t_{Ret} = 1.21 min; method LCMSBAS1

N6-Benzyl-N8-[1-(2-methoxy-ethyl)-piperidin-4-yl]-3,N6-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine-6,8-diamine III-3



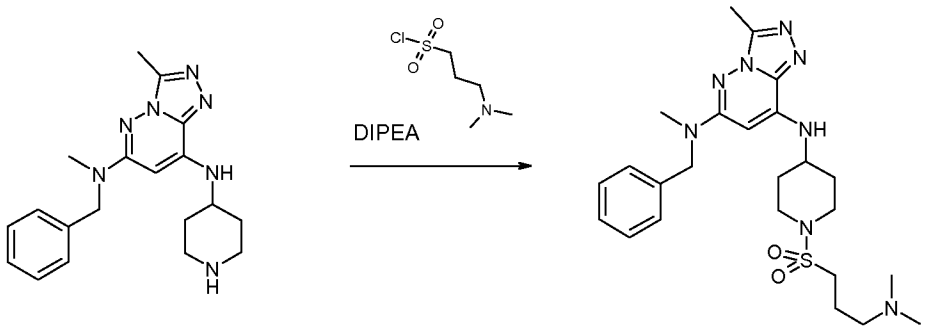
N6-Benzyl-3,N6-dimethyl-N8-piperidin-4-yl-[1,2,4]triazolo[4,3-b]pyridazine-6,8-diamine (0.05 g; 0.11 mmol) was slurred up in 0.3 ml DMA. 2-bromoethyl methyl ether (0.01 ml; 0.14 mmol) and DIPEA (0.04 ml; 0.23 mmol) were added and

stirred at 50 °C for 16 hours. The crude material was purified by using reversed phase chromatography under basic conditions.

Yield: 39 % (0.02 g; 0.04 mmol)

HPLC-MS: $(M+H)^+$ = 410; t_{Ret} = 1.18 min; method LCMSBAS1

N6-Benzyl-N8-[1-(3-dimethylamino-propane-1-sulfonyl)-piperidin-4-yl]-3,N6-dimethyl-[1,2,4]triazolo[4,3-b]pyridazine-6,8-diamine III-7

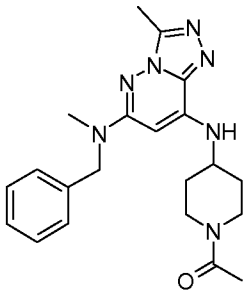
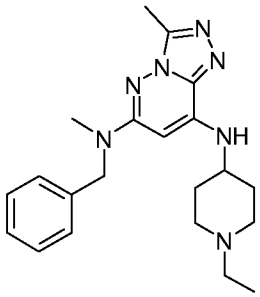
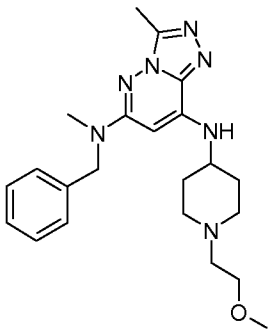
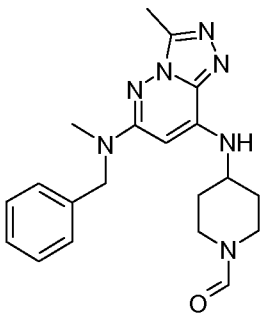


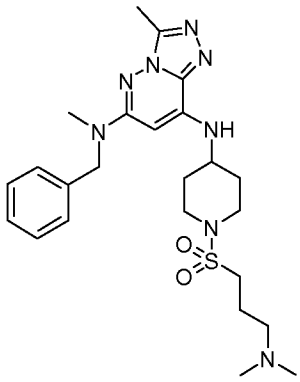
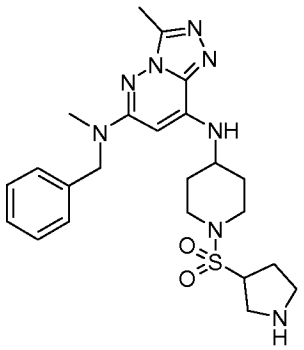
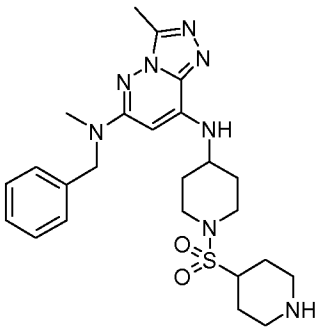
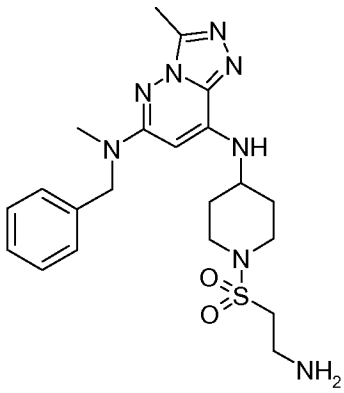
N6-Benzyl-3,N6-dimethyl-N8-piperidin-4-yl-[1,2,4]triazolo[4,3-b]pyridazine-6,8-diamine (0.05 g; 0.11 mmol; purity 80 %) was slurred up in 0.3 ml DMA. 3-Dimethylamino-propane-1-sulfonyl chloride Hydrochlorid (0.03 g; 0.14 mmol) and DIPEA (0.06 ml; 0.34 mmol) were added and stirred at 50 °C for 16 hours. Another portion of 3-Dimethylamino-propane-1-sulfonyl chloride Hydrochlorid (0.03 g; 0.14 mmol) and DIPEA (0.06 ml; 0.34 mmol) were added and stirred at 50 °C for additional 16 hours. The crude material was purified by using reversed phase chromatography under acid conditions.

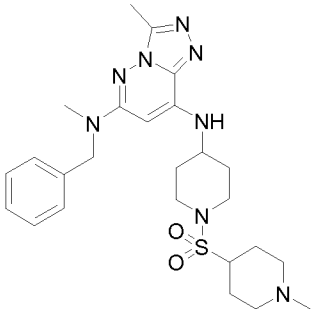
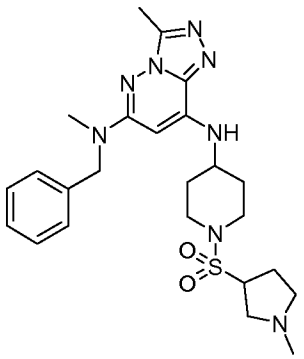
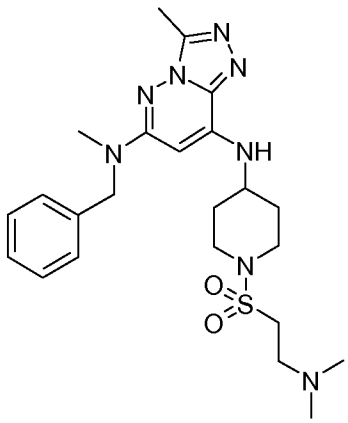
Yield: 51 % (0.03 g; 0.06 mmol)

HPLC-MS: $(M+H)^+$ = 501; t_{Ret} = 1.18 min; method LCMSBAS1

According to **III-1**, **III-2**, **III-3**, **III-6** or **III-7** the following examples were synthesized.

