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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 December 2020 (30.12.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/260252 A1

(51) International Patent Classification:
A61P 35/00 (2006.01) *C07D 498/22* (2006.01)
C07D 487/22 (2006.01) *A61K 31/439* (2006.01)

(21) International Application Number:
PCT/EP2020/067451

(22) International Filing Date:
23 June 2020 (23.06.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
19181952.3 24 June 2019 (24.06.2019) EP

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

(72) Inventors: **ENGELHARDT, Harald**; Boehringer Ingelheim International GmbH, Corporate Patents, Binger Strasse 173, 55216 INGELHEIM AM RHEIN (DE). **BOESE, Dietrich**; Boehringer Ingelheim International GmbH, Corporate Patents, Binger Strasse 173, 55216 INGELHEIM AM RHEIN (DE).

(74) Agent: **SIMON, Elke Anna Maria** et al.; Boehringer Ingelheim International 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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, 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, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

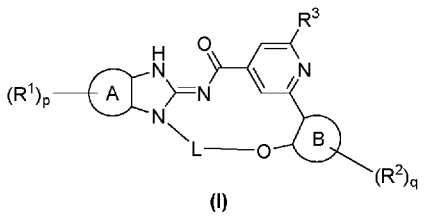
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, 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))*

WO 2020/260252 A1

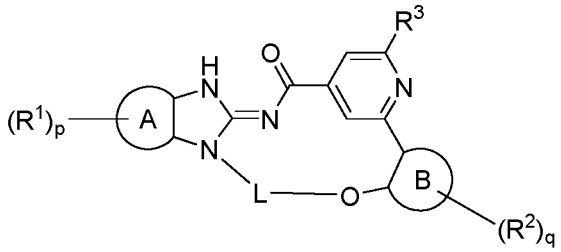
(54) Title: NEW MACROCYCLIC COMPOUNDS AND DERIVATIVES AS EGFR INHIBITORS



(I)

(57) Abstract: The present invention encompasses compounds of formula (I) wherein the groups R^1 to R^3, A, B and L and p and q have the meanings given in the claims and specification, their use as inhibitors of mutant EGFR, pharmaceutical compositions which contain compounds of this kind and their use as medicaments/medical uses, especially as agents for treatment and/or prevention of oncological diseases.

NEW MACROCYCLIC COMPOUNDS AND DERIVATIVES AS EGFR INHIBITORS



(I)

wherein the groups **R^1** to **R^3**, **A**, **B** and **L** and **p** and **q** have the meanings given in the claims and specification, their use as inhibitors of mutant EGFR, pharmaceutical compositions which contain compounds of this kind and their use as medicaments/medical uses, especially as agents for treatment and/or prevention of oncological diseases.

Background of the invention

The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that transduces mitogenic signals. Mutations in the *EGFR* gene are found in approximately 12 % to 47 % of non-small cell lung cancer (NSCLC) tumors with adenocarcinoma histology (Midha, 2015). The two most frequent *EGFR* alterations found in NSCLC tumors are short in-frame deletions in exon 19 (del19) of the *EGFR* gene and L858R, a single missense mutation in exon 21 (Konduri, 2016). These two mutations cause ligand-independent EGFR activation and are collectively referred to as EGFR M+. Del19 and L858R mutations in *EGFR* sensitize NSCLC tumors to the treatment with EGFR tyrosine kinase inhibitors (TKIs). Clinical experience shows an objective response rate of approximately 60-85 % in EGFR M+ NSCLC patients treated in 1st line with the 1st, 2nd and 3rd generation EGFR TKIs erlotinib, gefitinib, afatinib and osimertinib (Mitsudomi, 2010; Park, 2016; Soria, 2017; Zhou, 2011). These responses demonstrate that EGFR M+ NSCLC cells and tumors depend on oncogenic EGFR activity for survival and proliferation, establishing del19 or L858R mutated EGFR as a validated drug target and predictive biomarker for the treatment of NSCLC. The 1st generation EGFR TKIs erlotinib and gefitinib as well as the 2nd generation TKI afatinib are FDA-approved for the 1st line treatment of EGFR M+ NSCLC patients.

While tumor responses are accompanied by marked tumor shrinkage in patients, the

response is usually not durable and most patients relapse within 10 to 12 months of treatment with 1st and 2nd generation EGFR TKIs (Mitsudomi, 2010; Park, 2016; Soria, 2017; Zhou, 2011). The most prominent molecular mechanism underlying progression is the acquisition of a secondary mutation in *EGFR*, namely T790M (Blakely, 2012; Kobayashi, 2005), in 50 % to 70 % of patients progressing on 1st and 2nd generation EGFR inhibitors. This mutation attenuates the inhibitory activity of 1st and 2nd generation TKIs in cellular assays (see data in Table 16).

Mutant selective and covalent 3rd generation EGFR TKIs, such as osimertinib, have been developed that effectively inhibit the primary *EGFR* mutations del19 and L858R with and without the secondary T790M resistance mutation (Cross, 2014; Wang, 2016). The recently demonstrated efficacy of the 3rd generation EGFR TKI osimertinib in the 2nd line treatment of EGFR M+ T790M-positive NSCLC demonstrates clinically that tumor cell survival and proliferation is dependent on the mutated EGFR allele (Jänne, 2015; Mok, 2016). Approximately 70 % of EGFR M+ T790M-positive patients that were previously treated with earlier generation EGFR TKI respond to osimertinib treatment in 2nd line. However, disease progression occurs after an average duration of 10 months (Mok, 2016). The mechanisms underlying acquired resistance to 3rd generation EGFR TKIs have been studied in small cohorts of patients and are beginning to emerge (Ou, 2017). Recent data suggest that one major resistance mechanism is the acquisition of the tertiary *EGFR* mutation C797S in about 20-40 % of 2nd line patients relapsing on osimertinib TKI (Ortiz-Cuaran, 2016; Ou, 2017; Song, 2016; Thress, 2015; Yu, 2015). 3rd generation TKIs, such as osimertinib, covalently attach to EGFR *via* the residue C797 (Cross, 2014; Wang, 2016). In cellular models the C797S mutation abolishes the activity of 3rd generation TKIs tested (Thress, 2015) (see data in Table 16). In 2nd line patients, the mutation C797S is preferentially found in conjunction with the EGFR del19 genotype and on the same allele as the T790M mutation (*cis* configuration) (82 % of C797S+ patients) (Piotrowska, 2017). Crucially, the EGFR del19/L858R T790M C797S *cis* mutant kinase variant that emerges in 2nd line patients progressing on osimertinib (Ortiz-Cuaran, 2016; Ou, 2017; Song, 2016; Thress, 2015; Yu, 2015) can no longer be inhibited by 1st, 2nd or 3rd generation EGFR TKIs (Thress, 2015) (see data in Table 16). Based on the fact that the C797S mutation is detected at progression on osimertinib (Ortiz-Cuaran, 2016; Ou, 2017; Song, 2016; Thress, 2015; Yu, 2015), it is likely that tumor cell survival and proliferation in EGFR del19/L858R T790M C797S patients is dependent on this mutant allele and can be

inhibited by targeting this allele. Additional *EGFR* resistance mutations with a lower incidence than C797S were recently described in 2nd line EGFR M+ NSCLC patients progressing on osimertinib: L718Q, L792F/H/Y and C797G/N (Bersanelli, 2016; Chen, 2017; Ou, 2017).

The 3rd generation EGFR TKI osimertinib has recently also shown efficacy in previously untreated EGFR M+ NSCLC patients (Soria, 2017). Disease progression occurs after an average duration of 19 months. While the EGFR resistance mutation spectrum after 1st line osimertinib treatment has not been extensively studied yet, first available data also suggest the emergence of the mutation C797S that abrogates osimertinib activity (Ramalingam, 2017).

The fact that no approved EGFR TKI can inhibit the *EGFR* del19/L858R T790M C797S variant, an allele occurring after progression of patients on 2nd line osimertinib treatment, highlights the medical need for a next generation EGFR TKI, a "4th generation EGFR TKI". This 4th generation EGFR TKI should potently inhibit EGFR del19 or L858R irrespective of the presence of the two common resistance mutations T790M and C797S, especially EGFR del19 T790M C797S. The utility of such a 4th generation EGFR TKI would be enhanced by activity of the compound on additional resistance mutations, such as the potential osimertinib resistance mutations C797X (X = S, G, N) and L792F/H/Y. The broad activity of the molecule on the EGFR del19 or L858R variants also without T790M and/or C797S mutations would ensure that the new compound can effectively cope with the expected allelic complexity in patient tumors as a monotherapy agent. To facilitate efficacious dosing and reduce EGFR-mediated on-target toxicities, a 4th generation EGFR TKI should not inhibit wild-type EGFR. High selectivity across the human kinome would reduce off-target toxicity of the compound. Another desirable property of a 4th generation EGFR TKI is the ability to efficiently penetrate into the brain (blood-brain barrier penetration) in order to be able to treat brain metastasis and leptomeningeal disease. Lastly, a 4th generation EGFR TKI should display a reduced resistance liability compared to existing EGFR TKIs in order to increase the duration of response in patients.

The aforementioned properties of a 4th generation EGFR TKI would allow to treat patients progressing on 2nd line treatment with a 3rd generation TKI, such as osimertinib, (*e.g.* with the genotype EGFR del19/L858R T790M C797S), who have currently no targeted therapy treatment option. Furthermore, these properties also have the potential to allow a 4th generation EGFR TKI to provide a longer duration of response in earlier treatment line

patients, such as patients progressing on 1st line osimertinib treatment with EGFR C797S mutations as well as 1st line patients. The activity of a 4th generation EGFR TKI on resistance mutations such as T790M, C797X (X = S, G, N) and L792X (X = F, H, Y) has the potential to delay the development of resistance through EGFR *intra* target mutations in NSCLC tumors. The characteristics outlined above define a 4th generation EGFR TKI as the first EGFR TKI able to effectively target patients with NSCLC tumors carrying the EGFR del19/L858R T790M C797X/L792X variants. Furthermore, a 4th generation EGFR TKI will be the first C797X active compound that also inhibits T790M-positive alleles, possesses EGFR wild-type sparing activity and effectively penetrates into the brain.

The aforementioned characteristics have not been achieved in previously described EGFR inhibitor compounds. Over the past years, selective targeting of mutated EGFR has gained increasing attention. Until today several efforts to identify and optimize inhibitors, which target either the catalytic site of EGFR mutants or an allosteric site of the EGFR protein, have been made with limited success in respect of the above mentioned characteristics.

Recently, a number of EGFR inhibitors which can overcome EGFR resistance mutations including the mutation T790M, as well as the C797S mutation and combinations of both have been published (Zhang, 2017; Park, 2017; Chen, 2017; Bryan 2016; Juchum, 2017; Günther, 2017; WO 2017/004383). Most of the published molecules are non-covalent variants of quinazoline based 2nd generation EGFR inhibitors. (Patel, 2017; Park, 2017; Chen, 2017). However, these published molecules are either weak inhibitors with low selectivity over EGFR *wt* (Patel, 2017; Chen, 2017) or were designed to specifically bind only to the del19/T790M/C797S mutant without activity to other EGFR variant combinations and mutations (Park, 2017). Other published compound classes show activity only against the T790M and T790M/C797S resistance mutation in the L858R activation background (Bryan 2016; Juchum, 2017; Günther, 2017). However, since these mutations and mutation combinations were only observed in a small fraction of the patient population and since allelic complexity in metastatic tumors is likely high, they are very unlikely to fulfill the necessary criteria in order to be developed towards effective EGFR inhibitors.

The following prior art documents disclose non-covalent compounds as mutant selective EGFR inhibitors with activity toward T790M bearing EGFR: WO 2014/210354; WO 2014/081718; Heald, 2015; Hanan, 2014; Lelais, 2016; Chan, 2016.

Although the compounds from the above mentioned documents are claimed to be active against the two most common EGFR activation/resistance mutation combinations del19/T790M and L858/T790M, most of them display only weak activity against the more prevalent del19/T790M mutation, they also display no affinity towards EGFR harboring the primary activation mutations del19 and L858R alone. Such a selective inhibition of the double mutated EGFR over the activity against the single activation mutations is highly unfavorable due to the heterogeneity of EGFR mutations in patients and would likely lead to a limited efficacy. Additionally, most of the compounds show only a small selectivity towards EGFR *wt* which is known to be the major factor for common side effects in EGFR targeted therapies (diarrhea, skin-rash) leading to a target specific toxicity. This specific cytotoxic component is undesirable, because it potentially leads to adverse events in treated patients.

The following prior art documents disclose aminobenzimidazole based compounds as EGFR selective inhibitors with activity toward both oncogenic driver mutations L858R and del19 as well as activity against the T790M resistance mutation and combination of them: WO 2013/184757; WO 2013/184766, WO 2015/143148, WO 2015/143161, WO 2016/185333; Lelais, 2016; Jia, 2016.

The following prior art documents disclose further aminobenzimidazole based compounds: WO 2003/030902, WO 2003/041708, WO 2004/014369, WO 2004/014905, WO 2005/079791, WO 2007/133983, WO 2012/018668, WO 2014/036016, WO 2014/121942, WO 2016/176473, WO 2017/049068, WO 2017/049069.

Some of the compounds **(I)** according to the invention have such aminobenzimidazole scaffold as a substructure, but these published prior art compounds do not comprise a macrocycle. Aminobenzimidazoles as part of macrocycles are disclosed in WO 2014/121942 as IRAK inhibitors, which, however, only display a weak inhibitory actvitiy against EGFR mutants (see data in table 16). Furthermore, structurally related previously published aminobenzimidazoles are designed as covalent EGFR inhibitors bearing a reactive (warhead) group in the molecule. The activity of these inhibitors is mostly driven by a covalent binding to the C797 residue of the EGFR protein and is therefore dependent on the reactive group. This leads to a high susceptibility toward the C797S resistance mutation (Engel, 2016). Corresponding compounds without the reactive (warhead) group derived from these prior art aminobenzimidazoles, however, show only weak remaining activity against EGFR mutants (see data in Table 16). This renders them ineffective as

non-covalent EGFR inhibitors and limits their use as broad EGFR mutant inhibitors. Thus, against this background, the skilled person would not have considered the previously known aminobenzimidazole scaffold to be a promising starting point to identify EGFR inhibitors with the profile of a 4th generation EGFR inhibitor as hereinbefore defined.

None of the aforementioned published compounds shows the desired characteristics for an effective and clinically relevant EGFR resistance mutation targeting inhibitor.

In summary, compounds **(I)** according to the invention show a broad activity on EGFR del19 or EGFR L858R variants, with or without T790M and/or C797S mutations, which ensures that the compounds may effectively cope with the expected allelic complexity in patient tumors as a monotherapy agent. To facilitate efficacious dosing and reduce EGFR-mediated on-target toxicities, the compounds according to the invention have a reduced inhibitory potential regarding wild-type EGFR. Compounds **(I)** show a high selectivity across the human kinome, which may reduce off-target toxicity of the compounds. Another property of the compounds **(I)** according to the invention is the ability to potentially penetrate into the brain (blood-brain barrier penetration) in order to be used to treat brain metastasis and leptomeningeal disease. In addition to the inhibitory effect and potency, the compounds disclosed herein show good solubility and fine-tuned DMPK properties.

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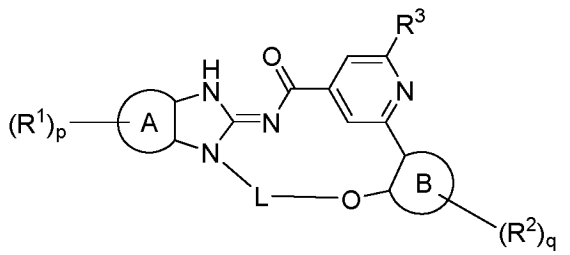
Detailed description of the invention

Compounds

It has now been found that, surprisingly, compounds of formula **(I)** wherein the groups $\mathbf{R^1}$ to $\mathbf{R^3}$, **A**, **B** and **L** and **p** and **q** have the meanings given hereinafter act as inhibitors of mutant EGFR which is involved in controlling cell proliferation. Thus, the compounds according to the invention may be used for example for the treatment of diseases

characterised by excessive or abnormal cell proliferation.

The present invention therefore relates to a compound of formula **(I)**



(I)

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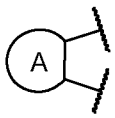
wherein

[A0]



is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

p is selected from the group consisting of 0, 1, 2 and 3;

each $\mathbf{R^1}$ is independently selected from the group consisting of $\mathbf{R^{a1}}$ and $\mathbf{R^{b1}}$;

$\mathbf{R^{a1}}$ is selected from the group consisting of C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-10 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-10 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted by one or more, identical or different $\mathbf{R^{b1}}$ and/or $\mathbf{R^{c1}}$;

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of $-OR^{c1}$, $-NR^{c1}R^{c1}$, halogen, -CN, $-C(O)R^{c1}$, $-C(O)OR^{c1}$, $-C(O)NR^{c1}R^{c1}$, $-S(O)_2R^{c1}$, $-S(O)_2NR^{c1}R^{c1}$, $-NHC(O)R^{c1}$, $-N(C_{1-4}alkyl)C(O)R^{c1}$, $-NHC(O)OR^{c1}$, $-N(C_{1-4}alkyl)C(O)OR^{c1}$ and the bivalent substituent =O;

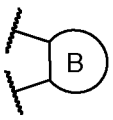
each $\mathbf{R^{c1}}$ is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-10 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-10 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted by

one or more, identical or different R^{d1} and/or R^{e1};

each R^{d1} is independently selected from the group consisting of $-OR^{e1}$, $-NR^{e1}R^{e1}$, halogen, -CN, $-C(O)R^{e1}$, $-C(O)OR^{e1}$, $-C(O)NR^{e1}R^{e1}$, $-S(O)_2R^{e1}$, $-S(O)_2NR^{e1}R^{e1}$, $-NHC(O)R^{e1}$, $-N(C_{1-4}alkyl)C(O)R^{e1}$, $-NHC(O)OR^{e1}$, $-N(C_{1-4}alkyl)C(O)OR^{e1}$ and the bivalent substituent =O;

each R^{e1} is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-10 membered heterocyclyl optionally substituted with C_{1-4} alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, C_{6-10}aryl, 5-10 membered heteroaryl and $(C_{1-4}alkyl)_2$amino-C_{1-4}alkyl;

[B0]



is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

q is selected from the group consisting of 0, 1 and 2;

each R^2 is independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, -CN, C_{1-4}alkoxy, C_{1-4}haloalkoxy and halogen;

[C0]

R^3 is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{2-4}alkenyl, C_{2-4}alkinyl, halogen, -CN, $-NH_2$, $-NH(C_{1-4}alkyl)$ and $-N(C_{1-4}alkyl)_2$; and

[D0]

L is selected from the group consisting of straight chain C_{3-7}alkylene, straight chain C_{3-7}alkenylene and straight chain C_{3-7}alkynylene, wherein one or two methylene groups $-CH_2-$ in such straight chain C_{3-7}alkylene, straight chain C_{3-7}alkenylene and straight chain C_{3-7}alkynylene are optionally and independently replaced by a group/atom selected from oxygen, -NH- and $-N(C_{1-4}alkyl)-$;

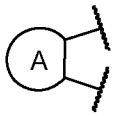
wherein such straight chain can be optionally substituted on carbon by one or more, identical or different substituent(s) selected from the group consisting of C_{1-4}alkyl, halogen and hydroxy;

wherein one carbon atom, two carbon atoms or one carbon atom and one nitrogen atom in such straight chain can be optionally bridged with C_{1-5}alkylene, wherein one

methylene group -CH_2- in such bridging C_{1-5}alkylene can be optionally replaced by oxygen, to form a C_{3-6}carbocycle or 3-6 membered nitrogen- and/or oxygen-containing heterocycle;

or a salt thereof.

In one aspect **[A1]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein



is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

p is selected from the group consisting of 1, 2 and 3;

each $\mathbf{R^1}$ is independently selected from the group consisting of $\mathbf{R^{a1}}$ and $\mathbf{R^{b1}}$;

$\mathbf{R^{a1}}$ is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted by one or more, identical or different $\mathbf{R^{b1}}$ and/or $\mathbf{R^{c1}}$;

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of -OR^{c1}, -$NR^{c1}R^{c1}$, halogen, -CN, -$C(O)R^{c1}$, -$C(O)OR^{c1}$, -$C(O)NR^{c1}R^{c1}$ and the bivalent substituent =O;

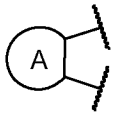
each $\mathbf{R^{c1}}$ is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted by one or more, identical or different $\mathbf{R^{d1}}$ and/or $\mathbf{R^{e1}}$;

each $\mathbf{R^{d1}}$ is independently selected from the group consisting of -OR^{e1}, -$NR^{e1}R^{e1}$, halogen, -CN, -$C(O)R^{e1}$, -$C(O)OR^{e1}$, -$C(O)NR^{e1}R^{e1}$ and the bivalent substituent =O;

each $\mathbf{R^{e1}}$ is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl optionally substituted with C_{1-4} alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, C_{6-10}aryl, 5-10 membered heteroaryl and $(C_{1-4}alkyl)_2$amino-C_{1-4}alkyl.