#	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
III-1		M+H=394; $t_{Ret.}$= 1.03	LCMSBAS1
III-2		M+H=380; $t_{Ret.}$= 1.21	LCMSBAS1
III-3		M+H=410; $t_{Ret.}$= 1.18	LCMSBAS1
III-4		M+H=380; $t_{Ret.}$= 1.07	LCMSBAS1

#	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
III-5		M+H=501; $t_{Ret.}$= 1.18	LCMSBAS1
III-6		M+H=485; $t_{Ret.}$= 1.07	LCMSBAS1
III-7		M+H=499; $t_{Ret.}$= 1.10	LCMSBAS1
III-8		M+H=459; $t_{Ret.}$= 1.05	LCMSBAS1

#	Structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-Method
III-9		M+H=513; $t_{Ret.}$= 1.17	LCMSBAS1
III-10		M+H=499; $t_{Ret.}$= 1.15	LCMSBAS1
III-11		M+H=487; $t_{Ret.}$= 1.17	LCMSBAS1

5

Biological Methods

BRD4-H4 tetraacetylated peptide inhibition AlphaScreen

This assay is used to determine whether the compounds inhibit the interaction between the first (BRD4-BD1) or the second (BRD4-BD2) bromodomain of BRD4 and the tetraacetylated histone H4 peptide.

Compounds are diluted in serial dilution 1:5 in assay buffer from 10mM stock in DMSO (100 µM start concentration) in white OptiPlate-384 (PerkinElmer). A mix consisting of 15nM GST-BRD4-BD1 protein (aa 44-168) or 150nM GST-BRD4-BD2 (aa 333-460) and 15 nM biotinylated Acetyl-Histone H4 (Lys5, 8, 12, 16) peptide is prepared in assay buffer (50mM HEPES pH=7.4; 25mM NaCl; 0,05% Tween 20; 0.1% bovine serum albumin (BSA); 10 mM dithiothreitol (DTT)). 6 µl of the mix is added to the compound dilutions. Subsequently, 6 µl of premixed AlphaLISA Glutathione Acceptor Beads and AlphaScreen Streptavidin Donor Beads from PerkinElmer (in assay buffer at a concentration of 10 µg/ml each) are added and the samples are incubated for 30 min at RT in the dark (shaking 300 rpm). Afterwards, the signal is measured in a PerkinElmer Envision HTS Multilabel Reader using the AlphaScreen protocol from PerkinElmer.

Each plate contains negative controls where biotinylated Acetyl-Histone H4 peptide and GST-BRD4-BD1 or GST-BRD4-BD2 are left out and replaced by assay buffer. Negative control values are entered as low basis value when using the software GraphPad Prism for calculations. Furthermore, a positive control (probe molecule JQ1+ with protein/ peptide mix) is pipetted. Determination of IC_{50} values are carried out using GraphPad Prism 3.03 software (or updates thereof).

Table summarizing the IC_{50} of the compounds of the invention exemplified above

#	BRD4-BD1 IC_{50} [nM]	#	BRD4-BD1 IC_{50} [nM]	#	BRD4-BD1 IC_{50} [nM]
I-1	3	**II-1**	10	**III-1**	61
I-2	83	**II-2**	117	**III-2**	3
I-3	67	**II-3**	3	**III-3**	3
I-4	25	**II-4**	37	**III-4**	40
I-5	83	**II-5**	105	**III-5**	37
I-6	74	**II-6**	8	**III-6**	33
		II-7	8	**III-7**	57
		II-8	4	**III-8**	32
		II-9	3	**III-9**	40
		II-10	38	**III-10**	44
		II-11	64	**III-11**	39
		II-12	51		
		II-13	1996		
		II-14	26		
		II-15	29		
		II-16	711		
		II-17	140		
		II-18	31		
		II-19	105		
		II-20	43		
		II-21	72		

On the basis of their biological properties the compounds of general formula **(1)** according to the invention, their tautomers, racemates, enantiomers, diastereomers, mixtures thereof and the salts of all the above-mentioned forms are suitable for

treating diseases characterised by virus infection, inflammatory diseases and abnormal cell proliferation, such as cancer.

For example, the following cancers may be treated with compounds according to the invention, without being restricted thereto: brain tumours such as for example acoustic neurinoma, astrocytomas such as pilocytic astrocytomas, fibrillary astrocytoma, protoplasmic astrocytoma, gemistocytary astrocytoma, anaplastic astrocytoma and glioblastoma, brain lymphomas, brain metastases, hypophyseal tumour such as prolactinoma, HGH (human growth hormone) producing tumour and ACTH producing tumour (adrenocorticotropic hormone), craniopharyngiomas, medulloblastomas, meningeomas and oligodendrogliomas; nerve tumours (neoplasms) such as for example tumours of the vegetative nervous system such as neuroblastoma sympathicum, ganglioneuroma, paraganglioma (pheochromocytoma, chromaffinoma) and glomus-caroticum tumour, tumours on the peripheral nervous system such as amputation neuroma, neurofibroma, neurinoma (neurilemmoma, Schwannoma) and malignant Schwannoma, as well as tumours of the central nervous system such as brain and bone marrow tumours; intestinal cancer such as for example carcinoma of the rectum, colon carcinoma, colorectal carcinoma, anal carcinoma, carcinoma of the large bowel, tumours of the small intestine and duodenum; eyelid tumours such as basalioma or basal cell carcinoma; pancreatic cancer or carcinoma of the pancreas; bladder cancer or carcinoma of the bladder; lung cancer (bronchial carcinoma) such as for example small-cell bronchial carcinomas (oat cell carcinomas) and non-small cell bronchial carcinomas (NSCLC) such as plate epithelial carcinomas, adenocarcinomas and large-cell bronchial carcinomas; breast cancer such as for example mammary carcinoma such as infiltrating ductal carcinoma, colloid carcinoma, lobular invasive carcinoma, tubular carcinoma, adenocystic carcinoma and papillary carcinoma; non-Hodgkin's lymphomas (NHL) such as for example Burkitt's lymphoma, low-malignancy non-Hodgkin's lymphomas (NHL) and mucosis fungoides; uterine cancer or endometrial carcinoma or corpus carcinoma; CUP syndrome (Cancer of Unknown Primary); ovarian cancer or ovarian carcinoma such as mucinous, endometrial or serous cancer; gall bladder cancer; bile duct

cancer such as for example Klatskin tumour; testicular cancer such as for example seminomas and non-seminomas; lymphoma (lymphosarcoma) such as for example malignant lymphoma, Hodgkin's disease, non-Hodgkin's lymphomas (NHL) such as chronic lymphatic leukaemia, leukaemic reticuloendotheliosis, immunocytoma, plasmocytoma (multiple myeloma (MM)), immunoblastoma, Burkitt's lymphoma, T-zone mycosis fungoides, large-cell anaplastic lymphoblastoma and lymphoblastoma; laryngeal cancer such as for example tumours of the vocal cords, supraglottal, glottal and subglottal laryngeal tumours; bone cancer such as for example osteochondroma, chondroma, chondroblastoma, chondromyxoid fibroma, osteoma, osteoid osteoma, osteoblastoma, eosinophilic granuloma, giant cell tumour, chondrosarcoma, osteosarcoma, Ewing's sarcoma, reticulo-sarcoma, plasmocytoma, fibrous dysplasia, juvenile bone cysts and aneurysmatic bone cysts; head and neck tumours such as for example tumours of the lips, tongue, floor of the mouth, oral cavity, gums, palate, salivary glands, throat, nasal cavity, paranasal sinuses, larynx and middle ear; liver cancer such as for example liver cell carcinoma or hepatocellular carcinoma (HCC); leukaemias, such as for example acute leukaemias such as acute lymphatic/lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML); chronic leukaemias such as chronic lymphatic leukaemia (CLL), chronic myeloid leukaemia (CML); stomach cancer or gastric carcinoma such as for example papillary, tubular and mucinous adenocarcinoma, signet ring cell carcinoma, adenosquamous carcinoma, small-cell carcinoma and undifferentiated carcinoma; melanomas such as for example superficially spreading, nodular, lentigo-maligna and acral-lentiginous melanoma; renal cancer such as for example kidney cell carcinoma or hypernephroma or Grawitz's tumour; oesophageal cancer or carcinoma of the oesophagus; penile cancer; prostate cancer; throat cancer or carcinomas of the pharynx such as for example nasopharynx carcinomas, oropharynx carcinomas and hypopharynx carcinomas; retinoblastoma such as for example vaginal cancer or vaginal carcinoma; plate epithelial carcinomas, adenocarcinomas, in situ carcinomas, malignant melanomas and sarcomas; thyroid carcinomas such as for example papillary, follicular and medullary thyroid carcinoma, as well as anaplastic carcinomas; spinalioma,

epidormoid carcinoma and plate epithelial carcinoma of the skin; thymomas, cancer of the urethra and cancer of the vulva.

Preferred cancers, which may be treated with compounds according to the invention, are hematopoietic malignancies (including but not limited to AML, MM), as well as solid tumors including but not limited to lung, liver, colon, brain, thyroid, pancreas, breast, ovary and prostate cancer.

The new compounds may be used for the prevention, short-term or long-term treatment of the above-mentioned diseases, optionally also in combination with radiotherapy or other "state-of-the-art" compounds, such as e.g. cytostatic or cytotoxic substances, cell proliferation inhibitors, anti-angiogenic substances, steroids or antibodies.

The compounds of general formula (I) may be used on their own or in combination with other active substances according to the invention, optionally also in combination with other pharmacologically active substances.

Chemotherapeutic agents which may be administered in combination with the compounds according to the invention, include, without being restricted thereto, hormones, hormone analogues and antihormones (e.g. tamoxifen, toremifene, raloxifene, fulvestrant, megestrol acetate, flutamide, nilutamide, bicalutamide, aminoglutethimide, cyproterone acetate, finasteride, buserelin acetate, fludrocortisone, fluoxymesterone, medroxyprogesterone, octreotide), aromatase inhibitors (e.g. anastrozole, letrozole, liarozole, vorozole, exemestane, atamestane), LHRH agonists and antagonists (e.g. goserelin acetate, luprolide), inhibitors of growth factors (growth factors such as for example "platelet derived growth factor" and "hepatocyte growth factor", inhibitors are for example "growth factor" antibodies, "growth factor receptor" antibodies and tyrosine kinase inhibitors, such as for example cetuximab, gefitinib, imatinib, lapatinib and trastuzumab); antimetabolites (e.g. antifolates such as methotrexate, raltitrexed, pyrimidine analogues such as 5-fluorouracil, capecitabin and gemcitabin, purine and adenosine analogues such as mercaptopurine, thioguanine, cladribine and pentostatin, cytarabine, fludarabine); antitumour antibiotics (e.g. anthracyclins such as

doxorubicin, daunorubicin, epirubicin and idarubicin, mitomycin-C, bleomycin, dactinomycin, plicamycin, streptozocin); platinum derivatives (e.g. cisplatin, oxaliplatin, carboplatin); alkylation agents (e.g. estramustin, meclorethamine, melphalan, chlorambucil, busulphan, dacarbazin, cyclophosphamide, ifosfamide, temozolomide, nitrosoureas such as for example carmustin and lomustin, thiotepa); antimitotic agents (e.g. Vinca alkaloids such as for example vinblastine, vindesin, vinorelbin and vincristine; and taxanes such as paclitaxel, docetaxel); topoisomerase inhibitors (e.g. epipodophyllotoxins such as for example etoposide and etopophos, teniposide, amsacrin, topotecan, irinotecan, mitoxantron) and various chemotherapeutic agents such as amifostin, anagrelid, clodronat, filgrastin, interferon alpha, leucovorin, rituximab, procarbazine, levamisole, mesna, mitotane, pamidronate and porfimer.