In another aspect **[A2]** the invention relates to a compound of formula **(I)** or a salt thereof,

wherein



is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

p is selected from the group consisting of 1, 2 and 3;

each $\mathbf{R^1}$ is independently selected from the group consisting of $\mathbf{R^{a1}}$ and $\mathbf{R^{b1}}$;

$\mathbf{R^{a1}}$ is selected from the group consisting of $C_{1\text{-}6}$alkyl and 3-10 membered heterocyclyl, wherein the $C_{1\text{-}6}$alkyl and 3-10 membered heterocyclyl are all optionally substituted by one or more, identical or different $\mathbf{R^{b1}}$ and/or $\mathbf{R^{c1}}$;

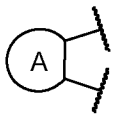
each $\mathbf{R^{b1}}$ is independently selected from the group consisting of $-OR^{c1}$, $-NR^{c1}R^{c1}$, halogen, -CN, $-C(O)R^{c1}$, $-C(O)OR^{c1}$, $-C(O)NR^{c1}R^{c1}$ and the bivalent substituent =O;

each $\mathbf{R^{c1}}$ is independently selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, $C_{3\text{-}10}$cycloalkyl and 3-10 membered heterocyclyl, wherein the $C_{1\text{-}6}$alkyl, $C_{3\text{-}10}$cycloalkyl, and 3-10 membered heterocyclyl are all optionally substituted by one or more, identical or different $\mathbf{R^{d1}}$ and/or $\mathbf{R^{e1}}$;

each $\mathbf{R^{d1}}$ is independently selected from the group consisting of $-OR^{e1}$, $-NR^{e1}R^{e1}$, halogen, -CN, $-C(O)R^{e1}$, $-C(O)OR^{e1}$, $-C(O)NR^{e1}R^{e1}$ and the bivalent substituent =O;

each $\mathbf{R^{e1}}$ is independently selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, $C_{3\text{-}10}$cycloalkyl, 3-10 membered heterocyclyl optionally substituted with $C_{1\text{-}4}$ alkyl, $C_{1\text{-}4}$alkoxy-$C_{1\text{-}4}$alkyl and $(C_{1\text{-}4}\text{alkyl})_2$amino-$C_{1\text{-}4}$alkyl.

In another aspect **[A3]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein



is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

p is selected from the group consisting of 1, 2 and 3;

each $\mathbf{R^1}$ is independently selected from the group consisting of (a), (b), (c) and (d):

(a) $-(O)_n-(CH_2)_m-A$, wherein

A is 3-11 membered heterocyclyl optionally substituted with one or more, identical or different substituents selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxy-C_{1-4}alkyl, -C(O)O-C_{1-4}alkyl, -C(O)-C_{1-4}alkyl, C_{3-6}cycloalkyl, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$ and the bivalent substituent =O;

n is 0 or 1;

m is selected from the group consisting of 0, 1 and 2;

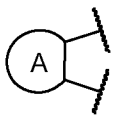
(b) -NR^AR^A, wherein

each $\mathbf{R^A}$ is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, C_{1-4}alkyl substituted with 4-7 membered heterocyclyl, (C_{1-4}alkyl)$_2$amino-C_{1-4}alkyl and (C_{1-4}alkyl)$_2$amino-C_{1-4}alkoxy-C_{1-4}alkyl;

(c) C_{1-6}alkyl optionally substituted with a substituent selected from the group consisting of -N(C_{1-4}alkyl)$_2$, -NH(C_{1-4}alkyl), -C(O)NH-C_{1-4}alkyl, -C(O)-heterocyclyl with a 5-7 membered heterocyclyl, -OH, -CN and -C(O)O-C_{1-4}alkyl;

(d) -O-C_{1-6}alkyl, -C(O)NH-C_{1-4}alkyl,-C(O)N(C_{1-4}alkyl)$_2$, -C(O)O-C_{1-6}alkyl, -CN, halogen and -C(O)-heterocyclyl with a 5-7 membered heterocyclyl optionally substituted with C_{1-6}alkyl.

In another aspect **[A4]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein



is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

p is selected from the group consisting of 1, 2 and 3;

each $\mathbf{R^1}$ is selected from the group consisting of (a), (c) and (d):

(a) -$(O)_n$-$(CH_2)_m$-A, wherein

A is 3-11 membered heterocyclyl optionally substituted with one or more, identical or different C_{1-4}alkyl,

n is 0 or 1;

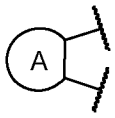
m is selected from the group consisting of 0, 1 and 2;

(c) C_{1-6}alkyl optionally substituted with a substituent selected from the group consisting of -N(C_{1-4}alkyl)$_2$ and -NH(C_{1-4}alkyl);

(d) -O-C_{1-6}alkyl, -C(O)NH-C_{1-4}alkyl,-C(O)N(C_{1-4}alkyl)$_2$, -C(O)O-C_{1-6}alkyl, halogen and

-C(O)-heterocyclyl with a 5-7 membered heterocyclyl optionally substituted with C_{1-6}alkyl.

In another aspect **[A5]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein



is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

p is selected from the group consisting of 1, 2 and 3;

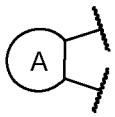
each $\mathbf{R^1}$ is $-(O)_n-(CH_2)_m-A$, wherein

A is 3-11 membered heterocyclyl optionally substituted with one or more, identical or different C_{1-4}alkyl,

n is 0 or 1;

m is selected from the group consisting of 0, 1 and 2.

In another aspect **[A6]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein

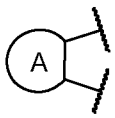


is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

p is selected from the group consisting of 1, 2 and 3;

each $\mathbf{R^1}$ is selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, heterocyclyl-C_{1-4}alkoxy with a 5-7 membered heterocyclyl which is optionally substituted with C_{1-4}alkyl, heterocyclyl-C_{1-4}alkyl with a 5-7 membered heterocyclyl which is optionally substituted with C_{1-4}alkyl, 5-7 membered heterocyclyl optionally substituted with C_{1-4}alkyl, $(C_{1-4}alkyl)_2N$-C_{1-4}alkyl, $-C(O)N(C_{1-4}alkyl)_2$, -C(O)-heterocyclyl with a 5-7 membered heterocyclyl optionally substituted with C_{1-4}alkyl and $-C(O)O-C_{1-4}$alkyl.

In another aspect **[A7]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein

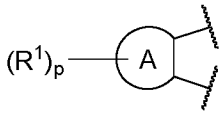


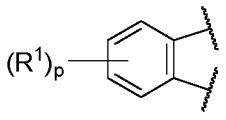
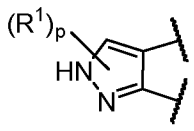
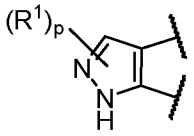
is selected from the group consisting of phenylene and 5-6 membered

heteroarylene;

p is 0.

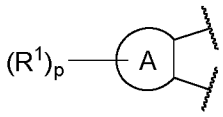
In further aspects **[A8]**, **[A9]**, **[A10]**, **[A11]**, **[A12]**, **[A13]** and **[A14]**, the invention relates to a compound of formula **(I)** or a salt thereof, wherein


is selected from the group consisting of


, 
and 
, wherein

R^1 and **p** are defined as in any one of aspects **[A0]**, **[A1]**, **[A2]**, **[A3]**, **[A4]**, **[A5]** or **[A6]**.

In another aspect **[A15]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein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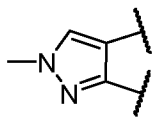
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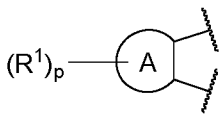
In another aspect **[A16]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein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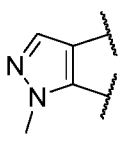
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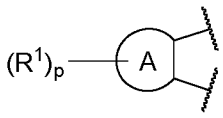
In further aspects **[A17]**, **[A18]**, **[A19]**, **[A20]**, **[A21]**, **[A22]** and **[A23]**, the invention relates to a compound of formula **(I)** or a salt thereof, wherein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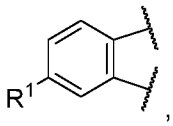
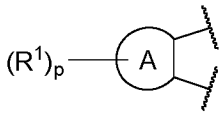

, wherein

R^1 is defined as in any one of aspects **[A0]**, **[A1]**, **[A2]**, **[A3]**, **[A4]**, **[A5]** or **[A6]**.

In further aspects **[A24]**, **[A25]**, **[A26]**, **[A27]**, **[A28]**, **[A29]** and **[A30]**, the invention relates to a compound of formula **(I)** or a salt thereof, wherein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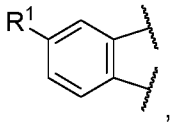
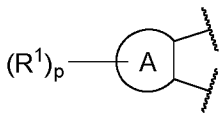

, wherein

R^1 is defined as in any one of aspects **[A0]**, **[A1]**, **[A2]**, **[A3]**, **[A4]**, **[A5]** or **[A6]**.

In another aspect **[A31]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein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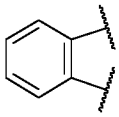
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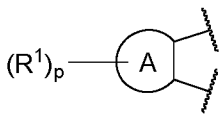
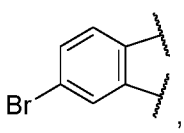
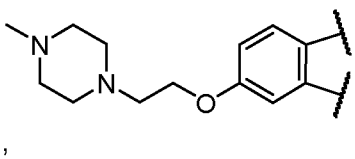
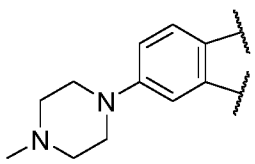
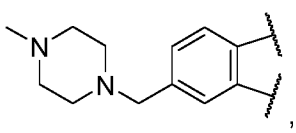
In another aspect **[A32]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein


is selected from the group consisting of


, 
, 
, 
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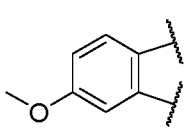
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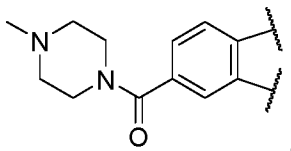
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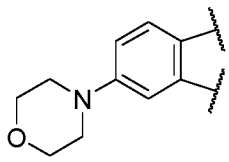
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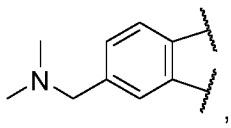
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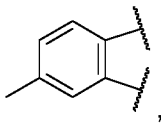
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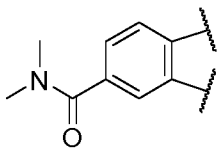
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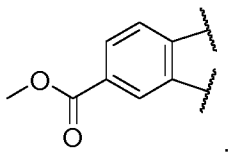
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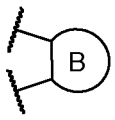
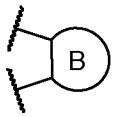
In another aspect **[B1]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein


is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

q is 0.

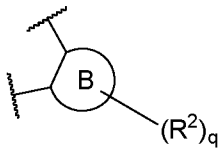
In another aspect **[B2]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein

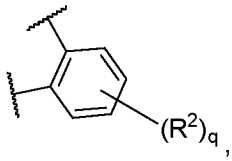

is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

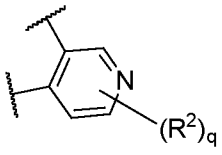
q is 1;

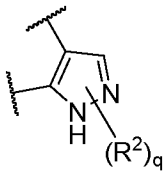
$\mathbf{R^2}$ is selected from the group consisting of $C_{1\text{-}4}$alkyl and halogen.

In further aspects **[B3]**, **[B4]** and **[B5]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein


is selected from the group consisting of



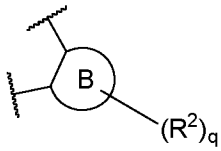
, 

and 

, wherein

R^2 and **q** are defined as in any one aspects **[B0]**, **[B1]** or **[B2]**.

In another aspect **[B6]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein



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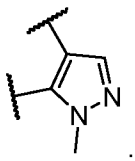
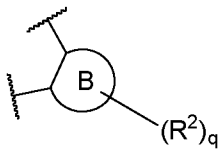


.

In another aspect **[B7]** the invention relates to a compound of formula **(I)** or a salt thereof,



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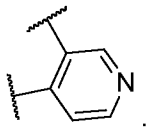
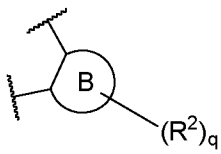
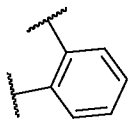


.

In another aspect **[B8]** the invention relates to a compound of formula **(I)** or a salt thereof,



is


.

In another aspect **[C1]** the invention relates to a compound of formula **(I)** or a salt thereof,

wherein R^3 is selected from the group consisting of hydrogen, C_{1-4}alkyl, halogen and -CN.

In another aspect **[C2]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein R^3 is hydrogen.

In another aspect **[C3]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein R^3 is -CN.

In another aspect **[C4]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein R^3 is C_{1-4}alkyl.

In another aspect **[C5]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein R^3 is methyl.

In another aspect **[C6]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein R^3 is halogen, preferably chlorine or fluorine.

In another aspect **[D1]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein

L is straight chain C_{3-7}alkylene, wherein one or two methylene groups $-CH_2-$ in such straight chain C_{3-7}alkylene are optionally and independently replaced by a group/atom selected from oxygen, -NH- and -N(C_{1-4}alkyl)-;

wherein such straight chain can be optionally substituted on carbon by one or more, identical or different substituent(s) selected from the group consisting of C_{1-4}alkyl, halogen and hydroxy;

wherein one carbon atom, two carbon atoms or one carbon atom and one nitrogen atom in such straight chain can be optionally bridged with C_{1-5}alkylene, wherein one methylene group $-CH_2-$ in such bridging C_{1-5}alkylene can be optionally replaced by oxygen, to form a C_{3-6}carbocycle or 3-6 membered nitrogen- and/or oxygen-containing heterocycle;

In another aspect **[D2]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein

L is straight chain C_{3-7}alkylene,

wherein the straight chain C_{3-7}alkylene can be optionally substituted by one or more, identical or different substituent(s) selected from the group consisting of C_{1-4}alkyl,

halogen and hydroxy;

wherein one carbon atom or two carbon atoms in the straight chain C_{3-7}alkylene can be optionally bridged with C_{1-5}alkylene to form a C_{3-6}carbocycle.

In another aspect **[D3]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein

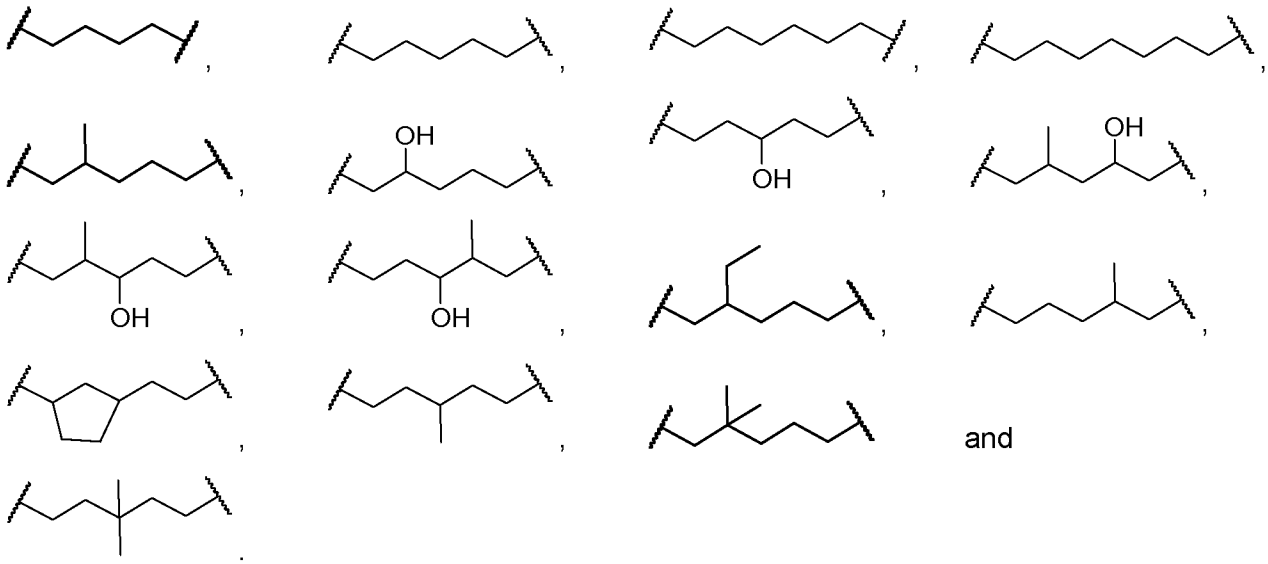
L is selected from the group consistig of straight chain C_4alkylene, straight chain C_5alkylene, straight chain C_6alkylene and straight chain C_7alkylene,

wherein the straight chain C_4alkylene, straight chain C_5alkylene, straight chain C_6alkylene and straight chain C_7alkylene can be optionally substituted by one or more, identical or different substituent(s) selected from the group consisting of C_{1-4}alkyl, halogen and hydroxy;

wherein one carbon atom or two carbon atoms in such straight chain C_4alkylene, straight chain C_5alkylene, straight chain C_6alkylene and straight chain C_7alkylene can be optionally bridged with C_{1-5}alkylene to form a C_{3-6}carbocycle.

In another aspect **[D4]** the invention relates to a compound of formula **(I)** or a salt thereof, wherein

L is selected from the group consistig of



All the above-mentioned structural aspects **[A1]** to **[A32]**, **[B1]** to **[B8]**, **[C1]** to **[C6]** and **[D1]** to **[D4]** are preferred embodiments of the corresponding aspects **[A0]**, **[B0]**, **[C0]** and **[D0]**, respectively. The structural aspects **[A0]** to **[A32]**, **[B0]** to **[B8]**, **[C0]** to **[C6]**, **[D0]** to

[D4] relating to different molecular parts of the compounds **(I)** according to the invention may be combined with one another as desired in combinations **[A][B][C][D]** to obtain preferred compounds **(I)**. Each combination **[A][B][C][D]** represents and defines individual embodiments or generic subsets of compounds **(I)** according to the invention.

Preferred embodiments of the invention with structure **(I)** are example compounds **I-1** to **I-57** and any subset thereof.

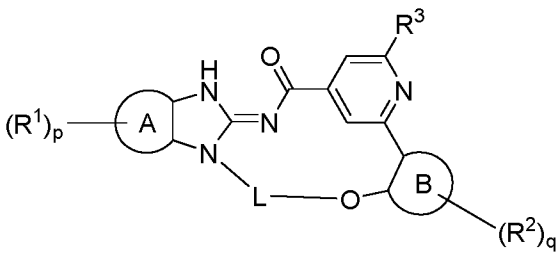
All synthetic intermediates generically defined as well es specifically disclosed herein and their salts are also part of the invention.

All individual synthetic reaction steps as well as reaction sequences comprising these individual synthetic reaction steps, both generically defined or specifically disclosed herein, are also part of the invention.

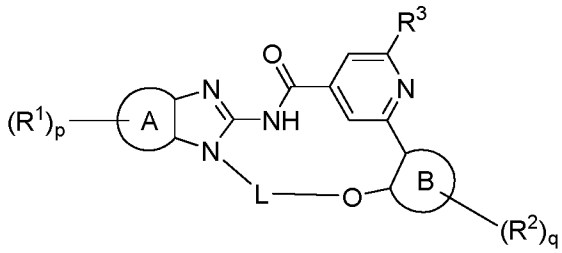
The present invention further relates to hydrates, solvates, polymorphs, metabolites, derivatives, isomers and prodrugs of a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein).

The present invention further relates to tautomers of a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein).

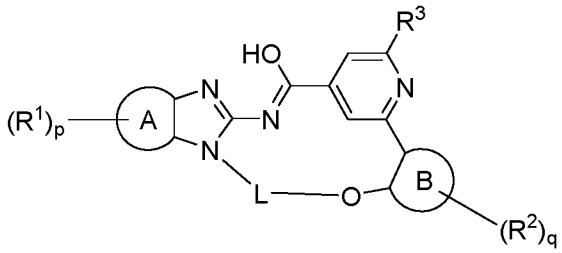
Specifically, a compound of formula **(I)** may exist in any of the following tautomeric forms **A**, **B** and **C**, which shall all be part of the invention and shall all be covered by formula **(I)**:



A



B



C

The present invention further relates to a hydrate of a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein).

The present invention further relates to a solvate of a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein).

Compounds of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) which *e.g.* bear ester groups are potential prodrugs the ester being cleaved under physiological conditions and are also part of the invention.

The present invention further relates to a pharmaceutically acceptable salt of a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein).

The present invention further relates to a pharmaceutically acceptable salt of a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) with anorganic or organic acids or bases.

Medical Uses – Methods of Treatment

The present invention is directed to compounds of formula **(I)** (including all individual embodiments and generic subsets disclosed herein), which are useful in the treatment and/or prevention of a disease and/or condition associated with or modulated by mutant EGFR, especially wherein the inhibition of the mutant EGFR is of therapeutic benefit,

including but not limited to the treatment and/or prevention of cancer.

In one aspect the invention relates to a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – for use as a medicament.

In another aspect the invention relates to a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – for use in a method of treatment of the human or animal body.

In another aspect the invention relates to a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – for use in the treatment and/or prevention of a disease and/or condition wherein the inhibition of mutant EGFR is of therapeutic benefit, including but not limited to the treatment and/or prevention of cancer.

In another aspect the invention relates to a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – for use in the treatment and/or prevention of cancer.

In another aspect the invention relates to a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – for use in a method of treatment and/or prevention of cancer in the human or animal body.

In another aspect the invention relates to a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – for use in the treatment and/or prevention of cancer.

In another aspect the invention relates to a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – for use in a method of treatment and/or prevention of cancer in the human or animal body.

In another aspect the invention relates to a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – for use as herein defined, wherein said compound is administered before, after or together with at least one other pharmacologically active substance.

In another aspect the invention relates to a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – for use as herein defined, wherein said compound is administered in combination with at least one other pharmacologically active substance.

In another aspect the invention relates to a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – for use in the treatment or in a method of treatment as herein defined.