Other possible combination partners are 2-chlorodesoxyadenosine, 2-fluorodesoxycytidine, 2-methoxyoestradiol, 2C4, 3-alethine, 131-I-TM-601, 3CPA, 7-ethyl-10-hydroxycamptothecin, 16-aza-epothilone B, A 105972, A 204197, aldesleukin, alitretinoin, altretamine, alvocidib, amonafide, anthrapyrazole, AG-2037, AP-5280, apaziquone, apomine, aranose, arglabin, arzoxifene, atamestane, atrasentan, auristatin PE, AVLB, AZ10992, ABX-EGF, ARRY-300, ARRY-142886/AZD-6244, ARRY-704/AZD-8330, AS-703026, azacytidine, azaepothilone B, azonafide, BAY-43-9006, BBR-3464, BBR-3576, bevacizumab, biricodar dicitrate, BCX-1777, bleocin, BLP-25, BMS-184476, BMS-247550, BMS-188797, BMS-275291, BNP-1350, BNP-7787, BIBW 2992(afatinib), BIBF 1120 (Vargatef^{TM}), bleomycinic acid, bleomycin A, bleomycin B, bryostatin-1, bortezomib, brostallicin, busulphan, CA-4 prodrug, CA-4, CapCell, calcitriol, canertinib, canfosfamide, capecitabine, carboxyphthalatoplatin, CCI-779, CEP-701, CEP-751, CBT-1 cefixime, ceflatonin, ceftriaxone, celecoxib, celmoleukin, cemadotin, CH4987655/RO-4987655, chlorotrianisene, cilengitide, ciclosporin, CDA-II, CDC-394, CKD-602, clofarabin, colchicin, combretastatin A4, CHS-828, CLL-Thera, CMT-3 cryptophycin 52, CTP-37, CP-461, CV-247, cyanomorpholinodoxorubicin, cytarabine, D 24851,

decitabine, deoxorubicin, deoxyrubicin, deoxycoformycin, depsipeptide, desoxyepothilone B, dexamethasone, dexrazoxanet, diethylstilbestrol, diflomotecan, didox, DMDC, dolastatin 10, doranidazole, E7010, E-6201, edatrexat, edotreotide, efaproxiral, eflornithine, EKB-569, EKB-509, elsamitrucin, epothilone B, epratuzumab, ER-86526, erlotinib, ET-18-OCH3, ethynylcytidine, ethynyloestradiol, exatecan, exatecan mesylate, exemestane, exisulind, fenretinide, floxuridine, folic acid, FOLFOX, FOLFIRI, formestane, galarubicin, gallium maltolate, gefinitib, gemtuzumab, gimatecan, glufosfamide, GCS-IOO, G17DT immunogen, GMK, GPX-100, GSK-5126766, GSK-1120212, GW2016, granisetron, hexamethylmelamine, histamine, homoharringtonine, hyaluronic acid, hydroxyurea, hydroxyprogesterone caproate, ibandronate, ibritumomab, idatrexate, idenestrol, IDN-5109, IMC-1C11, immunol, indisulam, interferon alpha-2a, interferon alfa-2b, interleukin-2, ionafarnib, iproplatin, irofulven, isohomohalichondrin-B, isoflavone, isotretinoin, ixabepilone, JRX-2, JSF-154, J-107088, conjugated oestrogens, kahalid F, ketoconazole, KW-2170, lobaplatin, leflunomide, lenograstim, leuprolide, leuporelin, lexidronam, LGD-1550, linezolid, lutetium texaphyrin, lometrexol, losoxantrone, LU 223651, lurtotecan, mafosfamide, marimastat, mechloroethamine, methyltestosteron, methylprednisolone, MEN-10755, MDX-H210, MDX-447, MGV, midostaurin, minodronic acid, mitomycin, mivobulin, MK-2206, MLN518, motexafin gadolinium, MS-209, MS-275, MX6, neridronate, neovastat, nimesulide, nitroglycerin, nolatrexed, norelin, N-acetylcysteine, 06-benzylguanine, omeprazole, oncophage, ormiplatin, ortataxel, oxantrazole, oestrogen, patupilone, pegfilgrastim, PCK-3145, pegfilgrastim, PBI-1402, PEG-paclitaxel, PEP-005, P-04, PKC412, P54, PI-88, pelitinib, pemetrexed, pentrix, perifosine, perillylalcohol, PG-TXL, PG2, PLX-4032/RO-5185426, PT-100, picoplatin, pivaloyloxymethylbutyrate, pixantrone, phenoxodiol O, PKI166, plevitrexed, plicamycin, polyprenic acid, porfiromycin, prednisone, prednisolone, quinamed, quinupristin, RAF-265, ramosetron, ranpirnase, RDEA-119/BAY 869766, rebeccamycin analogues, revimid, RG-7167, rhizoxin, rhu-MAb, risedronate, rituximab, rofecoxib, Ro-31-7453, RO-5126766, RPR 109881A, rubidazon, rubitecan, R-flurbiprofen, S-9788, sabarubicin, SAHA, sargramostim, satraplatin, SB 408075, SU5416, SU6668,

SDX-101, semustin, seocalcitol, SM-11355, SN-38, SN-4071, SR-27897, SR-31747, SRL-172, sorafenib, spiroplatin, squalamine, suberanilohydroxamic acid, sutent, T 900607, T 138067, TAS-103, tacedinaline, talaporfin, tariquitar, taxotere, taxoprexin, tazarotene, tegafur, temozolamide, tesmilifene, testosterone, testosterone propionate, tesmilifene, tetraplatin, tetrodotoxin, tezacitabine, thalidomide, theralux, therarubicin, thymectacin, tiazofurin, tipifarnib, tirapazamine, tocladesine, tomudex, toremofin, trabectedin, TransMID-107, transretinic acid, traszutumab, tretinoin, triacetyluridine, triapine, trimetrexate, TLK-286TXD 258, urocidin, valrubicin, vatalanib, vincristine, vinflunine, virulizin, WX-UK1, vectibix, Volasertib (or other polo-like kinae inhibitors), xeloda, XELOX, XL-281, XL-518/R-7420, YM-511, YM-598, ZD-4190, ZD-6474, ZD-4054, ZD-0473, ZD-6126, ZD-9331, ZDI839, zoledronat and zosuquidar.

Suitable preparations include for example tablets, capsules, suppositories, solutions - particularly solutions for injection (s.c., i.v., i.m.) and infusion - elixirs, emulsions or dispersible powders. The content of the pharmaceutically active compound(s) should be in the range from 0.1 to 90 wt.-%, preferably 0.5 to 50 wt.-% of the composition as a whole, i.e. in amounts which are sufficient to achieve the dosage range specified below. The doses specified may, if necessary, be given several times a day.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example

collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection and infusion are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, whilst if water is used as the diluent, for example, organic solvents may optionally be used as solvating agents or dissolving aids, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc,

chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose) emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

The preparations are administered by the usual methods, preferably by oral or transdermal route, most preferably by oral route. For oral administration the tablets may, of course contain, apart from the abovementioned carriers, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tabletting process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

For parenteral use, solutions of the active substances with suitable liquid carriers may be used.