In another aspect the invention relates to the use of a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – for preparing a pharmaceutical composition for the treatment and/or prevention of cancer.

In another aspect the invention relates to the use of a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – as herein defined wherein said compound is administered before, after or together with at least one other pharmacologically active substance.

In another aspect the invention relates to the use of a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – as herein defined for the treatment.

In another aspect the invention relates to a method for the treatment and/or prevention of a disease and/or condition wherein the inhibition of mutant EGFR is of therapeutic benefit comprising administering a therapeutically effective amount of a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – to a human being.

In another aspect the invention relates to a method for the treatment and/or prevention of cancer comprising administering a therapeutically effective amount of a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – to a human being.

In another aspect the invention relates to a method as herein defined wherein the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – is administered before, after or together with at least one other pharmacologically active substance.

In another aspect the invention relates to a method as herein defined wherein the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – is administered in combination with a therapeutically effective amount of at least one other pharmacologically active substance.

In another aspect the invention relates to a method for the treatment as herein defined.

In another aspect the invention relates to a kit comprising

- a first pharmaceutical composition or dosage form comprising a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) and, optionally, one or more pharmaceutically acceptable carriers, excipients and/or vehicels, and
- at least a second pharmaceutical composition or dosage form comprising another pharmacologically active substance and, optionally, one or more pharmaceutically acceptable carriers, excipients and/or vehicels.

In another aspect the invention relates to a pharmaceutical composition comprising at least one (preferably one) compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – and one or more pharmaceutically acceptable excipient(s).

In another aspect the invention relates to a pharmaceutical preparation comprising a compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) – or a pharmaceutically acceptable salt thereof – and at least one (preferably one) other pharmacologically active substance.

In one aspect the disease/condition/cancer to be treated/prevented with the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein), or in the medical uses, uses, methods of treatment and/or prevention as herein defined is selected from the group consisting of lung cancer, brain cancers, colorectal cancer, bladder cancer, urothelial cancer, breast cancer, prostate cancer, ovarian cancer, head and neck cancer, pancreatic cancer, gastric cancer and mesothelioma, including metastasis (in particular brain metastasis) of all cancers listed.

In another aspect the disease/condition/cancer to be treated/prevented with the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein), or in the medical uses, uses, methods of treatment and/or prevention as

herein defined is lung cancer. Preferably, the lung cancer to be treated is *non*-small cell lung cancer (NSCLC) including, *e.g.*, locally advanced or metastatic NSCLC, NSCLC adenocarcinoma, NSCLC with squamous histology and NSCLC with *non*-squamous histology. Most preferably, the lung cancer to be treated is NSCLC adenocarcinoma.

In another aspect the disease/condition/cancer to be treated/prevented with the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein), or in the medical uses, uses, methods of treatment and/or prevention as herein defined is a disease/condition/cancer, preferably cancer (including all embodiments as disclosed herein), with an EGFR genotype selected from genotypes 1 to 16 according to table A (del19 = Exon 19 deletion, specifically, *e.g.*, delE746_A750 (most common), delE746_S752insV, delL747_A750insP, delL747_P753insS and delS752_I759):

Table A

#	EGFR genotype
1	EGFR del19
2	EGFR del19 T790M
3	EGFR del19 C797S
4	EGFR del19 C797X (preferably C797G or C797N)
5	EGFR del19 T790M C797S
6	EGFR del19 T790M C797X (preferably C797G or C797N)
7	EGFR del19 L792X (preferably L792F, L792H or L792Y)
8	EGFR del19 T790M L792X (preferably L792F, L792H or L792Y)
9	EGFR L858R
10	EGFR L858R T790M
11	EGFR L858R C797S
12	EGFR L858R C797X (preferably C797G or C797N)
13	EGFR L858R T790M C797S
14	EGFR L858R T790M C797X (preferably C797G or C797N)
15	EGFR L858R L792X (preferably L792F, L792H or L792Y)
16	EGFR L858R T790M L792X (preferably L792F, L792H or L792Y)

Thus, in one aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR del19 genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR del19 genotype have the compound of

formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a first line treatment, *i.e.* the patients are treatment naïve in respect of EGFR TKIs.

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR del19 T790M genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR del19 T790M genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a second line treatment, *i.e.* the patients are progressing on first line therapy with a 1st or 2nd generation EGFR TKI (*i.e.* treatment with gefitinib, erlotinib, afatinib or dacomitinib).

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR del19 C797S genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR del19 C797S genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a second line treatment, *i.e.* the patients are progressing on first line therapy with a 3rd generation EGFR TKI (*i.e.* treatment with osimertinib, olmutinib, nazartinib or AC0010).

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR del19 C797X (preferably C797G or C797N) genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR del19 C797X (preferably C797G or C797N) genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a second line treatment, *i.e.* the patients are progressing on first line therapy with a 3rd generation EGFR TKI (*i.e.* treatment with osimertinib, olmutinib, nazartinib or AC0010).

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR del19 T790M C797S genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR del19 T790M C797S genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a third line treatment, *i.e.* the patients progressed on first line therapy with a 1st or 2nd generation EGFR TKI (*i.e.* treatment with gefitinib, erlotinib, afatinib or dacomitinib) upon T790M acquisition and are progressing on second line therapy with a 3rd generation EGFR TKI (*i.e.* treatment with osimertinib,

olmutinib, nazartinib or AC0010) upon C797S acquisition.

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR del19 T790M C797X (preferably C797G or C797N) genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR del19 T790M C797X (preferably C797G or C797N) genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a third line treatment, *i.e.* the patients progressed on first line therapy with a 1st or 2nd generation EGFR TKI (*i.e.* treatment with gefitinib, erlotinib, afatinib or dacomitinib) upon T790M acquisition and are progressing on second line therapy with a 3rd generation EGFR TKI (*i.e.* treatment with osimertinib, olmutinib, nazartinib or AC0010) upon C797X (preferably C797G or C797N) acquisition.

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR del19 L792X (preferably L792F, L792H or L792Y) genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR del 19 L792X (preferably L792F, L792H or L792Y) genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a second line treatment, *i.e.* the patients are progressing on first line therapy with a 3rd generation EGFR TKI (*i.e.* treatment with osimertinib, olmutinib, nazartinib or AC0010).

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR del19 T790M L792X (preferably L792F, L792H or L792Y) genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR del19 T790M L792X (preferably L792F, L792H or L792Y) genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a third line treatment, *i.e.* the patients progressed on first line therapy with a 1st or 2nd generation EGFR TKI (*i.e.* treatment with gefitinib, erlotinib, afatinib or dacomitinib) upon T790M acquisition and are progressing on second line therapy with a 3rd generation EGFR TKI (*i.e.* treatment with osimertinib, olmutinib, nazartinib or AC0010) upon L792X (preferably L792F, L792H or L792Y) acquisition.

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR L858R genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR L858R genotype have the compound of

formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a first line treatment, *i.e.* the patients are treatment naïve in respect of EGFR TKIs.

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR L858R T790M genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR L858R T790M genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a second line treatment, *i.e.* the patients are progressing on first line therapy with a 1st or 2nd generation EGFR TKI (*i.e.* treatment with gefitinib, erlotinib, afatinib or dacomitinib).

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR L858R C797S genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR L858R C797S genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a second line treatment, *i.e.* the patients are progressing on first line therapy with a 3rd generation EGFR TKI (*i.e.* treatment with osimertinib, olmutinib, nazartinib or AC0010).

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR L858R C797X (preferably C797G or C797N) genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR L858R C797X (preferably C797G or C797N) genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a second line treatment, *i.e.* the patients are progressing on first line therapy with a 3rd generation EGFR TKI (*i.e.* treatment with osimertinib, olmutinib, nazartinib or AC0010).

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR L858R T790M C797S genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR L858R T790M C797S genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a third line treatment, *i.e.* the patients progressed on first line therapy with a 1st or 2nd generation EGFR TKI (*i.e.* treatment with gefitinib, erlotinib, afatinib or dacomitinib) upon T790M acquisition and are progressing on second line therapy with a 3rd generation EGFR TKI (*i.e.* treatment with osimertinib,

olmutinib, nazartinib or AC0010) upon C797S acquisition.

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR L858R T790M C797X (preferably C797G or C797N) genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR L858R T790M C797X (preferably C797G or C797N) genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a third line treatment, *i.e.* the patients progressed on first line therapy with a 1st or 2nd generation EGFR TKI (*i.e.* treatment with gefitinib, erlotinib, afatinib or dacomitinib) upon T790M acquisition and are progressing on second line therapy with a 3rd generation EGFR TKI (*i.e.* treatment with osimertinib, olmutinib, nazartinib or AC0010) upon C797X (preferably C797G or C797N) acquisition.

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR L858R L792X (preferably L792F, L792H or L792Y) genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR L858R L792X (preferably L792F, L792H or L792Y) genotype have the compound of formula **(I)** administered as a second line treatment, *i.e.* the patients are progressing on first line therapy with a 3rd generation EGFR TKI (*i.e.* treatment with osimertinib, olmutinib, nazartinib or AC0010).

In another aspect the cancer (including all embodiments as disclosed herein) to be treated is a cancer with an EGFR L858R T790M L792X (preferably L792F, L792H or L792Y) genotype. Preferably, the cancer patients to be treated and suffering from a cancer with an EGFR L858R T790M L792X (preferably L792F, L792H or L792Y) genotype have the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein) administered as a third line treatment, *i.e.* the patients progressed on first line therapy with a 1st or 2nd generation EGFR TKI (*i.e.* treatment with gefitinib, erlotinib, afatinib or dacomitinib) upon T790M acquisition and are progressing on second line therapy with a 3rd generation EGFR TKI (*i.e.* treatment with osimertinib, olmutinib, nazartinib or AC0010) upon L792X (preferably L792F, L792H or L792Y) acquisition.

In another aspect the pharmacologically active substance to be used together/in combination with the compound of formula **(I)** (including all individual embodiments and generic subsets disclosed herein), or in the medical uses, uses, methods of treatment and/or prevention as herein defined can be selected from any one or more of the following

(preferably there is only one additional pharmacologically active substance used in all these embodiments):

1. inhibitors of EGFR and/or of mutants thereof
    a. EGFR TKIs, *e.g.* afatinib, erlotinib, gefitinib, lapatinib, dacomitinib, osimertinib, olmutinib, nazartinib, AC0010;
    b. EGFR antibodies, *e.g.* cetuximab, panitumumab, necitumumab;
2. inhibitors of MEK and/or of mutants thereof
    a. *e.g.* trametinib, cobimetinib, binimetinib, selumetinib, refametinib;
3. inhibitors of c-MET and/or of mutants thereof
    a. *e.g.* savolitinib, cabozantinib, foretinib;
    b. MET antibodies, *e.g.* emibetuzumab;
4. mitotic kinase inhibitors
    a. *e.g.* CDK4/6 inhibitors
        i. *e.g.* palbociclib, ribociclib, abemaciclib;
5. immunotherapeutic agents
    a. *e.g.* immune checkpoint inhibitors
        i. *e.g. anti*-CTLA4 mAb, *anti*-PD1 mAb, *anti*-PD-L1 mAb, *anti*-PD-L2 mAb, *anti*-LAG3 mAb, *anti*-TIM3 mAb;
        ii. preferred are *anti*-PD1 mAb;
        iii. *e.g.* ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, pidilizumab, PDR-001 (BAP049-Clone-E disclosed and used in WO 2017/019896);
    b. *e.g.* immuno modulators
        i. *e.g.* CD73 inhibitors or CD73 inhibitory antibodies
6. *anti*-angiogenic agents
    a. *e.g.* bevacizumab, nintedanib;
7. apoptosis inducers
    a. *e.g.* Bcl-2 inhibitors
        i. *e.g.* venetoclax, obatoclax, navitoclax;
    b. *e.g.* Mcl-1 inhibitors
        i. *e.g.* AZD-5991, AMG-176, S-64315;

8. *m*TOR inhibitors
    a. *e.g.* rapamycin, temsirolimus, everolimus, ridaforolimus;
9. histone deacetylase inhibitors
10. IL6 inhibitors
11. JAK inhibitors

Other pharmacologically active substances which may be used in combination with compounds **(I)** according to the invention (including all individual embodiments and generic subsets disclosed herein) are, *e.g.*, state-of-the-art or standard-of-care compounds, such as *e.g.* cell proliferation inhibitors, *anti*-angiogenic substances, steroids or immune modulators/checkpont inhibitors, and the like.

Further examples of pharmacologically active substances which may be administered in combination with the compounds **(I)** according to the invention (including all individual embodiments and generic subsets disclosed herein), 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 and/or of their corresponding receptors (growth factors such as for example platelet derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insuline-like growth factors (IGF), human epidermal growth factor (HER, *e.g.* HER2, HER3, HER4) and hepatocyte growth factor (HGF) and/or their corresponding receptors), inhibitors are for example (*anti*-)growth factor antibodies, (*anti*-)growth factor receptor antibodies and tyrosine kinase inhibitors, such as for example cetuximab, gefitinib, afatinib, nintedanib, imatinib, lapatinib, bosutinib, bevacizumab and trastuzumab); antimetabolites (*e.g.* antifolates such as methotrexate, raltitrexed, pyrimidine analogues such as 5-fluorouracil (5-FU), ribonucleoside and deoxyribonucleoside analogues, capecitabine and gemcitabine, purine and adenosine analogues such as mercaptopurine, thioguanine, cladribine and pentostatin, cytarabine (ara C), fludarabine); antitumour antibiotics (*e.g.* anthracyclins such as doxorubicin, doxil (pegylated liposomal doxorubicin hydrochloride, myocet (non-pegylated liposomal

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); angiogenesis inhibitors (*e.g.* tasquinimod), tubuline inhibitors; DNA synthesis inhibitors, PARP inhibitors, topoisomerase inhibitors (*e.g.* epipodophyllotoxins such as for example etoposide and etopophos, teniposide, amsacrin, topotecan, irinotecan, mitoxantrone), serine/threonine kinase inhibitors (*e.g.* PDK 1 inhibitors, Raf inhibitors, A-Raf inhibitors, B-Raf inhibitors, C-Raf inhibitors, mTOR inhibitors, mTORC1/2 inhibitors, PI3K inhibitors, PI3Kα inhibitors, dual mTOR/PI3K inhibitors, STK 33 inhibitors, AKT inhibitors, PLK 1 inhibitors, inhibitors of CDKs, Aurora kinase inhibitors), tyrosine kinase inhibitors (*e.g.* PTK2/FAK inhibitors), protein protein interaction inhibitors (*e.g.* IAP activator, Mcl-1, MDM2/MDMX), MEK inhibitors, ERK inhibitors, FLT3 inhibitors, BRD4 inhibitors, IGF-1R inhibitors, TRAILR2 agonists, Bcl-xL inhibitors, Bcl-2 inhibitors, Bcl-2/Bcl-xL inhibitors, ErbB receptor inhibitors, BCR-ABL inhibitors, ABL inhibitors, Src inhibitors, rapamycin analogs (*e.g.* everolimus, temsirolimus, ridaforolimus, sirolimus), androgen synthesis inhibitors, androgen receptor inhibitors, DNMT inhibitors, HDAC inhibitors, ANG1/2 inhibitors, CYP17 inhibitors, radiopharmaceuticals, proteasome inhibitors, immunotherapeutic agents such as immune checkpont inhibitors (*e.g.* CTLA4, PD1, PD-L1, PD-L2, LAG3, and TIM3 binding molecules/immunoglobulins, such as *e.g.* ipilimumab, nivolumab, pembrolizumab), ADCC (antibody-dependent cell-mediated cytotoxicity) enhancers (*e.g.* anti-CD33 antibodies, anti-CD37 antibodies, anti-CD20 antibodies), t-cell engagers (*e.g.* bi-specific T-cell engagers (BiTEs®) like *e.g.* CD3 x BCMA, CD3 x CD33, CD3 x CD19), PSMA x CD3), tumor vaccines and various chemotherapeutic agents such as amifostin, anagrelid, clodronat, filgrastin, interferon, interferon alpha, leucovorin, procarbazine, levamisole, mesna, mitotane, pamidronate and porfimer.

Any disease/condition/cancer, medical use, use, method of treatment and/or prevention as disclosed or defined herein (including molecular/genetic features/genotype) may be treated/performed with any compound of formula **(I)** as disclosed or defined herein (including all individual embodiments and generic subsets disclosed herein).

Formulations

Suitable preparations for administering the compounds **(I)** of the invention will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions – particularly solutions for injection (s.c., i.v., i.m.) and infusion (injectables) – elixirs, syrups, sachets, emulsions, inhalatives 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) of the invention with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants. 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 above-mentioned 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.

The dosage range of the compounds of formula **(I)** applicable per day is usually from 1 mg to 2000 mg, preferably from 1 to 1000 mg.

The dosage for intravenous use is from 1 mg to 1000 mg with different infusion rates, preferably between 5 mg and 500 mg with different infusion rates.

However, it may sometimes be necessary to depart from the amounts specified, depending on the body weight, age, the route of administration, severity of the disease, the individual response to the drug, the nature of its formulation and the time or interval over which the drug is administered (continuous or intermittent treatment with one or multiple doses per day). 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 formulae **(I)**)	80 mg
lactose	55 mg
corn starch	190 mg
microcrystalline cellulose	35 mg
polyvinylpyrrolidone	15 mg
sodiumcarboxymethyl 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)	Tablets	per tablet
	active substance according to formulae **(I)**	25 mg
	lactose	50 mg
	microcrystalline cellulose	24 mg
	magnesium stearate	1 mg
		100 mg

The active substance, lactose and cellulose are mixed together. The mixture is screened, then either moistened with water, kneaded, wet-granulated and dried or dry-granulated or directely final blend with the magnesium stearate and compressed to tablets of suitable shape and size. When wet-granulated, additional lactose or cellulose and magnesium stearate is added and the mixture is compressed to produce tablets of suitable shape and size.

D)	Ampoule solution	
	active substance according to formulae **(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.

Definitions

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to:

The use of the prefix $\mathbf{C_{x-y}}$, wherein **x** and **y** each represent a positive integer (**x** < **y**), indicates that the chain or ring structure or combination of chain and ring structure as a whole, specified and mentioned in direct association, may consist of a maximum of **y** and

a minimum of **x** carbon atoms.

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

The indication of the number of carbon atoms in groups that consist of a combination of carbon chain and carbon ring structure (*e.g.* cycloalkylalkyl, arylalkyl) relates to the total number of carbon atoms of all the carbon ring and carbon chain members. Obviously, a ring structure has at least three members.

In general, for groups comprising two or more subgroups (*e.g.* heteroarylalkyl, heterocycylalkyl, cycloalkylalkyl, arylalkyl) the last named subgroup is the radical attachment point, for example, the substituent aryl-C_{1-6}alkyl means an aryl group which is bound to a C_{1-6}alkyl group, the latter of which is bound to the core or to the group to which the substituent is attached.

In groups like HO, H_2N, (O)S, $(O)_2S$, NC (cyano), HOOC, F_3C or the like, the skilled artisan can see the radical attachment point(s) to the molecule from the free valences of the group itself.

Alkyl denotes monovalent, saturated hydrocarbon chains, which may be present in both straight-chain (unbranched) 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 H_3C-, H_3C-CH_2-, H_3C-CH_2-CH_2-, H_3C-$CH(CH_3)$-, H_3C-CH_2-CH_2-CH_2-, H_3C-CH_2-$CH(CH_3)$-, H_3C-$CH(CH_3)$-CH_2-, H_3C-$C(CH_3)_2$-, H_3C-CH_2-CH_2-CH_2-CH_2-, H_3C-CH_2-CH_2-$CH(CH_3)$-, H_3C-CH_2-$CH(CH_3)$-CH_2-, H_3C-$CH(CH_3)$-CH_2-CH_2-, H_3C-CH_2-$C(CH_3)_2$-, H_3C-$C(CH_3)_2$-CH_2-, H_3C-$CH(CH_3)$-$CH(CH_3)$- and H_3C-CH_2-$CH(CH_2CH_3)$-.

Further examples of **alkyl** are 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

(-$C(CH_3)_2CH_2CH_3$), 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 (-$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (*n*-hexyl; -$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (-$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (-$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (-$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$), 2,3-dimethyl-1-butyl (-$CH_2CH(CH_3)CH(CH_3)CH_3$), 2,2-dimethyl-1-butyl (-$CH_2C(CH_3)_2CH_2CH_3$), 3,3-dimethyl-1-butyl (-$CH_2CH_2C(CH_3)_3$), 2-methyl-1-pentyl (-$CH_2CH(CH_3)CH_2CH_2CH_3$), 3-methyl-1-pentyl (-$CH_2CH_2CH(CH_3)CH_2CH_3$), 1-heptyl (*n*-heptyl), 2-methyl-1-hexyl, 3-methyl-1-hexyl, 2,2-dimethyl-1-pentyl, 2,3-dimethyl-1-pentyl, 2,4-dimethyl-1-pentyl, 3,3-dimethyl-1-pentyl, 2,2,3-trimethyl-1-butyl, 3-ethyl-1-pentyl, 1-octyl (*n*-octyl), 1-nonyl (*n*-nonyl); 1-decyl (*n*-decyl) *etc.*

By the terms propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl *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 (combined) group such as for example C_{x-y}**alkyl**amino or C_{x-y}**alkyl**oxy.

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_2CH_3 and -CH_2CH_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-$CH_2)$-, -$(C(CH_3)_2)$-, -$(CH(CH_2CH_3))$-, -$(CH(CH_3)$-$CH_2)$-, -$(CH_2$-$CH(CH_3))$-, -$(CH_2$-CH_2-CH_2-$CH_2)$-, -$(CH_2$-CH_2-$CH(CH_3))$-, -$(CH(CH_3)$-CH_2-$CH_2)$-, -$(CH_2$-$CH(CH_3)$-$CH_2)$-, -$(CH_2$-$C(CH_3)_2)$-, -$(C(CH_3)_2$-$CH_2)$-, -$(CH(CH_3)$-$CH(CH_3))$-, -$(CH_2$-$CH(CH_2CH_3))$-, -$(CH(CH_2CH_3)$-$CH_2)$-, -$(CH(CH_2CH_2CH_3))$-, -$(CH(CH(CH_3))_2)$- and -$C(CH_3)(CH_2CH_3)$-.

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, hexylene *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 (combined) group such as for example in HO-C_{x-y}**alkylene**amino or H_2N-C_{x-y}**alkylene**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 and a carbon atom can only be part of one 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 (combined) 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 and a carbon atom can only be part of one 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 (combined) group as for example in HO-C_{x-y}**alkenylene**amino or H_2N-C_{x-y}**alkenylene**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, hex-1-ynyl, hex-2-ynyl, hex-3-ynyl, hex-4-ynyl, hex-5-ynyl *etc.*

By the generic terms propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl 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, *etc.*

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 (combined) group, as for example in C_{x-y}**alkynyl**amino or C_{x-y}**alkynyl**oxy.

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, hexynylene 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 (combined) group, as for example in HO-C_{x-y}**alkynylene**amino or H_2N-C_{x-y}**alkynylene**oxy.

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 $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, $-CHFCF_3$, $-CH_2CF_3$, $-CF_2CH_3$, $-CHFCH_3$, $-CF_2CF_2CF_3$, $-CF_2CH_2CH_3$, $-CF=CF_2$, $-CCl=CH_2$, $-CBr=CH_2$, $-C\equiv C-CF_3$, $-CHFCH_2CH_3$, $-CHFCH_2CF_3$ *etc.*

From the previously defined **haloalkyl (haloalkenyl, haloalkynyl)** are also derived the terms **haloalkylene (haloalkenylene, haloalkynylene)**. **Haloalkylene (haloalkenylene, haloalkynylene)**, unlike **haloalkyl (haloalkenyl, haloalkynyl)**, is bivalent and requires

two binding partners. Formally, the second valency is formed by removing a hydrogen atom from a **haloalkyl (haloalkenyl, haloalkynyl)**.

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-containing groups are part of another (combined) 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 in common. In spiro-hydrocarbon rings one carbon atom (spiroatom) belongs to two rings together.

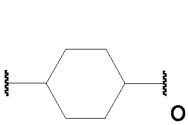
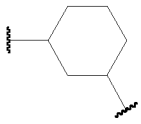
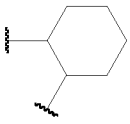
If a **cycloalkyl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. **Cycloalkyl** itself may be linked as a substituent to the molecule *via* every suitable position 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 (decahydronaphthyl), 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 (combined) group as for example in C_{x-y}**cycloalkyl**amino, C_{x-y}**cycloalkyl**oxy or C_{x-y}**cycloalkyl**alkyl.

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 (combined) group as for example in HO-C_{x-y}**cycloalkylene**amino or H_2N-C_{x-y}**cycloalkylene**oxy.

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.

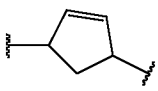
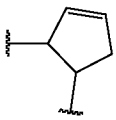
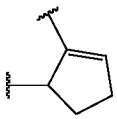
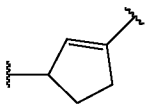
If a **cycloalkenyl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. **Cycloalkenyl** itself may be linked as a substituent to the molecule *via* every suitable position 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-enyl *etc.*

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

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 if **cycloalkenylene** is part of another (combined) group as for example in HO-C_{x-y}**cycloalkenylene**amino or H_2N-C_{x-y}**cycloalkenylene**oxy.

Aryl denotes mono-, bi- or tricyclic carbocycles with at least one aromatic carbocycle. Preferably, it denotes 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 partially saturated.

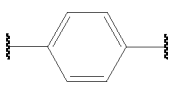
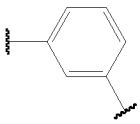
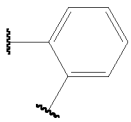
If an **aryl** is to be substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon atoms. **Aryl** itself may be linked as a substituent to the molecule *via* every suitable position of the ring system.

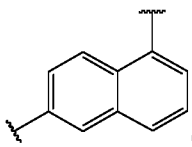
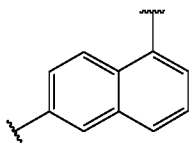
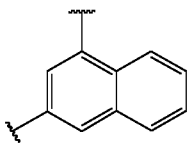
Examples of **aryl** are phenyl, naphthyl, indanyl (2,3-dihydroindenyl), indenyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl (1,2,3,4-tetrahydronaphthyl, tetralinyl), dihydronaphthyl (1,2- dihydronaphthyl), fluorenyl *etc.* Most preferred is phenyl.

The above definition of **aryl** also applies if **aryl** is part of another (combined) group as for example in **aryl**amino, **aryl**oxy or **aryl**alkyl.

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 for example:

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

naphthyl and  or  or  *etc.*

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

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 must be present between two oxygen atoms and between two sulphur atoms or between an oxygen and a 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). In a **heterocyclyl** there is no heteroaromatic ring, *i.e.* no heteroatom is part of an aromatic system.

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.

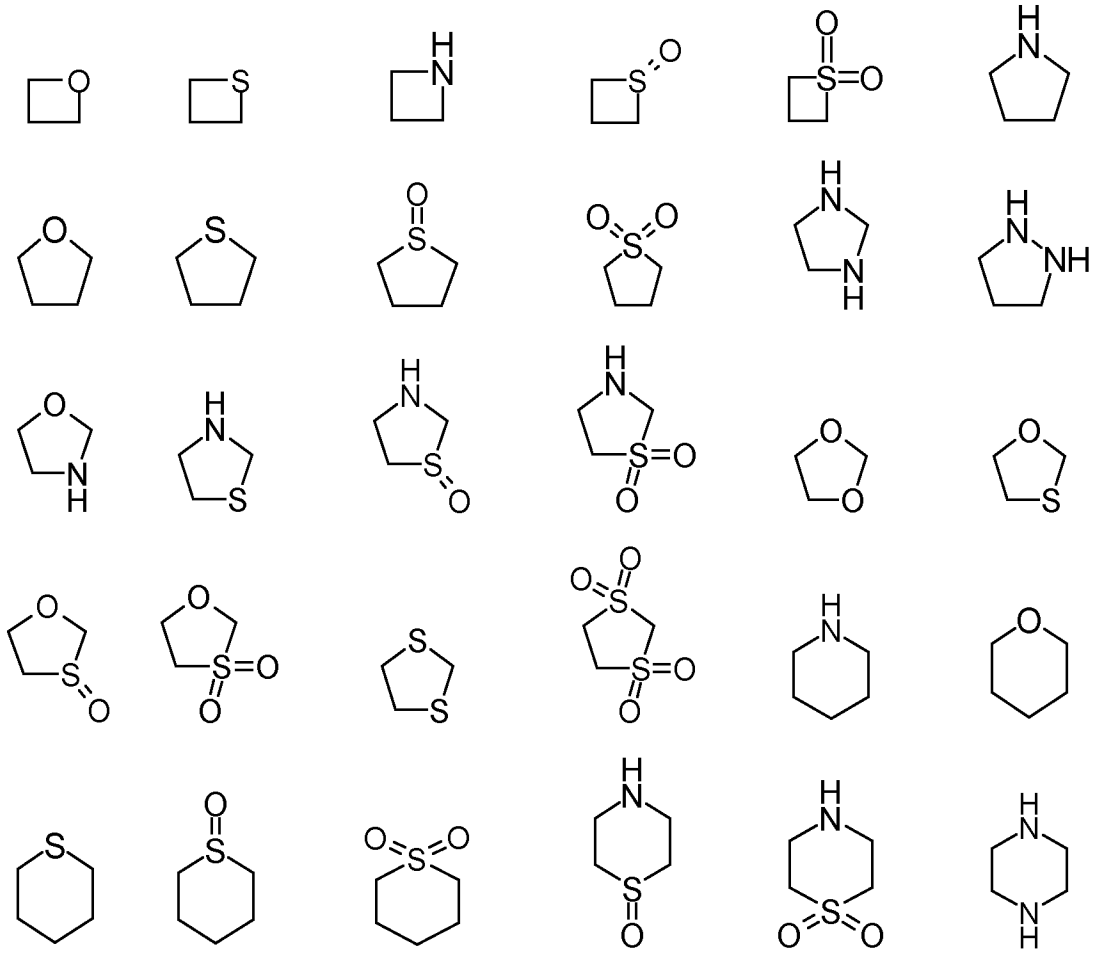
By unsaturated is meant that there is at least one double bond in the ring system in question, but no heteroaromatic system is formed. In bicyclic heterorings two rings are linked together so that they have at least two (hetero)atoms in common. In spiro-heterorings one carbon atom (spiroatom) belongs to two rings together.

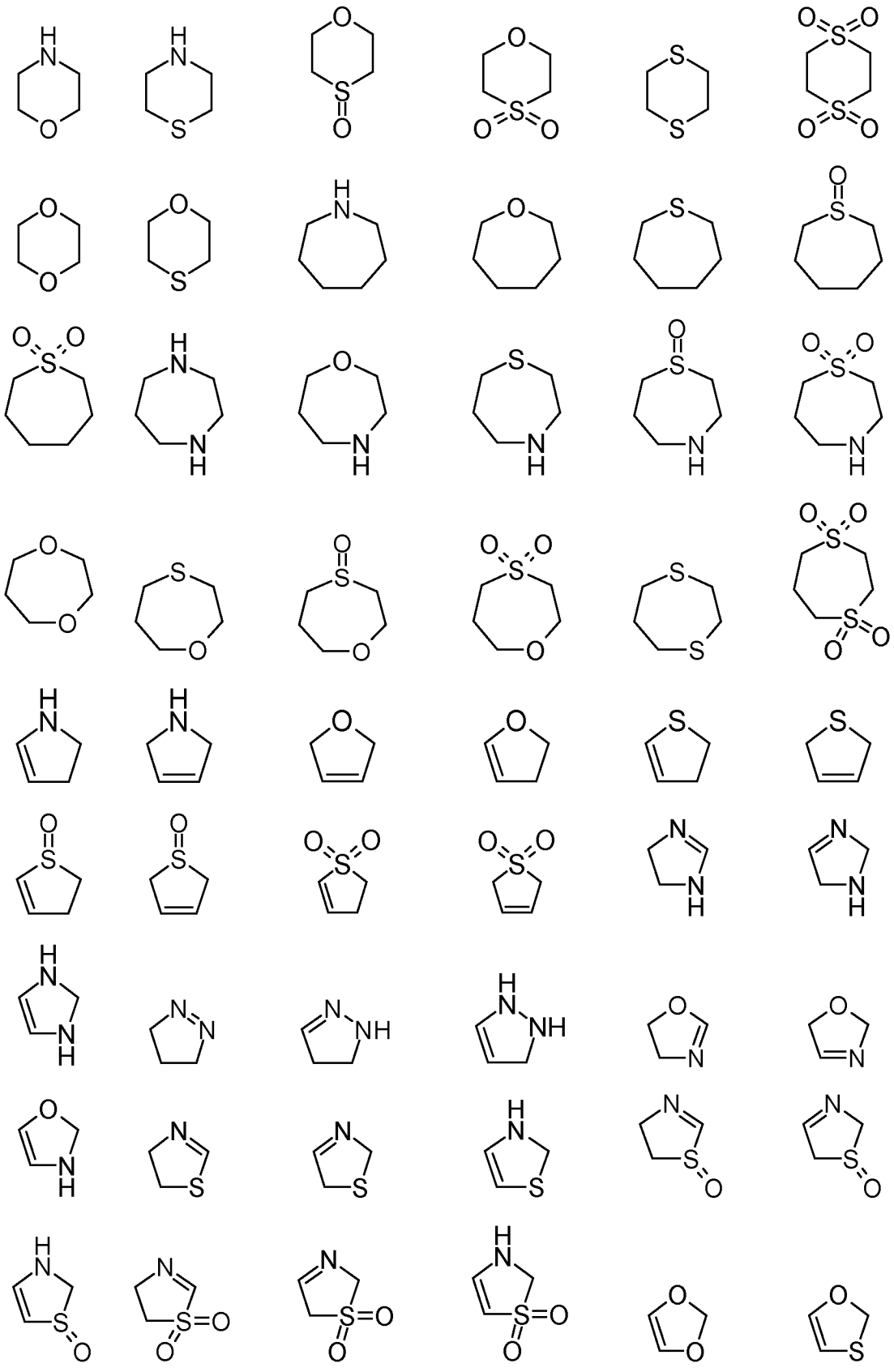
If a **heterocyclyl** is substituted, the substitutions may take place independently of one another, in the form of mono- or polysubstitutions in each case, on all the hydrogen-carrying carbon and/or nitrogen atoms. **Heterocyclyl** itself may be linked as a substituent to the molecule *via* every suitable position of the ring system. Substituents on **heterocyclyl** do not count for the number of members of a **heterocyclyl**.

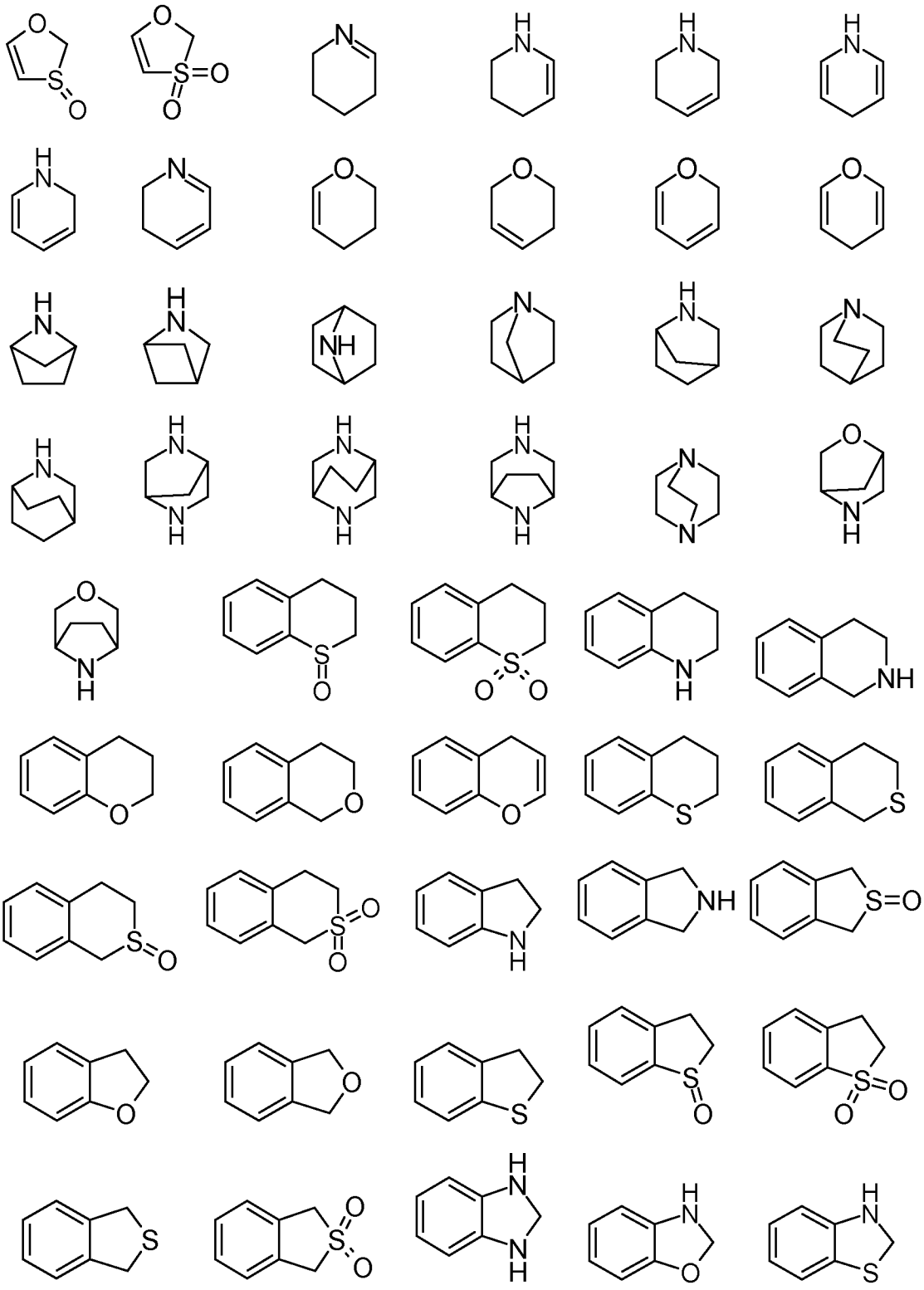
Examples of **heterocyclyl** are tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, thiazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, oxiranyl, aziridinyl, azetidinyl, 1,4-dioxanyl, azepanyl, diazepanyl, morpholinyl, thiomorpholinyl, homomorpholinyl, homopiperidinyl, 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,

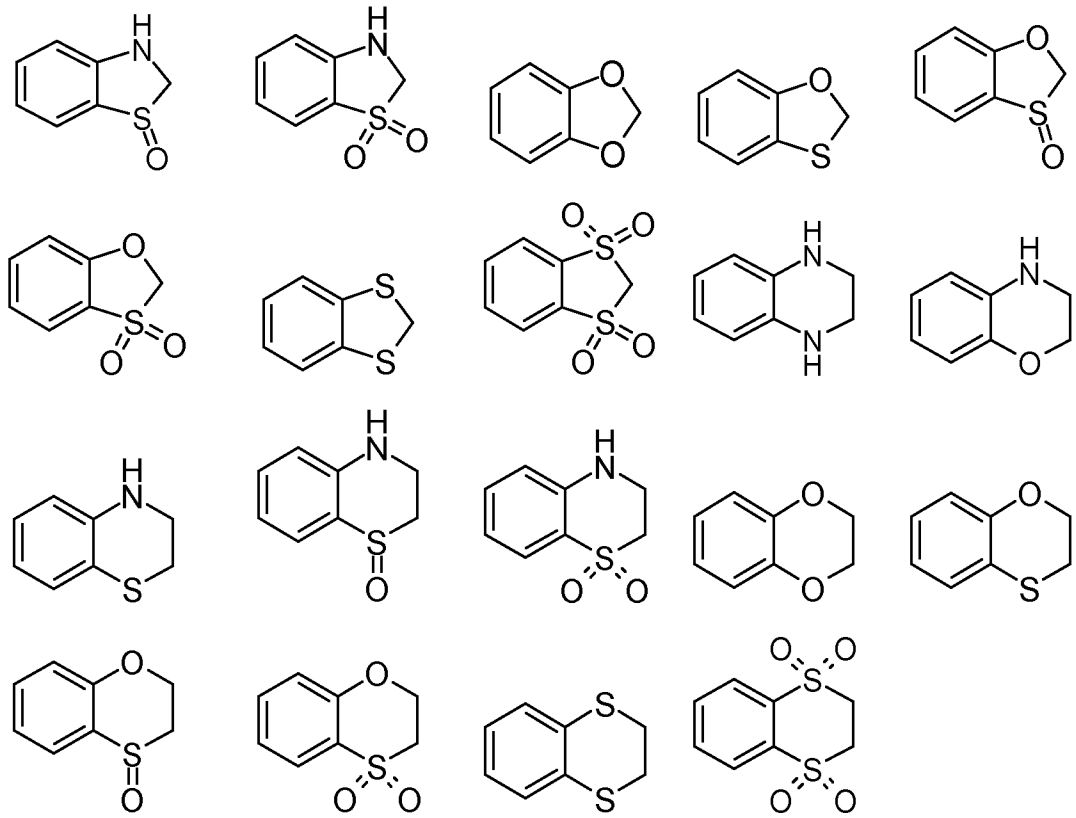
dihydro-pyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl-*S*-oxide, tetrahydrothienyl-*S,S*-dioxide, homothiomorpholinyl-*S*-oxide, 2,3-dihydroazet, 2*H*-pyrrolyl, 4*H*-pyranyl, 1,4-dihydropyridinyl, 8-aza-bicyclo[3.2.1]octyl, 8-aza-bicyclo[5.1.0]octyl, 2-oxa-5-azabicyclo[2.2.1]heptyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 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):









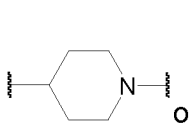
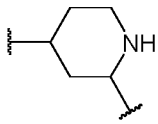
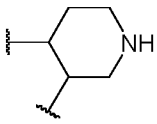
Preferably, heterocyclyls are 4 to 8 membered, monocyclic and have one or two heteroatoms independently selected from oxygen, nitrogen and sulfur.

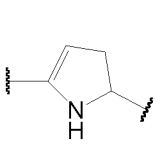
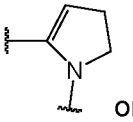
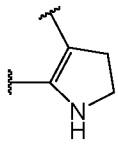
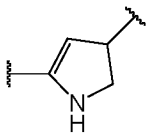
Preferred heterocyclyls are: piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, azetidinyl, tetrahydropyranyl, tetrahydrofuranyl.