However, it may sometimes be necessary to depart from the amounts specified, depending on the body weight, the route of administration, the individual response to the drug, the nature of its formulation and the time or interval over which the drug is administered. Thus, in some cases it may be sufficient to use less than the minimum dose given above, whereas in other cases the upper limit may have to be exceeded. When administering large amounts it may be advisable to divide them up into a number of smaller doses spread over the day.

The formulation examples which follow illustrate the present invention without restricting its scope:

Examples of pharmaceutical formulations

A)	Tablets	per tablet
	active substance according to formula **(I)**	100 mg
	lactose	140 mg
	corn starch	240 mg

polyvinylpyrrolidone	15 mg
magnesium stearate	5 mg
	500 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B) Tablets per tablet

active substance according to formula **(I)**	80 mg
lactose	55 mg
corn starch	190 mg
microcrystalline cellulose	35 mg
polyvinylpyrrolidone	15 mg
sodium-carboxymethyl starch	23 mg
magnesium stearate	2 mg
	400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodiumcarboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

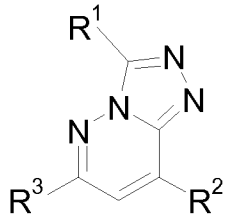
C) Ampoule solution

active substance according to formula **(I)**	50 mg
sodium chloride	50 mg
water for inj.	5 mL

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion. The ampoules contain 5 mg, 25 mg and 50 mg of active substance.

Claims

1. A compound of formula (I)



(I)

wherein,

R^1 is $-C_{1-3}$alkyl or $-C_{1-3}$haloalkyl;

R^2 is selected from $-NHR^4$, $-C_{1-5}$alkyl, $-C_{1-5}$haloalkyl, halogen and $-S-C_{1-3}$alkyl;

R^3 is selected from $-N(R^7, R^8)$, 5-12 membered heteroaryl, wherein the heteroaryl group is substituted with $-X-R^{10}$, and the heteroaryl group is optionally further substituted with one ore more groups independently selected from R^9;

R^4 is selected from $-C_{1-5}$alkyl and 5-12 memebered heterocycloalkyl, which can be optionally substituted with one or more groups independently selected from R^5;

R^5 is selected from $-C_{1-5}$alkyl, $-C_{1-5}$haloalkyl, $-C_{1-3}$alkylene-O-C_{1-3}alkyl, $-C(O)-C_{1-3}$alkyl, -C(O)-H and $-S(O)_2-R^6$;

R^6 is selected from $-C_{1-3}$alkylene-$N(C_{1-3}alkyl)_2$, $-C_{1-3}$alkylene-NH_2 and 5-12 membered heterocycloalkyl, wherein the heterocycloalkyl can be optionally substituted with $-C_{1-3}$alkyl;

R^7, R^8 can be the same or different and are independently selected from $-C_{1-3}$alkyl, $-C_{1-3}$alkylene-C_{6-10}aryl, $-C_{1-3}$alkylene-(5-12 membered

heteroaryl), wherein the aryl and the heteroaryl groups can be optionally substituted with one or more groups independently selected from halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, -C_{1-3}haloalkyl and -O-C_{1-3}haloalkyl;

R^9 is selected from-C_{1-5}alkyl, halogen, -C_{1-3}alkylene-O-C_{1-3}alkyl, -C_{1-5}alkylene-N(-C_{1-5}alkyl, -C_{1-5}alkyl), 5-12 memebered heterocycloalkyl,wherein the heterocycloalkyl group can be optionally substituted with -C_{1-3}alkyl, or

R^9 is selected from -C_{6-10}aryl and 5-12 memebered heteroaryl, wherein the aryl and heteroaryl groups can be optionally and independently substituted with one ore more groups selected from halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, -C_{1-3}haloalkyl, -O-C_{1-3}haloalkyl, -N(C_{1-5}alkyl, C_{1-5}alkyl) and -NH-C_{1-5}alkyl;

X is -C_{1-3}alkylene- or -O-;

R^{10} is-C_{6-10}aryl or 5-12 membered heteroaryl, each of which groups can be optionally substituted with one or more groups selected from halogen, -C_{1-3}alkyl, -O-C_{1-3}alkyl, -C_{1-3}haloalkyl, -O-C_{1-3}haloalkyl;

wherein the compounds of formula (I) may be optionally be present in the form of salts.

2. A compound according to claim 1, wherein R^1 is -CH_3.

3. A compound according to claim 1 or 2, wherein R^2 is NHR^4.

4. A compound according to claim 1, wherein R^2 is NHR^4 and R^3 is as defined in claim 1.

5. A compound according to claim 1, wherein R^3 is 5-12 membered heteroaryl and R^2 is as defined in claim 1.

6. A compound according to claim 1 or 2, wherein R^2 is -NHR^4 and R^4 is a 5-6 membered heterocycloalkyl, optionally substituted as defined in claim 1.

7. A compound according to claim 6, wherein R^4 is piperidine substituted with one group selected from -CH_3, -CH_2CH_3,-$CH_2CH_2CH_3$ and -$(CH_2)_2$-O-CH_3.

8. A compound according to anyone of claims 1 or 2, wherein R^2 is -NHR^4 and R^4 is -C_{1-3}alkyl.

9. A compound according to claim 8, wherein R^2 is -NHR^4 and R^4 is -CH_3 or -$CH(CH_3)_2$.

10. A compound according to anyone of claims 1 or 2, wherein R^2 is -C_{1-3}alkyl.

11. A compound according to anyone of claims 1 to 4 and 6 to 10, wherein R^3 is -$N(R^7,R^8)$, wherein R^7 is -C_{1-3}alkyl and R^8 is -C_{1-3}alkylene-C_{6-10}aryl, wherein the aryl can be optionally substituted with halogen.

12. A compound according to claim 11, wherein R^3 is -$N(CH_3)$-CH_2-phenyl, wherein the phenyl can be optionally substituted with halogen.

13. A compound according to anyone of claims 1 to 10, wherein R^3 is a 5-9 membered heteroaryl substituted with -X-R^{10} and optionally further substituted with one or more groups independently selected from R^9, wherein R^9, X and R^{10} are defined as in claim 1.

14. A compound according to claim 13, wherein -X-R^{10} is selected from -CH_2-phenyl, -CH_2-pyridyl, -O-pyridyl, -O-phenyl, each of which phenyl or pyridyl groups is optionally substituted with halogen or -C_{1-3}alkyl.

15. A compound according to claim 14, wherein -X-R^{10} is selected from -CH_2-phenyl, -CH_2-pyridyl, -O-pyridyl, -O-phenyl, each of which pyridyl or phenyl group is optionally substituted with –F or –CH_3.