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

If the free valency of a **heterocyclyl** 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.*

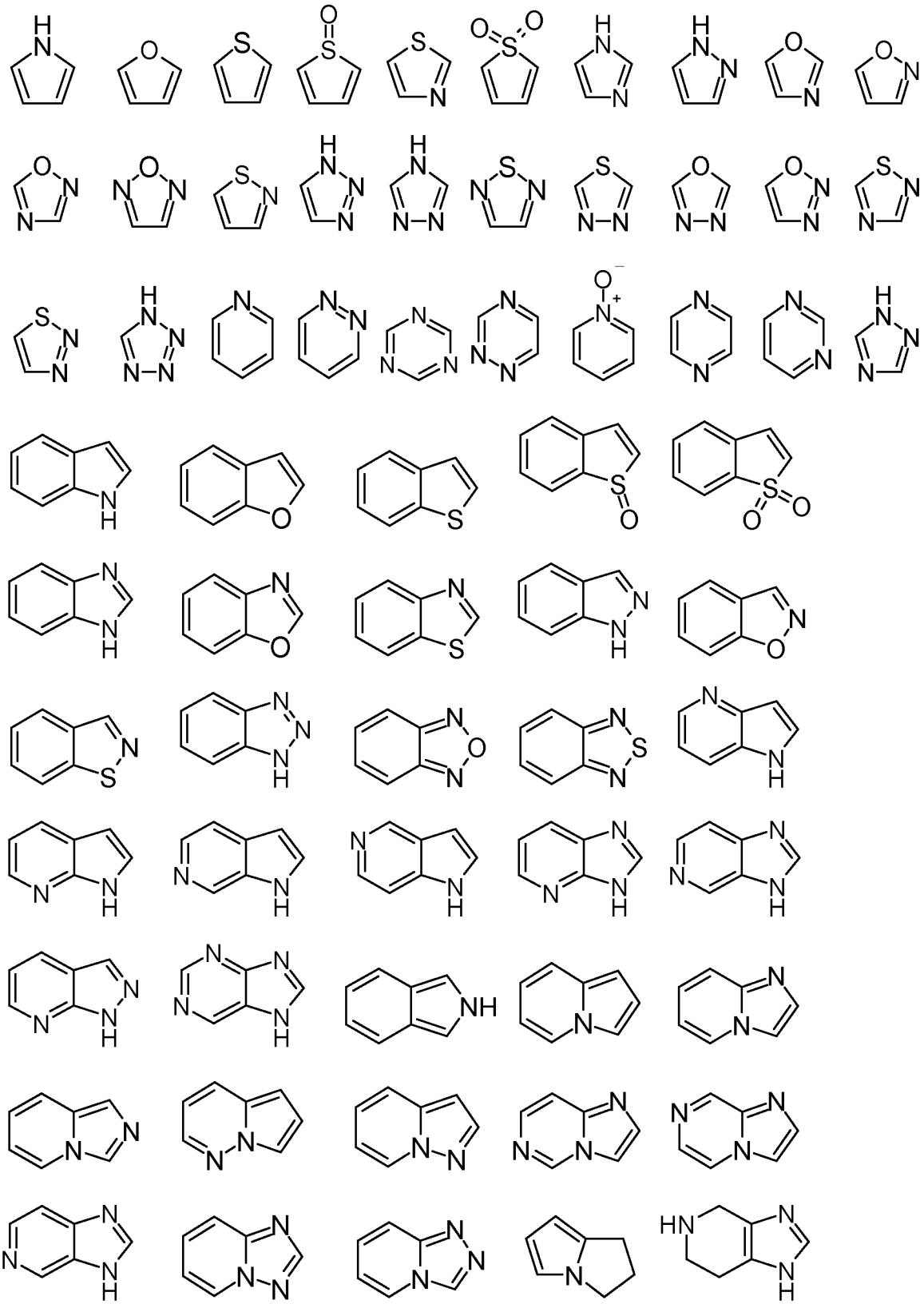
The above definition of **heterocyclylene** also applies if **heterocyclylene** is part of another (combined) group as for example in HO-**heterocyclylene**amino or H_2N-**heterocyclylene**oxy.

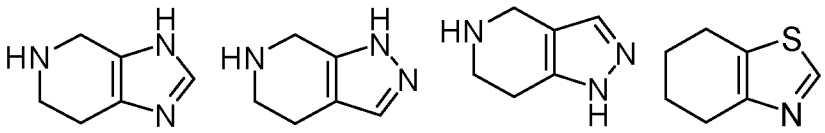
Heteroaryl denotes monocyclic heteroaromatic rings or polycyclic rings with at least one heteroaromatic ring, which compared with the corresponding **aryl** or **cycloalkyl (cycloalkenyl)** contain, instead of one or more carbon atoms, one or more identical or different heteroatoms, selected independently 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. Substituents on **heteroaryl** do not count for the number of members of a **heteroaryl**.

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, pyrimidopyridyl, 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):



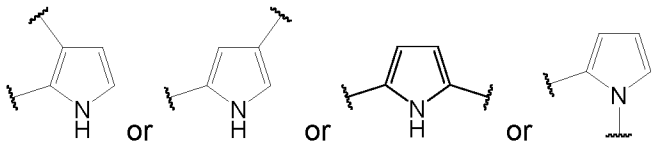


Preferably, heteroaryls are 5-6 membered monocyclic or 9-10 membered bicyclic, each with 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur.

The above definition of **heteroaryl** also applies if **heteroaryl** is part of another (combined) group as for example in **heteroaryl**amino, **heteroaryl**oxy or **heteroaryl**alkyl.

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

The term **heteroarylene** is also 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  *etc.*

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

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 substituents on carbon atoms, whereas the bivalent substituents =O and =NR may also be a substituent on sulphur. Generally, substitution may be carried out by a bivalent substituent only at ring systems and requires replacement of 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 (=O group or =NR group only, one or two =O groups possible or, *e.g.*, one =O group and one =NR group, each group replacing a free electron pair) of a ring system.

Stereochemistry/solvates/hydrates: Unless specifically indicated, throughout the specification and appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (*e.g.* enantiomers, diastereomers, *E*/*Z* isomers, *etc.*) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates and hydrates of the free compound or solvates and hydrates of a salt of the compound.

In general, substantially pure stereoisomers can be obtained according to synthetic principles known to a person skilled in the field, *e.g.* by separation of corresponding mixtures, by using stereochemically pure starting materials and/or by stereoselective synthesis. It is known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, *e.g.* starting from optically active starting materials and/or by using chiral reagents.

Enantiomerically pure compounds of this invention or intermediates may be prepared *via* asymmetric synthesis, for example by preparation and subsequent separation of appropriate diastereomeric compounds or intermediates which can be separated by known methods (*e.g.* by chromatographic separation or crystallization) and/or by using chiral reagents, such as chiral starting materials, chiral catalysts or chiral auxiliaries.

Further, it is known to the person skilled in the art how to prepare enantiomerically pure compounds from the corresponding racemic mixtures, such as by chromatographic separation of the corresponding racemic mixtures on chiral stationary phases, or by resolution of a racemic mixture using an appropriate resolving agent, *e.g.* by means of diastereomeric salt formation of the racemic compound with optically active acids or bases, subsequent resolution of the salts and release of the desired compound from the salt, or by derivatization of the corresponding racemic compounds with optically active chiral auxiliary reagents, subsequent diastereomer separation and removal of the chiral auxiliary group, or by kinetic resolution of a racemate (*e.g.* by enzymatic resolution); by

enantioselective crystallization from a conglomerate of enantiomorphous crystals under suitable conditions, or by (fractional) crystallization from a suitable solvent in the presence of an optically active chiral auxiliary.

Salts: The phrase "**pharmaceutically acceptable**" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein "**pharmaceutically acceptable salts**" refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

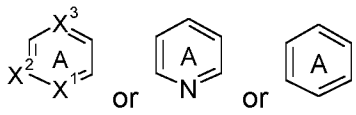
For example, such salts include salts from benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gentisic acid, hydrobromic acid, hydrochloric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, 4-methyl-benzenesulfonic acid, phosphoric acid, salicylic acid, succinic acid, sulfuric acid and tartaric acid.

Further pharmaceutically acceptable salts can be formed with cations from ammonia, L-arginine, calcium, 2,2'-iminobisethanol, L-lysine, magnesium, *N*-methyl-D-glucamine, potassium, sodium and tris(hydroxymethyl)-aminomethane.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base form of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

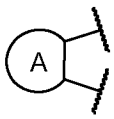
Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (*e.g.* trifluoro acetate salts), also comprise a part of the invention.

In a representation such as for example



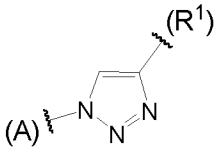
the letter A has the function of a ring designation in order to make it easier, for example, to indicate the attachment of the ring in question to other rings.

In a representation such as for example



the dashed lines indicate where ring A (with the respective definition of A) is condensed with an adjacent ring, *i.e.* two vicinal atoms of ring A are in common with such adjacent ring.

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.* $\mathbf{R^a}$, $\mathbf{R^b}$ etc). If such a group is used repeatedly to define a compound according to the invention in different parts of the molecule, it is pointed out 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

Ac	acetyl
AcCN	acetonitrile
aq.	aquatic, aqueous
ATP	adenosine triphosphate

Bn	benzyl
Boc	tert-butyloxycarbonyl
Bu	butyl
c	concentration
CSA	Camphorsulfonic acid
d	day(s)
dba	dibenzylideneacetone
TLC	thin layer chromatography
Davephos	2-dimethylamino-2'-dicyclohexylaminophosphinobiphenyl
DBA	dibenzylideneacetone
DCM	dichloromethane
DEA	diethylamine
DEAD	diethyl azodicarboxylate
DIPEA	*N*-ethyl-*N*,*N*-diisopropylamine (Hünig´s base)
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulphoxide
DPPA	diphenylphosphorylazide
dppf	1.1´-bis(diphenylphosphino)ferrocene
EDTA	ethylenediaminetetraacetic acid
EGTA	ethyleneglycoltetraacetic acid
eq	equivalent(s)
ESI	electron spray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
h	hour
HATU	O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyl-uronium hexafluorophosphate
HPLC	high performance liquid chromatography
IBX	2-iodoxy benzoic acid

i	iso
conc.	concentrated
LAH	lithium aluminium hydride
LC	liquid chromatography
LiHMDS	lithium bis(trimethylsilyl)amide
sln.	solution
Me	methyl
MeOH	methanol
min	minutes
MPLC	medium pressure liquid chromatography
MS	mass spectrometry
MTBE	methyl *tert*-butyl ether
NBS	*N*-bromo-succinimide
NIS	*N*-iodo-succinimide
NMM	*N*-methylmorpholine
NMP	*N*-methylpyrrolidone
NP	normal phase
n.a.	not available
PBS	phosphate-buffered saline
Ph	phenyl
Pr	propyl
Py	pyridine
rac	racemic
red.	reduction
Rf (R_f)	retention factor
RP	reversed phase
rt	ambient temperature
SEM	trimethylsilyl ethoxymethyl
SFC	supercritical fluid chromatography
S_N	nucleophilic substitution
T3P	propylphosphonic anhydride
TBAF	tetrabutylammonium fluoride
TBDMS	tert-butyldimethylsilyl

TBME	tert-butylmethylether
TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium tetrafluoroborate
tBu	tert-butyl
TEA	triethylamine
temp.	temperature
tert	tertiary
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
$t_{Ret.}$	retention time (HPLC)
TRIS	tris(hydroxymethyl)-aminomethane
TsOH	p-toluenesulphonic acid
UV	ultraviolet

Features and advantages of the present invention will become apparent from the following detailed examples which illustrate the principles of the invention by way of example without restricting its scope:

Preparation of the compounds according to the invention

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 according to the invention are named in accordance with CAS rules using the software Autonom (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 prevails.

Microwave reactions are carried out in an initiator/reactor made by Biotage or in an Explorer made by CEM or in Synthos 3000 or Monowave 3000 made by Anton Paar in sealed containers (preferably 2, 5 or 20 mL), preferably with stirring.

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/AcCN 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 **supercritical fluid chromatography (SFC)** of the intermediates and example compounds according to the invention is carried out on a JASCO SFC-system with the following colums: Chiralcel OJ (250 x 20 mm, 5 µm), Chiralpak AD (250 x 20 mm, 5 µm), Chiralpak AS (250 x 20 mm, 5 µm), Chiralpak IC (250 x 20 mm, 5 µm), Chiralpak IA (250 x 20 mm, 5 µm), Chiralcel OJ (250 x 20 mm, 5 µm), Chiralcel OD (250 x 20 mm, 5 µm), Phenomenex Lux C2 (250 x 20 mm, 5 µm).

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 characterizing 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 $t_{Ret.}$ = 0.00.

HPLC-methods (preparative)

NP1

NP purification:	GLASS COLUMN
Column:	100-200 mesh size silica gel
Solvent:	A: DCM; B: MeOH
Detection:	$KMnO_4$

Flow:	100 mL/min
Gradient:	0 – 60 min: 1 % B
	60 – 100 min: varying
	100 – 200 min: 10 % B

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: AcCN (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: AcCN (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)

LCMSBAS

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: AcCN (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

LCMSBAS1

HPLC:	Agilent 1200 Series
MS:	Agilent 6140
Column:	Waters X-Bridge C18 column, 2.5 µm particle size, 2.1 x 20 m
Solvent:	A: 20 mM NH_4HCO_3/NH_3 in H_2O; B: AcCN (HPLC grade)
Detection:	MS: positive and negative mode
	UV: bandwidth 170 nM in range from 230 - 400 nM
Mass range:	120 – 900 m/z
Flow:	1.00 mL/min
Column temperature:	60 °C
Gradient:	0.00 – 1.50 min: 10 % → 95 % B
	1.50 – 2.00 min: 95 % B
	2.00 – 2.10 min: 95 % → 10 % B

LCMS3, basisch_1

HPLC:	Agilent 1100 Series
MS:	Agilent LC/MSD (API-ES +/- 3000 V, Quadrupol, G6140)
Column:	Waters, X-Bridge C18, 2.5 µm, 2.1 x 20 mm column
Solvent:	A: 20 mM NH_4HCO_3/NH_3 in H_2O pH 9; B: AcCN (HPLC grade)
Detection:	MS: positive and negative mode
Mass range:	120 – 900 m/z
Flow:	1.00 mL/min
Column temperature:	60 °C
Gradient:	0.00 – 1.50 min: 10 % → 95 % B
	1.50 – 2.00 min: 95 % B
	2.00 – 2.10 min: 95 % → 10 % B

LCMS_TCG

HPLC:	Shimadzu LC20
MS:	API 2000
Column:	Column Zorbax Extend C18 (50 x 4.6 mm, 5u, 80A)
Solvent:	A: 10 mM NH_4OAc in H_2O; B: AcCN (HPLC grade)
Detection:	MS: positive mode
Mass range:	100 – 800 m/z
Flow:	1.00 mL/min
Column temperature:	25 °C
Gradient:	0.00 – 1.50 min: 20 % → 98 % B
	1.50 – 6.00 min: 98 % B
	6.00 – 7.00 min: 98 % → 20 % 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: AcCN (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 % B → 100 % B
	1.00 – 1.37 min: 100 % B
	1.37 – 1.40 min: 100 % → 5 % B

VAS

HPLC:	Agilent 1100/1200 Series
MS:	Agilent LC/MSD SL
Column:	YMC TriART C18 2.0 x 30mm, 3 µm
Solvent:	A: H_2O + 0.2 % formic acid; B: AcCN (HPLC grade)
Detection:	MS: positive and negative mode
Mass range:	105 – 1200 m/z
Flow:	1.40 mL/min
Column temperature:	35 °C

Gradient:	0.0 min: 5 % B
	0.0 – 1.00 min: 5 % B → 100 % B
	1.00 – 1.37 min: 100 % B
	1.37 – 1.40 min: 100 % B → 5 % B

4_BAS_PN

HPLC:	Agilent 1100 Series
MS:	Agilent LC/MSD SL
Column:	Waters, X-Bridge C18, 3.5 µm, 2.1 x 30 mm column
Solvent:	A: 20 mM NH_4HCO_3/NH_3 in H_2O pH 9; B: AcCN (HPLC grade)
Detection:	MS: positive and negative mode
Mass range:	150 – 900 m/z
Flow:	1.40 mL/min
Column temperature:	45 °C
Gradient:	0.00 – 1.00 min: 15 % → 95 % B
	1.00 – 1.37 min: 95 % B
	1.37 – 1.40 min: 95 % → 15 % B

2_FEC_PN

HPLC:	Agilent 1100 Series
MS:	Agilent LC/MSD SL
Column:	YMC Triart C18 2.0 x 30 mm, 3.0 µm
Solvent:	A: H_2O + 0.1 % HCOOH; B: AcCN (HPLC grade)
Detection:	MS: positive and negative mode
Mass range:	150 – 900 m/z
Flow:	1.40 mL/min
Column temperature:	45 °C
Gradient:	0.00 – 1.00 min: 15 % → 95 % B
	1.00 – 1.37 min: 95 % B
	1.37 – 1.40 min: 95 % → 15 % B

The compounds according to the invention and intermediates 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

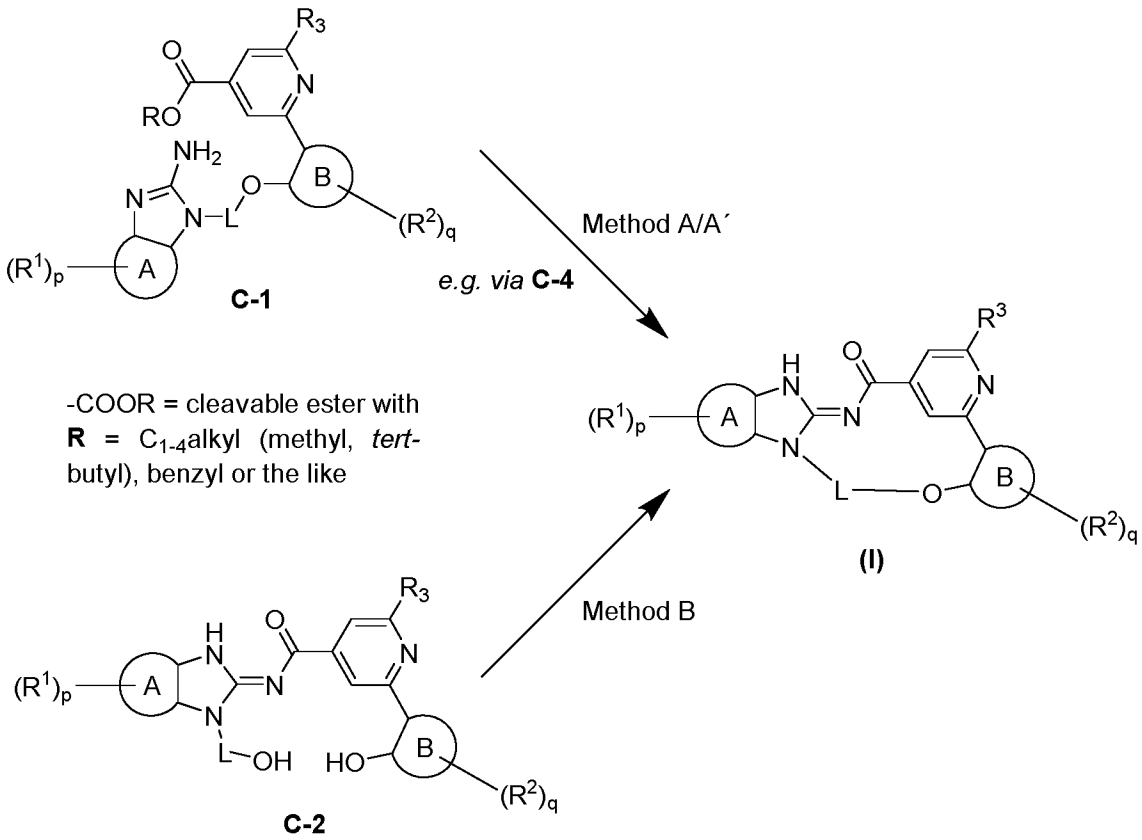
illustration of the invention without restricting its subject matter and the scope of the compounds claimed to these examples. Where the preparation of starting compounds is not described, they are commercially obtainable or their synthesis is described in the prior art or they may be prepared analogously to known prior art compounds or methods described herein, *i.e.* it is within the skills of an organic chemist to synthesize these compounds. Substances described in the literature can be prepared according to the published methods of synthesis.

General reaction scheme and summary of the synthesis route

Compounds **(I)** according to the invention can be synthesized using an amide formation for the macrocyclization starting from open-chain aminobenzimidazoles **C-1** (scheme 1, method A or A'). The macrocyclization can either be achieve directly using strong bases like, *e.g.*, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (scheme 1, method A) or the ester function of **C-1** is cleaved first and then coupling reagents like TBTU or HATU are used to form the amide bond (scheme 1, method A').

Alternatively, compounds **(I)** according to the invention can be synthesized applying an ether formation for the macrocyclization starting from open-chain aminobenzimidazoles **C-2** (scheme 1, method B). Different methods can be used for the ether formation like, *e.g.* MITSONOBU reaction or a two-step process in which the alcohol is first activated by transformation into a halogen or a sulfonester and ring closure by nucleophilic substitution.