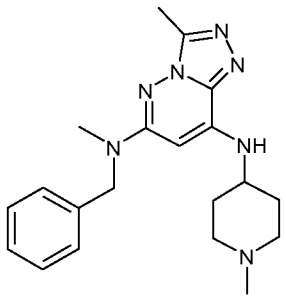
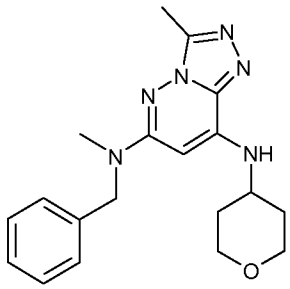
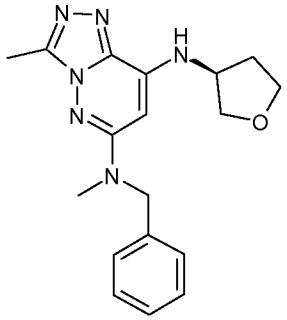
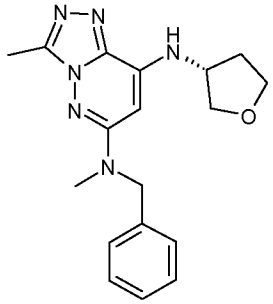
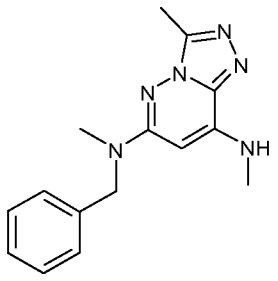
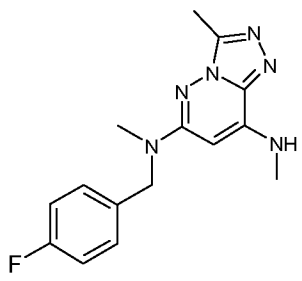
16. A compound according to claim 13, wherein R^3 is pyrazolyl substituted with -X-R^{10} and optionally further substituted with one or more groups

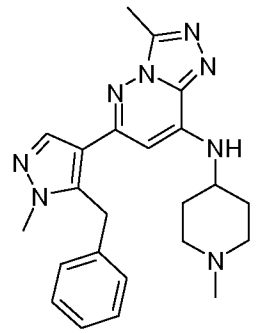
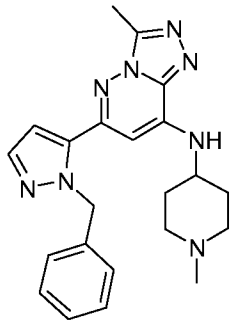
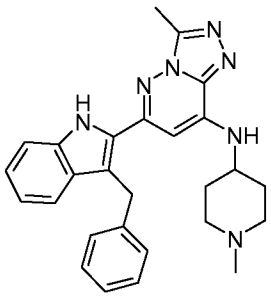
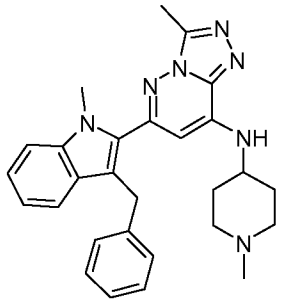
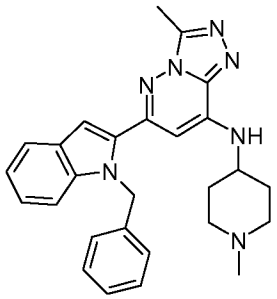
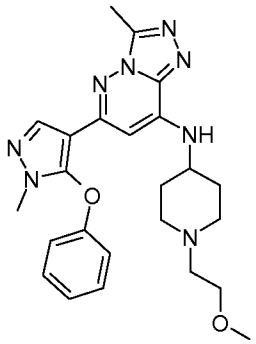
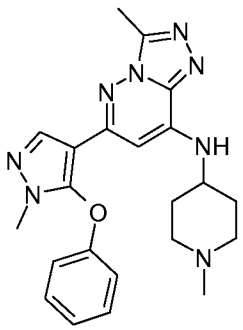
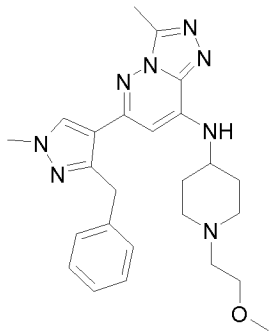
independently selected from R^9 wherein R^9, X and R^{10} are defined as in claim 1.

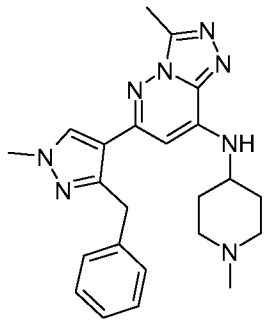
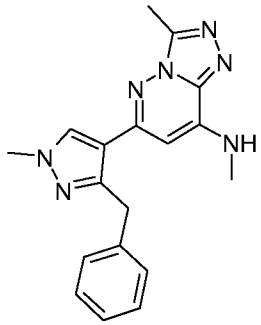
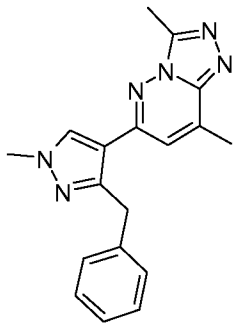
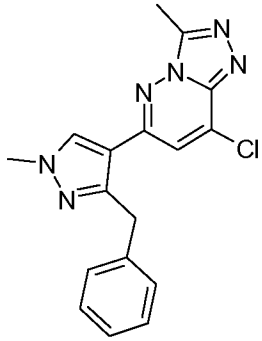
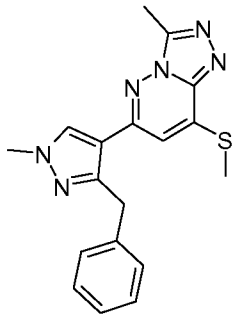
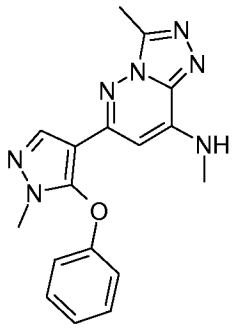
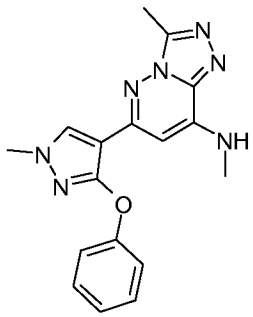
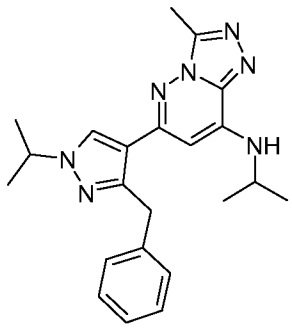
17. A compound according to claim 16, wherein R^3 is pyrazolyl substituted with -CH_2-pyridyl, -O-pyridyl, -CH_2-phenyl or -O-phenyl and optionally further substituted with -C_{1-3}alkyl.