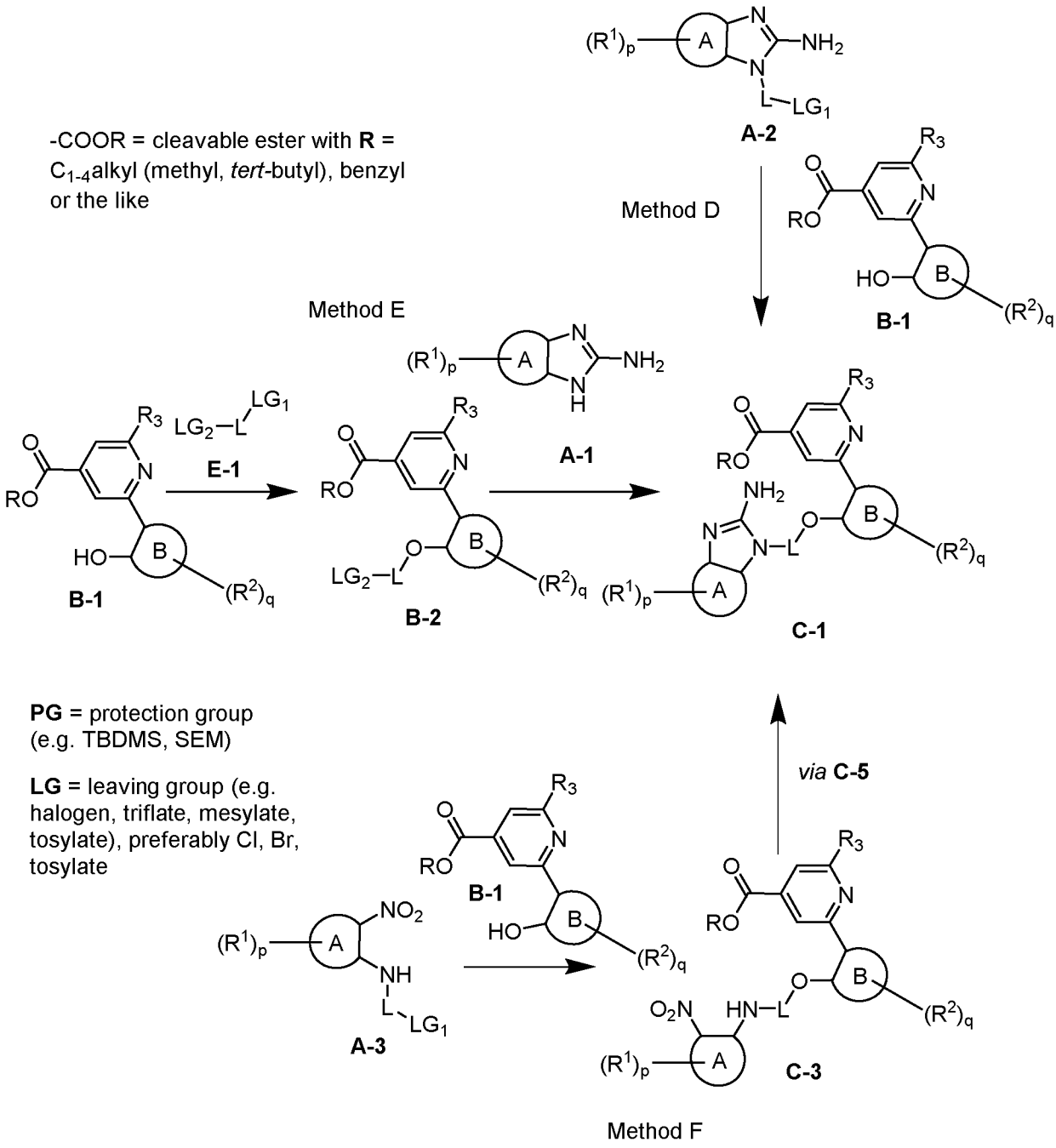
Scheme 1



Key ether intermediates **C-1** for macrocyclization can be synthesized applying three different strategies (scheme 2):

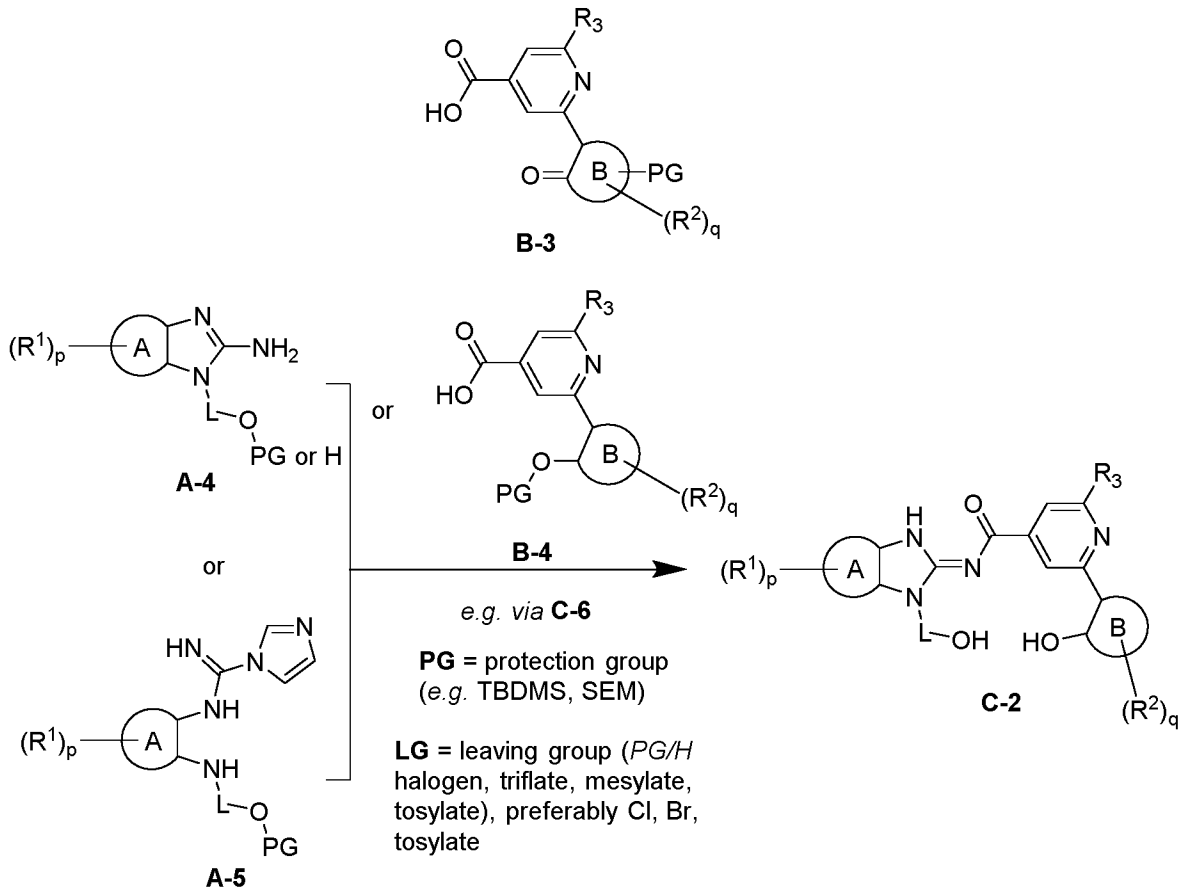
One possibility is an ether formation using intermediates **A-2** and **B-1** (scheme 2, method D). Second option is an alkylation reaction using aminobenzimidazole **A-1** and ether intermediate **B-2** obtained by reaction of intermediates **E-1** and **B-1** (→ Scheme 2, method E). The key step of the third ring closure strategy is an aminobenzimdazole formation reaction applying reagents like cyanogen bromide (see *e.g.* WO 2005/079791; WO 2005/070420; WO 2004/014905). To do so the nitro group of ether intermediate **C-3** needs to be reduced, which can, *e.g.*, be achieved using hydrogen gas and a catalyst like Pd/C or Ra-Ni. Intermediate **C-3** is synthesized by an ether formation reaction starting from **A-3** and **B-1** (→ Scheme 2, method F).

Scheme 2



Key amide intermediates **C-2** can be synthesized (→ scheme 3) by an amide formation using coupling reagents like HATU or TBTU and starting from intermediates **A-4** or **A-5** reacted with **B-3** or **B-4**.

Scheme 3



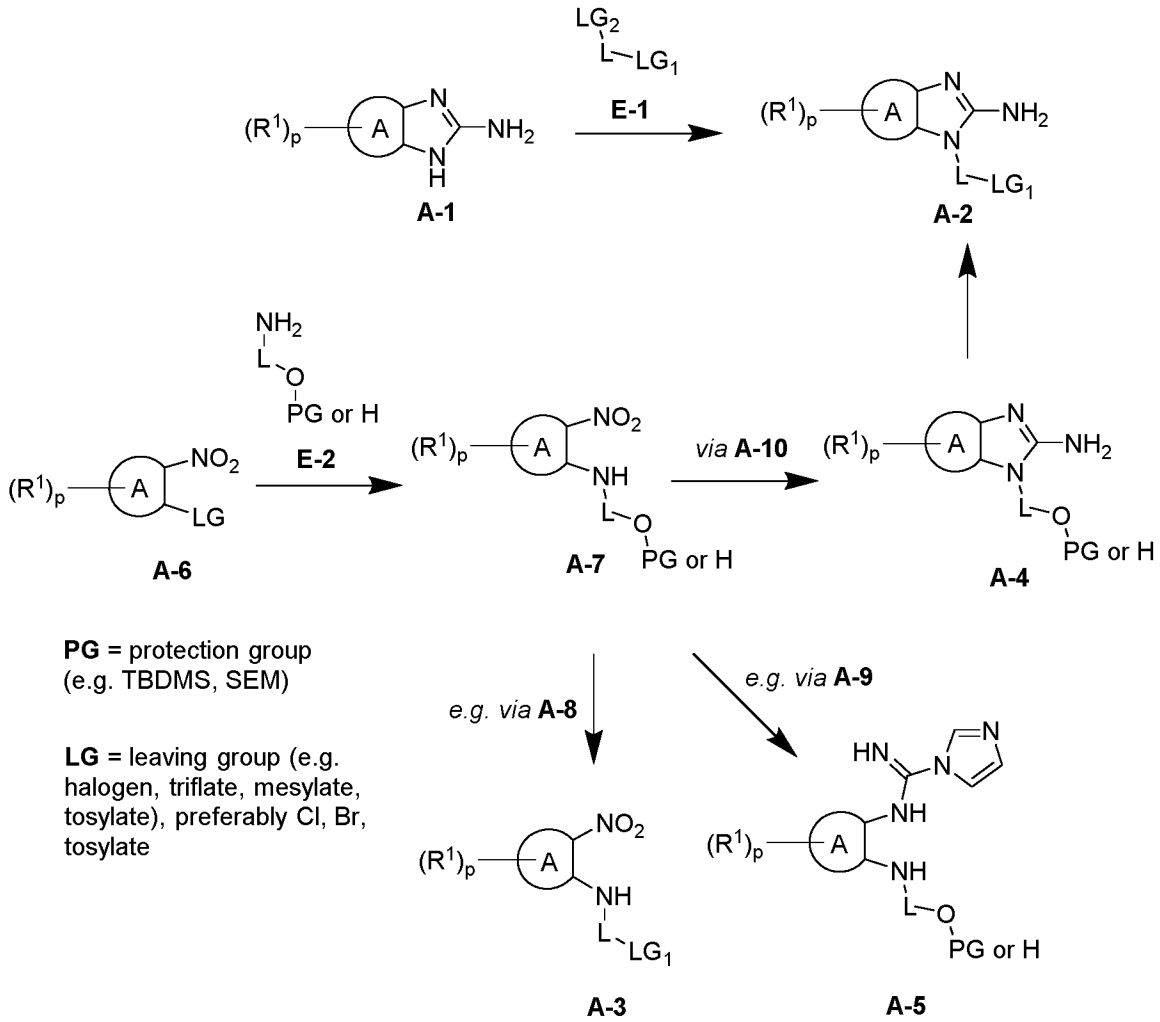
Aminobenzimidazole **A-2** can be synthesized (→ Scheme 4) applying an alkylation reaction starting from aminobenzimdazole **A-1** and an alkylating agent **E-1**. Furthermore, aminobenzimdazole **A-2** can be also obtained from **A-4** *via* a deprotecting reaction followed by transforming the hydroxy group into a halogen or a sulfonester. Aminobenzimdazole **A-4** can be synthesized applying a nucleophilic aromatic substitution reaction of **A-6** and **E-2** (see *e.g. Helvetica Chimica Acta* **2013**, 96, 2160-2172; *Organic Preparations and Procedures Int.* **2004**, 36, 76-81) followed by a reduction of the nitro group of **A-7** and applying an aminobenzimdazole formation reaction by using reagents like cyanogen bromide (*e.g.* WO 2005/079791; WO 2005/070420; WO 2004/014905).

Intermediate **A-3** can be synthesized from **A-7** *via* a deprotecting reaction followed by transforming the free hydroxy group into a halogen or a sulfonester.

Intermediates **A-5** can be synthesized from **A-7** by reduction of the nitro group of **A-7**

followed by a reaction with 1-(1*H*-imidazole-1-carboximidoyl)-1*H*-imidazole.

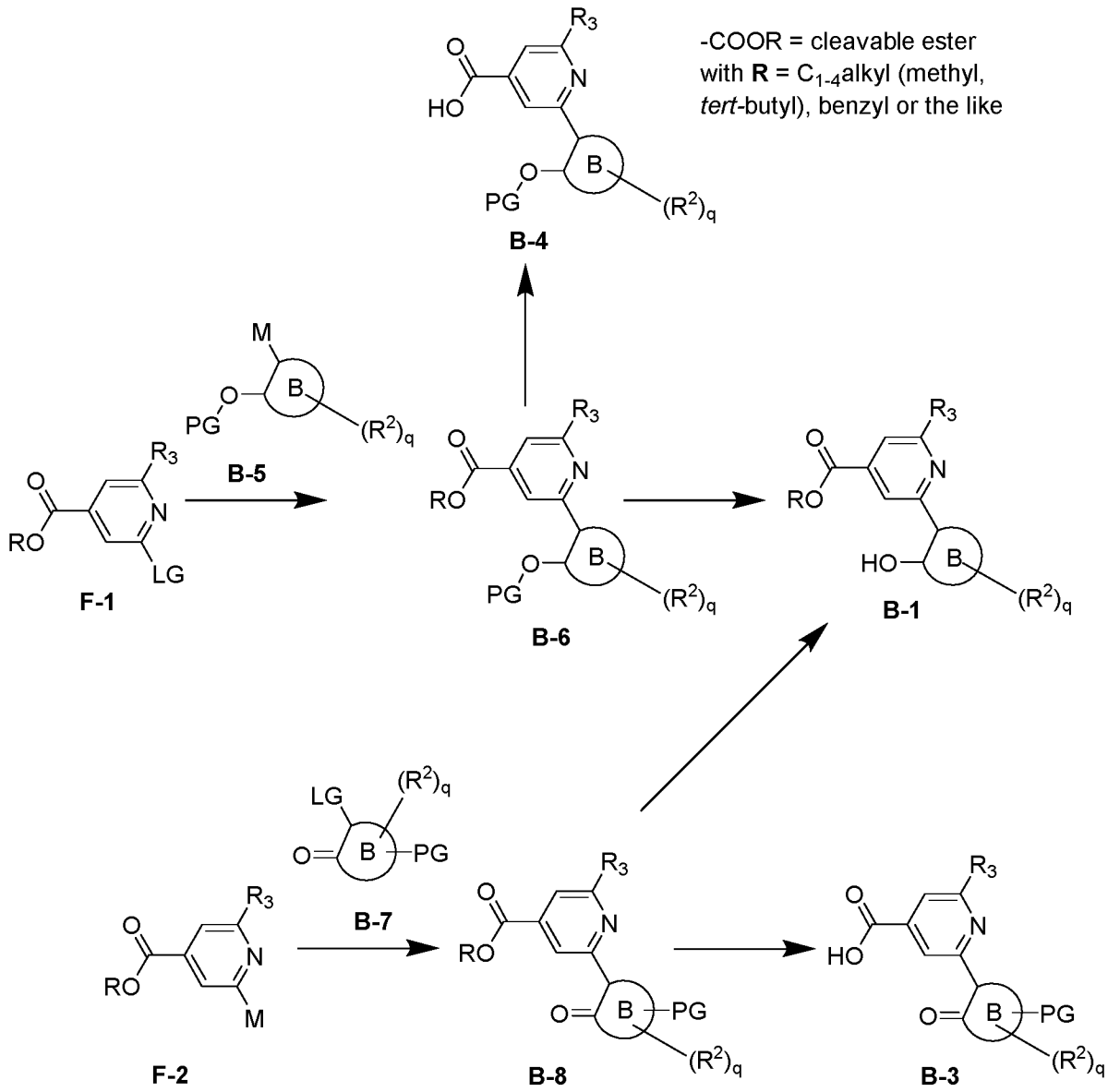
Scheme 4



Intermediate **B-1** can be either synthesized (→ Scheme 5) starting from 2-halogen-isonicotinic acid derivative **F-1** and boronic acid derivative **B-5** applying a SUZUKI reaction (see *e.g. J. Org. Chem.*, **2007**, 72, 4067-4072; *Org. Lett.*, **2011**, 13, 252-255; *J. Org. Chem.*, **2004**, 69, 7779-7782) followed by deprotection of the hydroxy group of **B-6**, or from boronic acid derivative **F-2** and electrophile **B-7** also applying a SUZUKI reaction followed by deprotection of the heteroaromatic ring system of **B-8**.

Intermediate **B-4** and **B-3** can be synthesized *via* ester cleavage of **B-6** and **B-8**, respectively.

Scheme 5



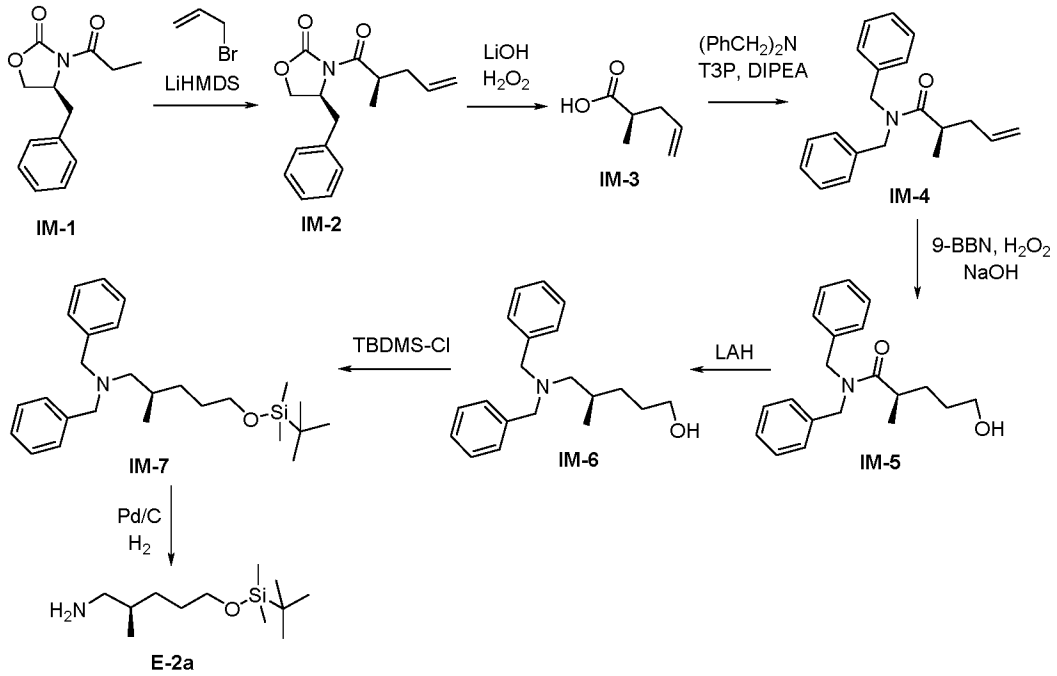
PG = protection group (e.g. TBDMS, SEM)

LG = leaving group (e.g. halogen, triflate, mesylate, tosylate), preferably Cl, Br, tosylate

M = hydrogen, boronic acid or boronic acid derivative, e.g. cyclic boronic acid esters but also $BF_3^-M^+$

Synthesis of intermediates E-2

*Synthesis of **E-2a***



Experimental procedure for the synthesis of **IM-2**

A stirred solution of starting material **IM-1** (10.0 g, 42.87 mmol) in THF (40.0 mL) is cooled to -78 °C. Sodium bis(trimethylsilyl)amide (47.2 mL, 47.16 mmol, 1.1 eq) is added and the reaction mixture is stirred at -78 °C for 1 h. Then allyl bromide (15.3 mL, 171.48 mmol, 4.0 eq) is added and the reaction mixture is stirred at -78 °C for 1 h. After that the reaction mixture is slowly warmed to rt. The reaction is quenched with a saturated aqueous solution of NH_4Cl and extracted with DCM (2 x). The combined organic layers are dried over $MgSO_4$, filtrated and the solvent is evaporated under reduced pressure to provide intermediate **IM-2** (HPLC-MS: $(M+H)^+$ = 274, $t_{Ret.}$ = 1.4 min, method LCMS3, basisch_1).

Experimental procedure for the synthesis of **IM-3**

To a stirred solution of **IM-2** (10.5 g, 38.42 mmol) in THF (40.0 mL) and water (10.0 mL) are added LiOH (2.8 g, 115.25 mmol, 3.0 eq) and H_2O_2 (11.9 mL, 115.25 mmol, 3.0 eq). The mixture is acidified to pH 1-2 using 1 N aqueous HCl solution and extracted with DCM (2 x). After drying the combined organic layers over $MgSO_4$ the solution is filtered and the solvent is evaporated under reduced pressure to afford product **IM-3**. The crude product is used for further synthesis without any additional purification.