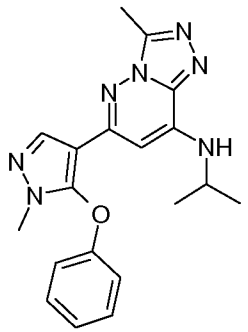
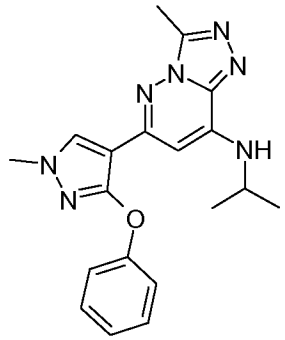
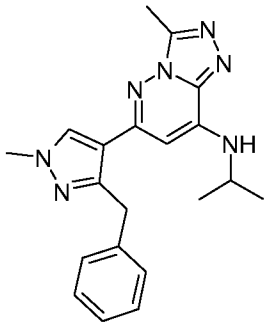
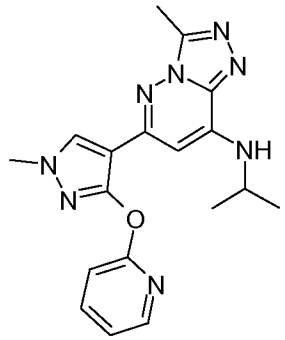
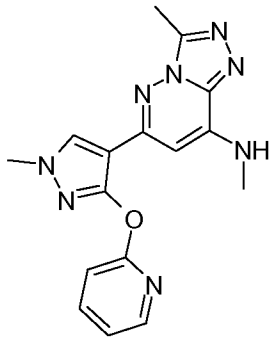
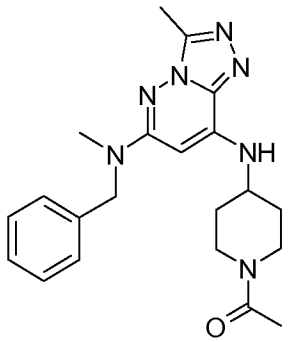
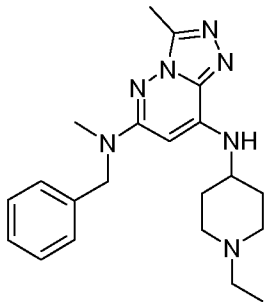
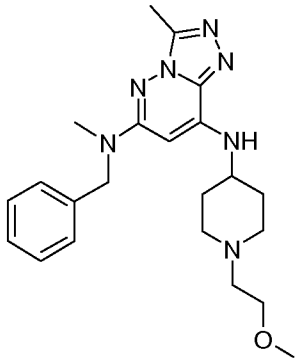
18. A compound according to claim 13, wherein R^9 is selected from -CH_3 and -$CH(CH_3)_2$.

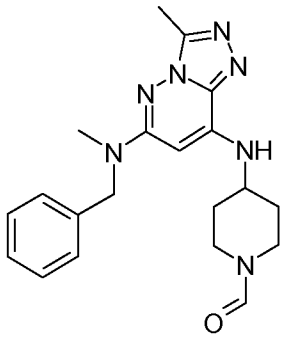
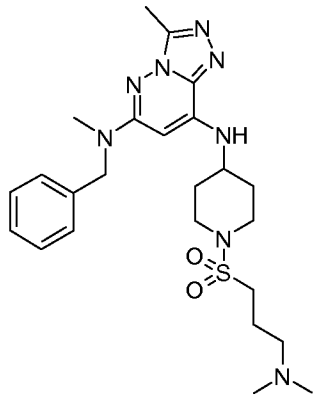
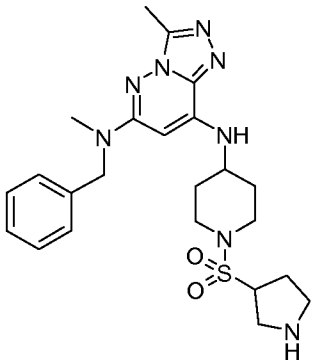
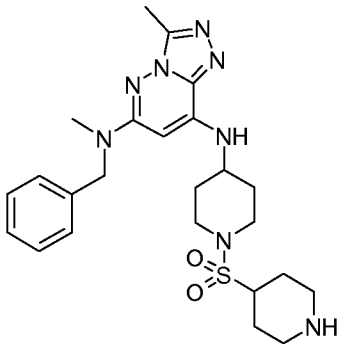
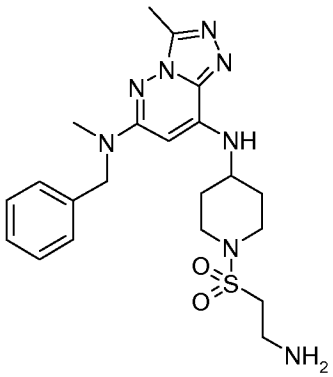
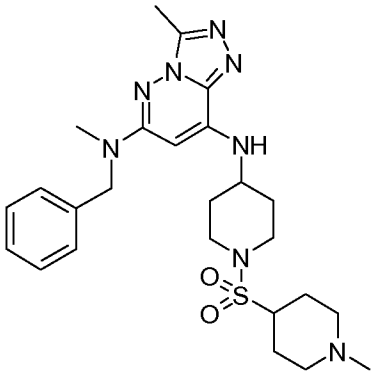
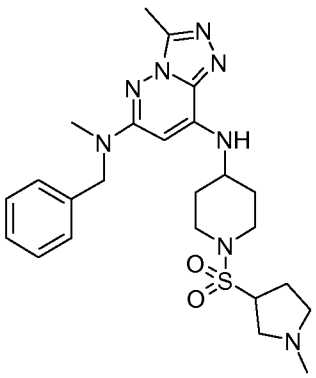
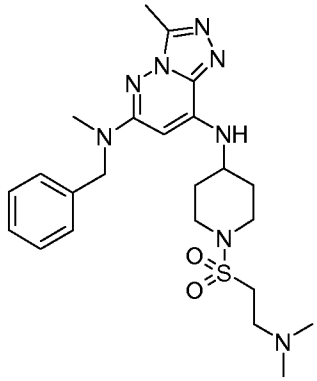
19. A compound according to claim 1 selected from

Ex Nr	Structure	Ex. Nr	Structure
I-1		I-2	
I-3		I-4	
I-5		I-6	

Ex Nr	Structure	Ex. Nr	Structure
II-1		II-2	
II-3		II-4	
II-5		II-6	
II-7		II-8	

Ex Nr	Structure	Ex. Nr	Structure
II-9		II-10	
II-11		II-12	
II-13		II-14	
II-15		II-16	

Ex Nr	Structure	Ex. Nr	Structure
II-17		II-18	
II-19		II-20	
II-21		III-1	
III-2		III-3	

Ex Nr	Structure	Ex. Nr	Structure
III-4		III-7	
III-8		III-9	
III-10		III-11	
III-12		III-13	

wherein the compound may be optionally be present in the form of salts.