Experimental procedure for the synthesis of **IM-4**

To a stirred solution of **IM-3** (4.3 g, 37.67 mmol) in dioxane (15.0 mL) are added DIPEA (19.3 mL, 113.02 mmol, 3.0 eq) and HATU (17.2 g, 45.21 mmol, 1.2 eq). The reaction mixture is stirred at rt for 5 min. Then dibenzylamine (7.4 g, 37.67 mmol, 1.0 eq) is added and stirring at rt is continued for 3 h. The crude product is purified by normal phase chromatography (DCM/MeOH 95:5) and reversed phase chromatography (method: prep. HPLC2) to afford the desired product **IM-4** (HPLC-MS: $(M+H)^+$ = 294, $t_{Ret.}$ = 1.5 min, method LCMS3, basisch_1).

Experimental procedure for the synthesis of **IM-5**

IM-4 (4.3 g, 14.66 mmol) is dissolved in THF (5.0 mL), cooled to 0 °C and a solution of 9-borabicyclo[3.3.1]nonane (73.3 mL, 36.64 mmol, 2.5 eq) in THF is added. The reaction mixture is stirred at rt for 1 h. Then 1 M aqueous NaOH solution is added. The reaction mixture is cooled to 0 °C before H_2O_2 (15.0 mL, 146.56 mmol, 10.0 eq) is added. After addition the reaction mixture is stirred at rt for 16 h. The reaction mixture is diluted with water and extracted with EtOAc (2 x). The combined organic layers are dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by reversed phase chromatography (method: prep. HPLC2) to obtain the desired product **IM-5** (HPLC-MS: $(M+H)^+$ = 312, $t_{Ret.}$ = 1.2 min, method LCMS3, basisch_1).

Experimental procedure for the synthesis of **IM-6**

IM-5 (30.0 g, 96.33 mmol) is dissolved in THF (300.0 mL) and the solution is cooled to 0 °C. 1 M $LiAlH_4$ in THF (674.3 mL, 674.33 mmol, 7.0 eq) is added and the reaction mixture is stirred at rt for 2 h. Then the reaction is quenched with a saturated aqueous Na_2SO_4 solution (1 mL), filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography (method: Combiflash) to afford product **IM-6** (HPLC-MS: $(M+H)^+$ = 298, $t_{Ret.}$ = 1.7 min, method LCMS3, basisch_1).

Experimental procedure for the synthesis of **IM-7**

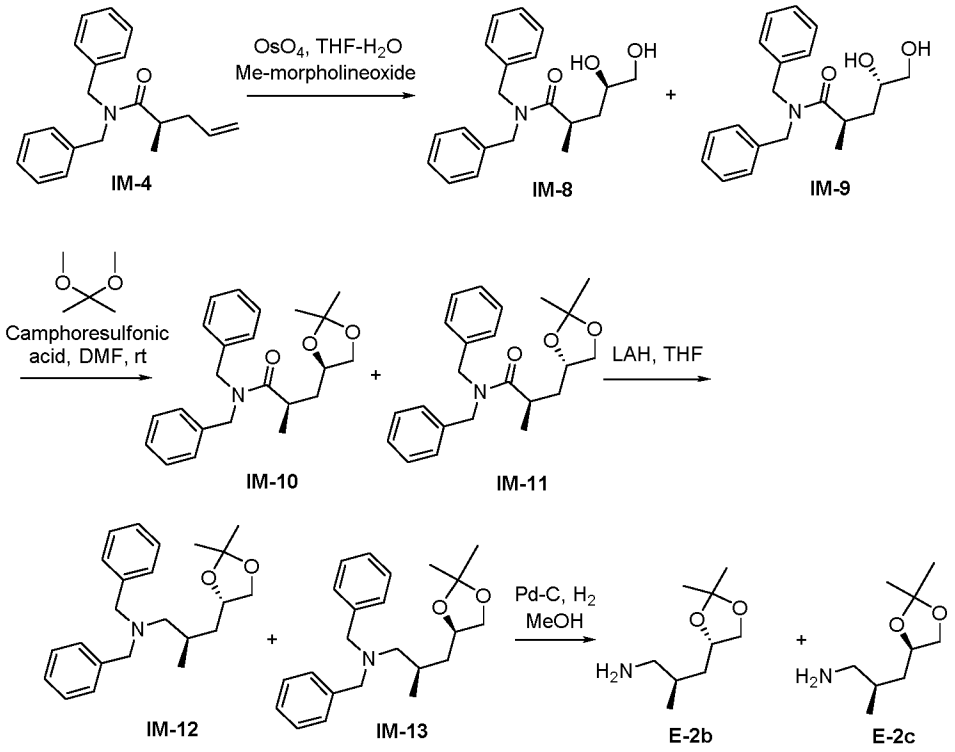
To a stirred solution of **IM-6** (10.0 g, 33.62 mmol) in DCM (100.0 mL) are added TEA (23.3 mL, 168.10 mmol, 5.0 eq), DMAP (4.1 g, 33.62 mmol, 1.0 eq) and TBDMS-Cl (6.1 g, 40.35 mmol, 1.2 eq). The reaction mixture is stirred at rt for 3 h. Then the reaction mixture is diluted with water and extracted with DCM. After drying over $MgSO_4$ and filtration the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography (method: Combiflash) to obtain the desired product **IM-7** (HPLC-

MS: $(M+H)^+$ = 412, $t_{Ret.}$ = 4.1 min, method LCMS_TCG).

Experimental procedure for the synthesis of **E-2a**

To a stirred solution of **IM-7** (75.0 g, 182.17 mmol) in MeOH (750.0 mL) is added Pd/C (3.9 g,18.22 mmol, 10 mol%, 0.1 eq) and the reaction mixture is stirred at rt under a pressure of 3 bar hydrogen for 3 h. The reaction mixture is filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography (method NP1) to obtain the pure product **E-2a** (HPLC-MS: $(M+H)^+$ = 232).

*Synthesis of **E-2b** and **E-2c***



Experimental procedure for the synthesis of **IM-8** and **IM-9**

To a stirred solution of **IM-4** (50.0 g, 0.170 mol) in water (750.0 mL) and THF (1.250 L) is added *N*-methyl-morpholineoxide (26.3 mL, 0.256 mol, 1.5 eq). After 10 min of stirring at rt OsO_4 (5.4 g, 1.70 mmol, 0.01 eq) is added to the reaction mixture. Stirring at rt is continued for 16 h. Then brine is added to the reaction mixture and extraction is done using EtOAc. The combined organic layers are dried over $MgSO_4$, filtered and concentrated to obtain the crude product. Purification by normal phase chromatography affords the pure product as a mixture of diastereomers **IM-8** and **IM-9** (HPLC-MS: $(M+H)^+$

= 328).

Experimental procedure for the synthesis of **IM-10** and **IM-11**

To a stirred solution of the mixture of diastereomers **IM-8** and **IM-9** (40.0 g, 0.122 mol) in DMF (400.0 mL) is added 2,2-dimethoxy propane (17.8 g, 0.171 mol, 1.4 eq). After stirring at rt for 10 min CSA (3.3 g, 0.014 mol, 0.1 eq) is added and the reaction mixture is stirred at rt for 16 h. Then brine is added to the reaction mixture and extraction is performed using EtOAc. The combined organic layers are washed with a saturated aqueous Na_2CO_3 solution, dried over $MgSO_4$, filtered and the filtrate is concentrated under reduced pressure to obtain the crude product. Purification and separation of the diastereomers by normal phase chromatography affords the pure products **IM-10** and **IM-11**.

Experimental procedure for the synthesis of **IM-12**

Diastereomer **IM-10** (11.5 g, 0.031 mol) is dissolved in THF (150.0 mL) and cooled to 0 °C. Then LAH (8.3 g, 0.219 mol, 7.0 eq) is added to the stirred solution and the reaction mixture is stirred at rt for 2 h. The reaction is quenched by the addition of a saturated aqueous Na_2SO_4 solution (1 mL), filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography to yield product **IM-12**.

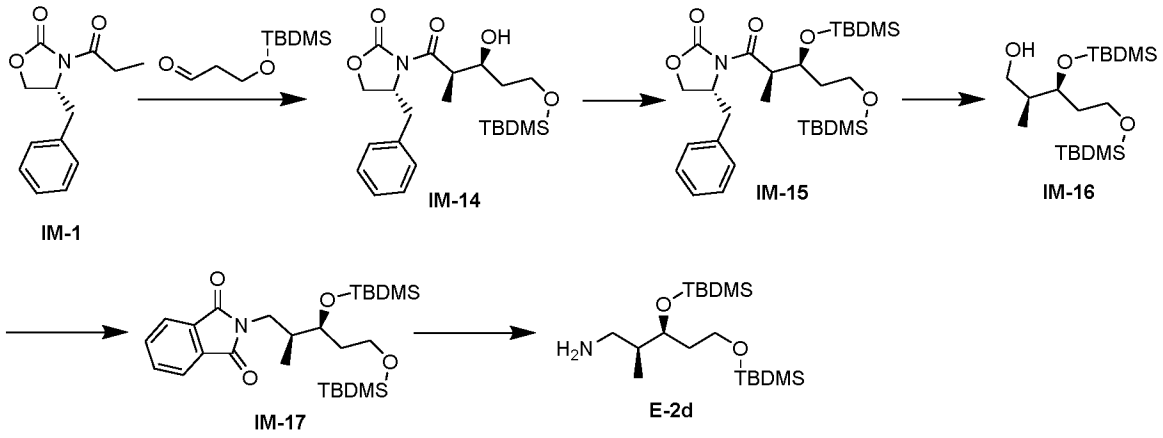
Product **IM-13** is available in an analogous manner starting from diastereomer **IM-11**.

Experimental procedure for the synthesis of **E-2b**

To a stirred solution of **IM-12** (5.7 g, 0.016 mol) in MeOH (60.0 mL) is added Pd/C (0.4 g, 2.0 mmol, 10 mol%, 0.1 eq) and the reaction mixture is stirred at rt under a pressure of 3 bar hydrogen for 3 h. Then the reaction mixture is filtered and concentrated under reduced pressure to afford the crude product, which is purified by normal phase chromatography to obtain product **E-2b**.

Product **E-2c** is available in an analogous manner starting from diastereomer **IM-13**.

*Synthesis of **E-2d***



Experimental procedure for the synthesis of **IM-14**

A stirred solution of **IM-1** (10.0 g, 42.87 mmol) in DCM (25.0 mL) is cooled to -78 °C and 1 M Bu_2BOTf in DCM (72.9 mL, 72.88 mmol, 1.7 eq) and TEA (14.6 mL, 107.18 mmol, 2.5 eq) is added. Then the reaction mixture is stirred at -78 °C for 10 min. Stirring is continued at 0 °C for 1 h. The reaction mixture is again cooled to -78 °C followed by the slow addition of 3-(*tert*-butyl-dimethyl-silanyloxy)-propionaldehyde (8.1 g, 42.87 mmol, 1.0 eq) and stirring at -78 °C for 20 min. After stirring at 0 °C for another hour the reaction is quenched by the successive addition of phosphate buffer (pH = 7; 40 mL), MeOH (112 mL) and 30 % H_2O_2 in MeOH (120 mL). Stirring is continued at 0 °C for 1 h. Afterwards water is added to the reaction mixture and extraction is done using DCM. The organic layer is dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography (*n*-hexane/EtOAc) to afford the desired product **IM-14**.

Experimental procedure for the synthesis of **IM-15**

A stirred solution of **IM-14** (8.0 g, 18.98 mmol) in DCM (80.0 mL) is cooled to 0 °C and 2,6-lutidine (5.5 mL, 47.45 mmol, 2.5 eq) and TBDMSOTf (5.7 mL, 24.67 mmol, 1.3 eq) are added. The reaction mixture is stirred at rt for 3 h. Then the reaction mixture is diluted with water and extracted with DCM. The organic layer is dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography to obtain the desired product **IM-15**.

Experimental procedure for the synthesis of **IM-16**

A stirred solution of **IM-15** (4.0 g, 7.47 mmol) in THF (15.0 mL) and H_2O (2.0 mL) is cooled

to 0 °C and $NaBH_4$ (1.4 g, 37.32 mmol, 5.0 eq) is added. The reaction mixture is stirred at rt for 16 h. Then the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography to yield the desired product **IM-16**.

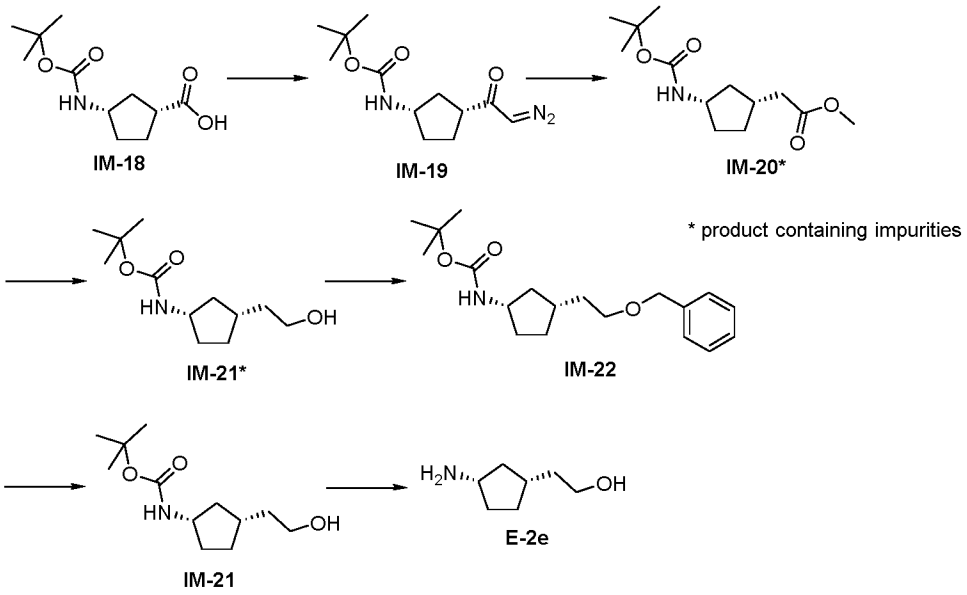
Experimental procedure for the synthesis of **IM-17**

A stirred solution of **IM-16** (2.8 g, 7.72 mmol) in THF (30.0 mL) is cooled to 0 °C and PPh_3 (5.1 g, 19.30 mmol, 2.5 eq) and DEAD (3.1 mL, 19.30 mmol, 2.5 eq) are added. The reaction mixture is stirred at 0 °C for 10 min. Then isoindole-1,3-dione (1.7 g, 11.58 mmol, 1.5 eq) is added and the reaction mixture is stirred at rt for 16 h. Afterwards the reaction is quenched by the addition of a saturated aqueous $NaHCO_3$ solution and extraction is done using EtOAc. The organic layer is dried over Na_2SO_4, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography to afford the desired product **IM-17**.

Experimental procedure for the synthesis of **E-2d**

To a stirred solution of **IM-17** (4.0 g, 8.13 mmol) in EtOH (40.0 mL) is added hydrazine hydrate (4.0 mL, 81.33 mmol, 10.0 eq) and the reaction mixture is stirred under reflux for 2 h. A white precipitate forms. The reaction mixture is cooled to rt and filtered. The filtrate is concentrated to dryness under reduced pressure. The residue is suspended in a saturated aqueous $NaHCO_3$ solution and extraction is done using MeOH/DCM (1:9). The organic layer is dried over Na_2SO_4, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography to get the desired product **E-2d**.

*Synthesis of **E-2e***



Experimental procedure for the synthesis of **IM-19**

A stirred solution of **IM-18** (10.0 g, 0.044 mol) and TEA (9.1 mL, 0.065 mol) in THF (20.0 mL) is cooled to – 20 °C and ethyl chloroformate (5.7 g, 0.052 mol) is added. The reaction mixture is stirred at – 20 °C for 1 h. Then a freshly prepared solution of diazomethane in diethyl ether (20.0 mL, 0.052 mol) is added to the reaction mixture and stirring is continued at rt for 2 h. Afterwards the reaction is quenched using a saturated aqueous citric acid solution. After that the mixture is extracted with EtOAc, the organic layer is dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. Purification is done by normal phase chromatography (*n*-hexane/EtOAc 98:2) to yield the crude product **IM-19**. The crude product is used for further synthesis without additional purification.

Experimental procedure for the synthesis of **IM-20**

The crude starting material **IM-19** (4.0 g, 0.016 mol) is dissolved in MeOH (25.0 mL) and TEA (8.8 mL, 0.063 mol) and silver benzoate (720 mg, 0.003 mol) are added. Then the reaction mixture is stirred at rt for 1 h. The solvent is removed under reduced pressure followed by quenching with a saturated aqueous solution of $NaHCO_3$. Extraction is performed using EtOAc. The organic layer is dried over Na_2SO_4 and the solvent is evaporated under reduced pressure. Purification by normal phase chromatography (*n*-hexane/EtOAc 7:3) affords the crude product **IM-20**, which is used for further synthesis without additional purification.

Experimental procedure for the synthesis of **IM-21**

The crude starting material **IM-20** (550 mg, 2.14 mmol) is dissolved in THF (25.0 mL) and 1 M LAH in THF (3.2 mL, 3.21 mmol) is added. The reaction mixture is stirred at rt for 2 h. After that the reaction is quenched by the addition of a saturated aqueous Na_2SO_4 solution and filtered. The filtrate is concentrated under reduced pressure and purified by normal phase chromatography (*n*-hexane/EtOAc 65:35) to obtain the crude product **IM-21**, which is used for further synthesis without additional purification.

Experimental procedure for the synthesis of **IM-22**

To a solution of the crude starting material **IM-21** (1.7 g, 7.41 mmol) in DMF (10.0 mL) is added NaH (534 mg, 11.12 mmol) and the reaction mixture is stirred at rt for 15 min. bromomethyl benzene (1.0 mL, 8.16 mmol, 1.1 eq) is added to the reaction mixture and stirring at rt is continued for 2 h. The reaction is quenched by the addition of a saturated aqueous solution of NH_4Cl and extraction is done using EtOAc. The organic layer is dried over Na_2SO_4, filtered and the solvent is evaporated under reduced pressure. The crude product is sequentially purified by normal phase chromatography and reversed phase HPLC (alkaline water/AcCN) to afford the pure product **IM-22**.

Experimental procedure for the synthesis of **IM-21**

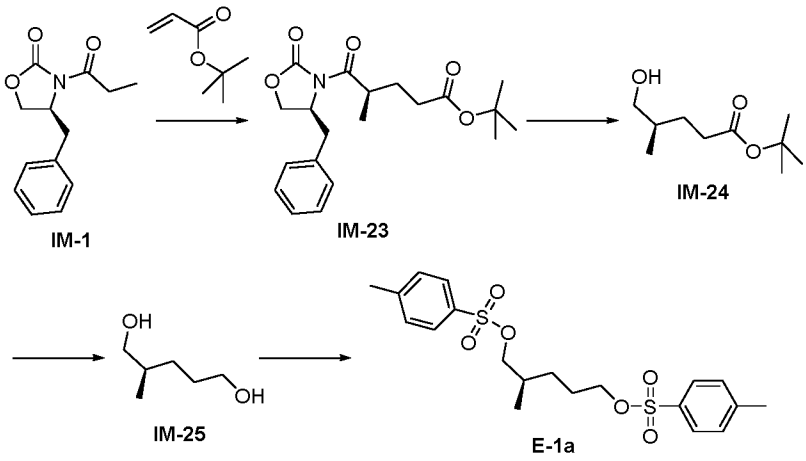
To a stirred solution of **IM-22** (3.8 g, 0.012 mol) in MeOH (100.0 mL) is added Pd/C (500 mg, 0.001 mol, 3 mol%) and the reaction mixture is stirred at rt under a pressure of 3 bar hydrogen for 6 h. The reaction mixture is filtered, concentrated under reduced pressure and purified by normal phase chromatography (*n*-hexane/EtOAc 65:35) to obtain the desired pure product **IM-21**.

Experimental procedure for the synthesis of **E-2e**

Starting material **IM-21** (5.0 g, 21.80 mmol) is dissolved in DCM (50.0 mL) and TFA (3.0 mL, 39.20 mmol) is added to the stirred solution. Stirring of the reaction mixture is continued at rt for 16 h. The solvents are removed under reduced pressure to obtain the product as TFA salt **E-2e**.

Synthesis of intermediates E-1

Synthesis of ***E-1a***



Experimental procedure for the synthesis of **IM-23**

A stirred solution of $TiCl_4$ (162.7 g, 0.857 mol) in DCM (600.0 mL) is cooled to 0 °C and titanium isopropylate (76.6 mL, 0.257 mol) is added. Stirring at 0 °C is continued for 10 min. Then DIPEA (166.7 mL, 0.943 mol) is added and after another 10 min of stirring at 0° C **IM-1** (100.0 g, 0.429 mol) is added to the reaction mixture. Afterwards the reaction mixture is stirred at 0 °C for 1 h. Finally, acrylic acid *tert*-butyl ester (186.7 mL, 1.286 mol) is added to the reaction mixture and stirring at 0 °C is continued for 6 h. The reaction is quenched by the addition of a saturated aqueous solution of NH_4Cl and extraction is done using DCM. The organic layer is washed with a saturated aqueous Na_2CO_3 solution, dried over $MgSO_4$ and filtered. After evaporation of the solvent the crude product is purified by normal phase chromatography to obtain product **IM-23**.

Experimental procedure for the synthesis of **IM-24**

A stirred solution of **IM-23** (120.0 g, 0.332 mol) in THF (600.0 mL) is cooled to 0 °C and $LiBH_4$ (8.0 g, 0.365 mol) and MeOH (6.0 mL) are added. After the addition the reaction mixture is stirred at rt for 2 h. The reaction is quenched with a saturated aqueous NH_4Cl solution and extraction is done using EtOAc. The organic layer is dried over Na_2SO_4, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography to yield product **IM-24**.