20. A compound of general formula (I) according to anyone of claims 1 to 19 - or the pharmaceutically acceptable salts thereof - for use in the treatment and/or prevention of cancer.

21. Pharmaceutical preparation comprising as active substance one or more compounds of general formula (I) according to anyone of claims 1 to 19 optionally in combination with conventional excipients and/or carriers.

22. Pharmaceutical preparation comprising a compound of general formula (I) according to anyone of claims 1 to 19 - or one of the pharmaceutically acceptable salts thereof - and at least one other cytostatic or cytotoxic active substance, different from formula (I).

23. A compound of general formula (I) according to anyone of claims 1 to 19 - or the pharmaceutically acceptable salts thereof - for use as medicaments.

24. A compound of general formula (I) according to anyone of claims 1 to 19 -or the pharmaceutically acceptable salts thereof - for use in the treatment of hematopoietic malignancies.

25. A compound of general formula (I) according to anyone of claims 1 to 19 -or the pharmaceutically acceptable salts thereof - for use in the treatment of AML or MM.

26. A compound of general formula (I) according to anyone of claims 1 to 19 -or the pharmaceutically acceptable salts thereof - for use in the treatment of lung, liver, colon, brain, thyroid, pancreas, breast, ovary and prostate cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/073758

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5025
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2012/174487 A2 (CONSTELLATION PHARMACEUTICALS INC [US]; ALBRECHT BRIAN K [US]; HARMANG) 20 December 2012 (2012-12-20) claims 1,2,5,6,20-30,32,33 -----	1,2,10, 20-26
X	KATRUSIAK, ANNA ET AL.: "Nucleophilic substitution and lipophilicity-structure relations in methylazolopyridazines", COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS., vol. 70, no. 9, 2005, pages 1372-1386, XP008160516, CZINSTITUTE OF ORGANIC CHEMISTRY & BIOCHEMISTRY, PRAGUE. ISSN: 0010-0765 page 1376, compound 18; page 1385, lines 3 to 6 ----- -/--	1,2,10

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 January 2014	14/01/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rufet, Jacques

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/161031 A1 (GLAXOSMITHKLINE LLC [US]; BAILEY JAMES MATTHEW [GB]) 29 December 2011 (2011-12-29) claims 1,29-33,35-37,39	1-26
A	WO 2007/075567 A1 (JANSSEN PHARMACEUTICA NV [BE]; LU TIANBAO [US]; ALEXANDER RICHARD [US]) 5 July 2007 (2007-07-05) claims 1,13,16-19	1-26
A	WO 2008/109104 A1 (UNIV CALIFORNIA [US]; KOLB HARTMUTH C [US]; WANG SI [US]; CHERUKUPALLI) 12 September 2008 (2008-09-12) claims 1-39	1-26
A	GB 1 480 621 A (LEPETIT SPA) 20 July 1977 (1977-07-20) page 1 to page 2, column 2, line 19; claim 1	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/073758

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012174487 A2	20-12-2012	NONE	
WO 2011161031 A1	29-12-2011	EP 2585465 A1	01-05-2013
		JP 2013529611 A	22-07-2013
		US 2013079335 A1	28-03-2013
		WO 2011161031 A1	29-12-2011
WO 2007075567 A1	05-07-2007	AR 058703 A1	20-02-2008
		AU 2006331912 A1	05-07-2007
		BR PI0620292 A2	08-11-2011
		CA 2634721 A1	05-07-2007
		CN 101374843 A	25-02-2009
		EA 200870085 A1	30-12-2008
		EC SP088573 A	30-07-2008
		EP 1966214 A1	10-09-2008
		GT 200800105 A	10-10-2008
		HN 2008000931 A	22-10-2013
		JP 5292102 B2	18-09-2013
		JP 2009525263 A	09-07-2009
		KR 20080085154 A	23-09-2008
		MA 30084 B1	01-12-2008
		NZ 568807 A	27-05-2011
		PE 00082011 A1	31-01-2011
		PE 07522007 A1	13-08-2007
		SV 2008002963 A	18-01-2010
		TW 200801007 A	01-01-2008
		US 2007203136 A1	30-08-2007
		US 2009098181 A1	16-04-2009
		UY 30041 A1	31-05-2007
		WO 2007075567 A1	05-07-2007
		ZA 200806277 A	29-09-2010
WO 2008109104 A1	12-09-2008	NONE	
GB 1480621 A	20-07-1977	AR 206514 A1	30-07-1976
		AR 206643 A1	06-08-1976
		AT 336604 B	10-05-1977
		AU 7305374 A	11-03-1976
		BE 820163 A1	16-01-1975
		CA 1034948 A1	18-07-1978
		CH 595382 A5	15-02-1978
		CH 599212 A5	12-05-1978
		DD 113543 A5	12-06-1975
		DE 2444322 A1	27-03-1975
		DK 496374 A	20-05-1975
		ES 430277 A1	16-12-1976
		ES 432243 A1	16-04-1977
		FI 265674 A	22-03-1975
		FR 2244519 A1	18-04-1975
		GB 1480621 A	20-07-1977
		HU 171789 B	28-03-1978
		IE 40651 B1	18-07-1979
		IL 45654 A	31-07-1977
		JP S537439 B2	17-03-1978
		JP S5058092 A	20-05-1975
		LU 70949 A1	06-03-1975
		NL 7411849 A	25-03-1975
		NO 743140 A	14-04-1975

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/073758

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		PL 91748 B1	31-03-1977
		RO 64487 A1	15-06-1979
		SE 419990 B	07-09-1981
		SU 545261 A3	30-01-1977
		SU 576940 A3	15-10-1977
		US 3915968 A	28-10-1975
		ZA 7405482 A	24-09-1975