Experimental procedure for the synthesis of **IM-25**

A stirred solution of **IM-24** (30.0 g, 0.159 mol) in THF (500.0 mL) is cooled to 0 °C and a 1

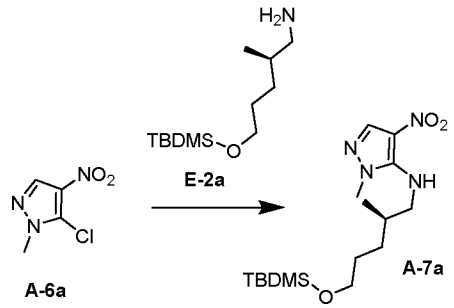
M solution of LAH in THF (200.0 mL, 0.200 mol) is cautiously added. The reaction mixture is stirred at rt for 16 h. The reaction is quenched with a 1 N aqueous NaOH solution and water. After that extraction is done using EtOAc. The organic layer is dried over Na_2SO_4, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography to yield product **IM-25**.

Experimental procedure for the synthesis of **E-1a**

To a stirred solution of **IM-25** (8.0 g, 67.70 mmol) in DCM (100.0 mL) are added TEA (46.3 mL, 338.48 mmol), DMAP (10.0 mg, 0.08 mmol) and tosyl chloride (38.6 g, 203.09 mmol). The reaction mixture is stirred at rt for 4 h. Extraction is done using water/DCM. The organic layer is dried over Na_2SO_4, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography (*n*-hexane/EtOAc 85:15) to obtain product **E-1a**.

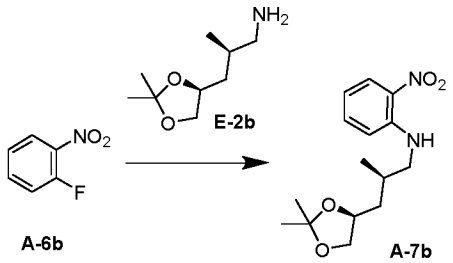
Synthesis of intermediates A-7

Experimental procedure for the synthesis of **A-7a**



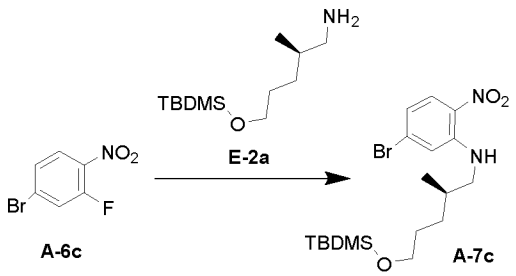
Starting material **A-6a** (375 mg, 2.21 mmol) and Na_2CO_3 (563 mg, 5.31 mmol) are dissolved in THF (3.8 mL) and **E-2a** (525 mg, 2.27 mmol) is added to the reaction mixture. The reaction mixture is stirred under microwave irradiation at 125 °C for 4 h. Then the solvent is evaporated under reduced pressure. Water is added to the residue and extraction is performed using DCM. The combined organic layers are dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. Purification is done by reversed phase chromatography (method: prep. HPLC1) affording product **A-7a**.

Experimental procedure for the synthesis of **A-7b**



A-6b (670 mg, 4.75 mmol) and K_2CO_3 (1.3 g, 9.47 mmol) are dissolved in AcCN (13.5 mL). **E-2b** (1.0 g, 4.73 mmol) is added and the reaction mixture is stirred at 80 °C for 16 h. After filtration of the reaction mixture the solvent is evaporated under reduced pressure and purification is performed by reversed phase chromatography (method: prep. HPLC1) to yield product **A-7b**.

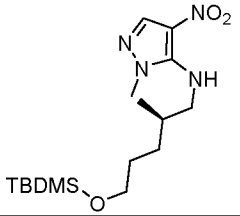
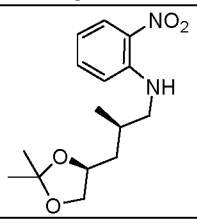
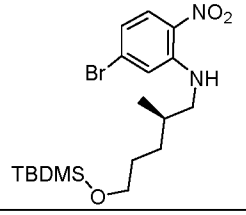
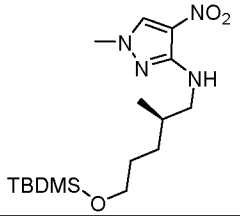
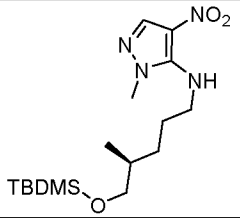
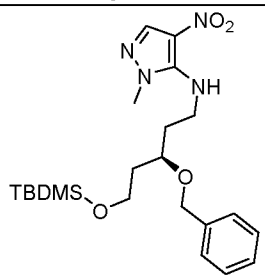
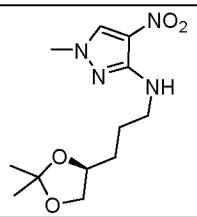
Experimental procedure for the synthesis of **A-7c**

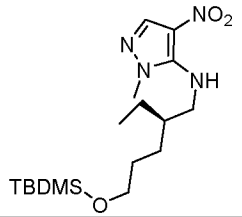
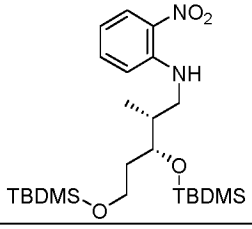
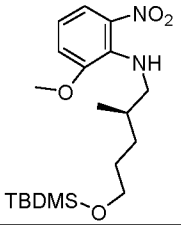
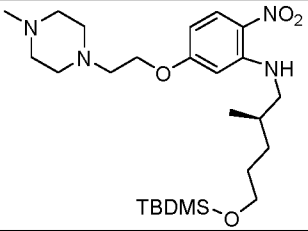
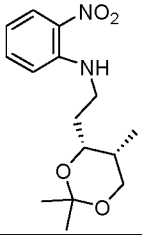
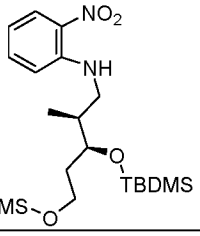
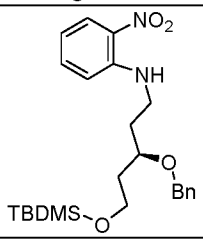


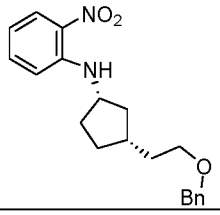
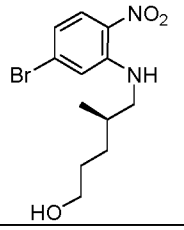
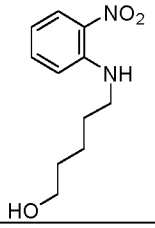
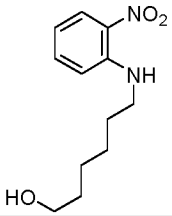
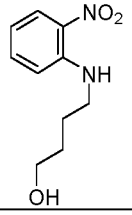
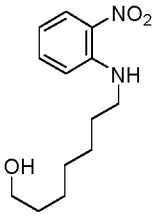
The starting materials **A-6c** (45 mg, 0.20 mmol), **E-2a** (50 mg, 0.21 mmol) and K_2CO_3 (100 mg, 0.72 mmol) are suspended in THF (0.5 mL) and the reaction mixture is stirred at 80 °C for 1 h. Stirring is continued at rt for 16 h. Then the reaction mixture is filtered and the solvent is evaporated under reduced pressure. The residue is purified by reversed phase chromatography (method: prep. HPLC1) to obtain product **A-7c**.

The following intermediates **A-7** (table 1) are available in an analogous manner starting from different building blocks **A-6** and **E-2**. Intermediates **A-7** can be deprotected to obtain the corresponding deprotected intermediates **A-8**.

Table 1:

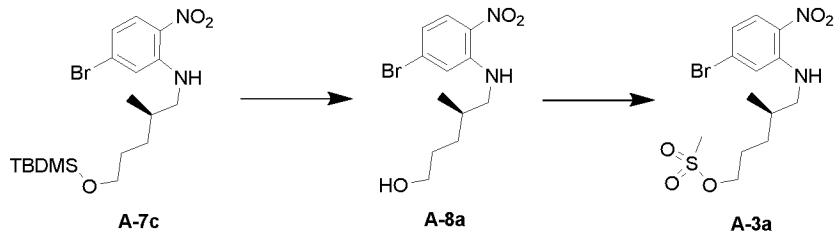
#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
A-7[a]		$(M+H)^+$ = 357; $t_{Ret.}$ = 1.8	LCMS3, basisch_1
A-7b		$(M+H)^+$ = 395; $t_{Ret.}$ = 1.1	VAB
A-7c		$(M+H)^+$ = 431/433; $t_{Ret.}$ = 1.38	VAB
A-7d		$(M+H)^+$ = 357; $t_{Ret.}$ = 0.63	VAB
A-7e		$(M+H)^+$ = 357; $t_{Ret.}$ = 0.66	VAB
A-7f		$(M+H)^+$ = 449; $t_{Ret.}$ = 1.23	VAB
A-7g		$(M+H)^+$ = 299; $t_{Ret.}$ = 0.96	VAB

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
A-7h		$(M+H)^+$ = 371; $t_{Ret.}$ = 1.26	VAB
A-7i		$(M+H)^+$ = 483; $t_{Ret.}$ = 1.98	LCMS3, basisch_1
A-7j		$(M+H)^+$ = 383	VAB
A-7k		$(M+H)^+$ = 495; $t_{Ret.}$ = 1.17	VAB
A-7l		$(M+H)^+$ = 295; $t_{Ret.}$ = 1.45	LCMS3, basisch_1
A-7m		$(M+H)^+$ = 482	VAB
A-7n		$(M+H)^+$ = 445; $t_{Ret.}$ = 1.34	VAB

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
A-7o		$(M+H)^+$ = 341; $t_{Ret.}$ = 0.97	LCMS3, basisch_1
A-8a		$(M+H)^+$ = 317/319; $t_{Ret.}$ = 1.00	VAB
A-8b		$(M+H)^+$ = 225; $t_{Ret.}$ = 0.95	VAS-Sun
A-8c		$(M+H)^+$ = 239; $t_{Ret.}$ = 1.01	VAS-Sun
A-8d		$(M+H)^+$ = 211; $t_{Ret.}$ = 1.05	LCMS3, basisch_1
A-8e		$(M+H)^+$ = 253; $t_{Ret.}$ = 1.04	VAS-Sun

Synthesis of intermediates A-3

Experimental procedure for the synthesis of **A-3a**

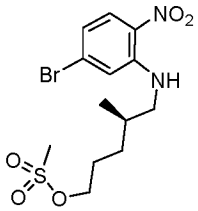
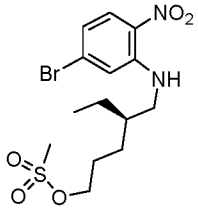


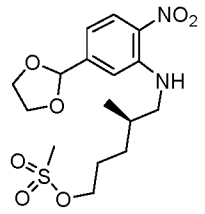
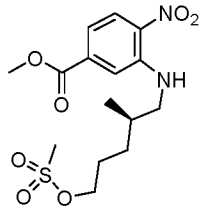
Starting material **A-7c** (70 mg, 0.16 mmol) is dissolved in 1,4-dioxane (4.0 mL) and a 1 N aqueous solution of HCl (1.0 mL, 1.00 mmol) is added to the solution. The reaction mixture is stirred at rt for 19 h. Then the solvent is evaporated under reduced pressure. The residue is purified by reversed phase chromatography (method: prep. HPLC1) to afford deprotected **A-8a** (HPLC-MS: $(M+H)^+$ = 317/319, $t_{Ret.}$ = 1.0 min, method VAB) as intermediate product.

A stirred solution of the deprotected intermediate **A-8a** (5.1 g, 15.44 mmol) and TEA (5.5 mL, 39.68 mmol) is cooled to 0 °C and a solution of methanesulfonyl chloride (1.8 mL, 22.16 mmol) in THF (20 mL) is cautiously added. The reaction mixture is stirred at 0 °C for 1 h. Then the reaction mixture is filtered. Purification is done by normal phase chromatography (cyclohexane/EtOAc) to yield product **A-3a**.

The following intermediates **A-3** (table 2) are available in an analogous manner starting from different building blocks **A-7**.

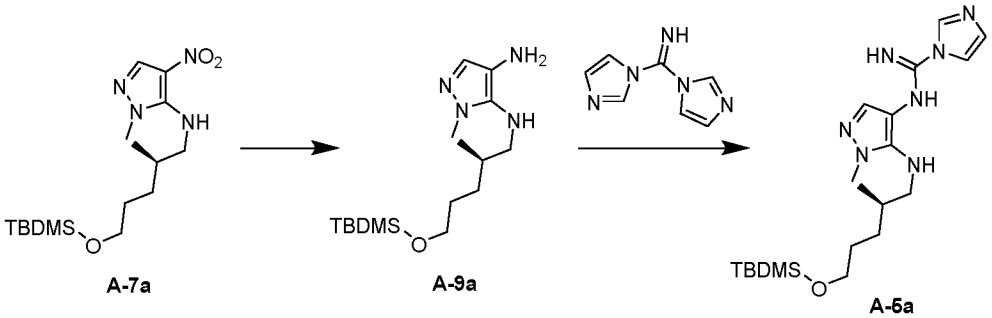
Table 2:

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
A-3a		$(M+H)^+$ = 395/397; $t_{Ret.}$ = 1.0	VAB
A-3b		$(M+H)^+$ = 410; $t_{Ret.}$ = 1.04	VAB

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
A-3c		$(M+H)^+$ = 489; $t_{Ret.}$ = 1.09	VAB
A-3d		$(M+H)^+$ = 375; $t_{Ret.}$ = 1.08	VAB

Synthesis of intermediates A-5

Experimental procedure for the synthesis of **A-5a**



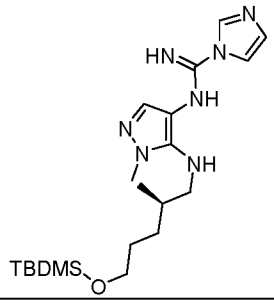
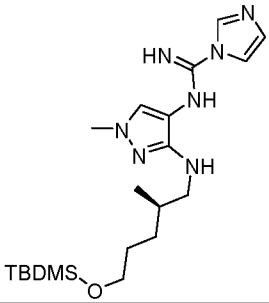
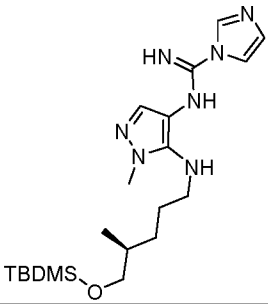
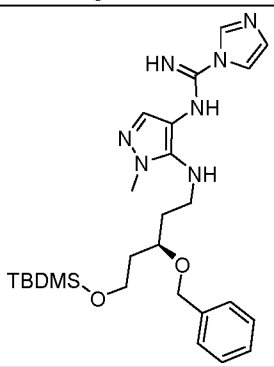
A-7a **A-9a** **A-5a**

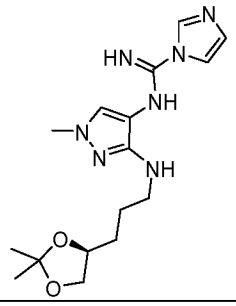
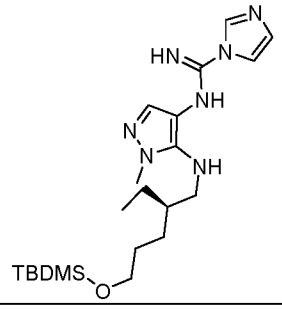
Starting material **A-7a** (368 mg, 1.03 mmol) is dissolved in THF (25 mL) and RANEY-Nickel (200 mg, 2.25 mmol, 2.2 eq) is added. The reaction mixture is stirred at rt under a pressure of 6 bar hydrogen for 25 h. After filtration of the reaction mixture the solvent is evaporated under reduced pressure to yield the intermediate product **A-9a** (HPLC-MS: $(M+H)^+$ = 327, $t_{Ret.}$ = 1.6 min, method LCMS3, basisch_1).

The crude intermediate product **A-9a** (336 mg, 1.03 mmol) is dissolved in THF (2 mL) and 1-(1*H*-imidazole-1-carboximidoyl)-1*H*-imidazole (250 mg, 1.55 mmol, 1.5 eq) is added. The reaction mixture is stirred at rt for 21 h. Then the solvent is evaporated under reduced pressure and purification is done by reversed phase chromatographie (method: prep. HPLC1) to obtain product **A-5a** (HPLC-MS: $(M+H)^+$ = 420, $t_{Ret.}$ = 1.4 min, method LCMS3, basisch_1).

The following intermediates **A-5** (table 3) are available in an analogous manner starting from different building blocks **A-7**.

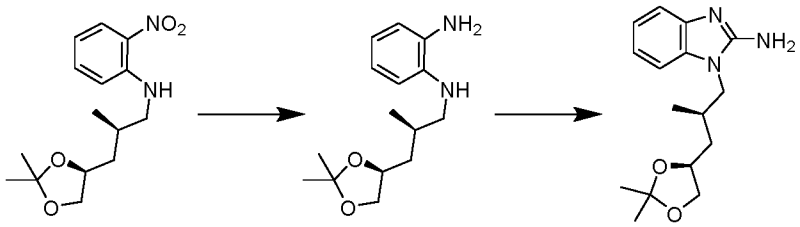
Table 3:

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
A-5a		$(M+H)^+$ = 420; $t_{Ret.}$ = 1.4	LCMS3, basisch_1
A-5b		$(M+H)^+$ = 420; $t_{Ret.}$ = 1.41	LCMS3, basisch_1
A-5c		$(M+H)^+$ = 420; $t_{Ret.}$ = 1.39	LCMS3, basisch_1
A-5d		$(M+H)^+$ = 512;	LCMS3, basisch_1

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
A-5e		$(M+H)^+$ = 362; $t_{Ret.}$ = 0.79	VAB
A-5f		$(M+H)^+$ = 434; $t_{Ret.}$ = 1.49	LCMS3, basisch_1

Synthesis of intermediates A-4

Experimental procedure for the synthesis of **A-4a**



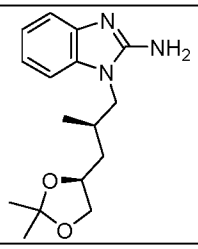
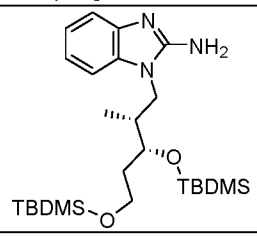
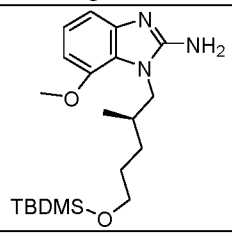
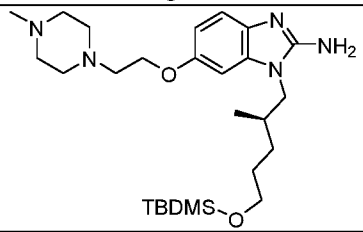
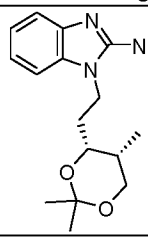
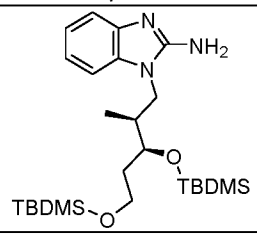
A-7b **A-10a** **A-4a**

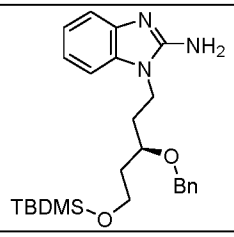
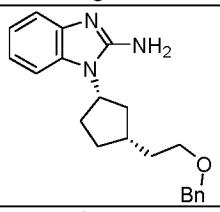
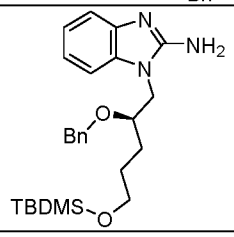
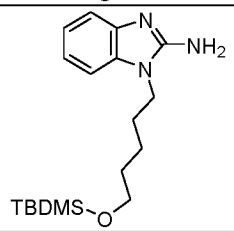
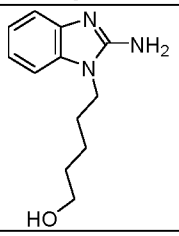
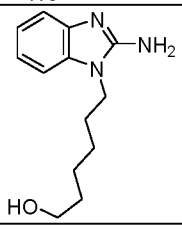
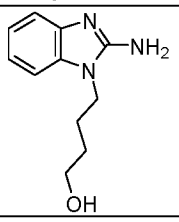
Starting material **A-7b** (990 mg, 3.36 mmol) is dissolved in MeOH (20.0 mL) and RANEY-Nickel (80 mg) is added. The reaction mixture is stirred at rt under a pressure of 5 bar hydrogen for 2 h. After filtration and evaporation of the solvent the crude intermediate product **A-10a** is used for further synthesis without any additional purification (HPLC-MS: $(M+H)^+$ = 265, $t_{Ret.}$ = 1.0 min, method VAB).

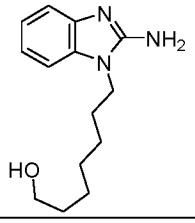
The crude intermediate product **A-10a** (888 mg, 3.36 mmol) is dissolved in *tert*-BuOH (50.0 mL) and 5 M CNBr in AcCN (1.0 mL) is added. The reaction mixture is stirred at 50 °C for 3 h. Afterwards the reaction mixture is mixed with a saturated aqueous solution of $NaHCO_3$, stirred for 15 min and extracted once with DCM. The organic phase is dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. Purification is done by reversed phase chromatography (method: prep. HPLC1) to afford product **A-4a**.

The following intermediates **A-4** (table 4) are available in an analogous manner starting from different building blocks **A-7**.

Table 4:

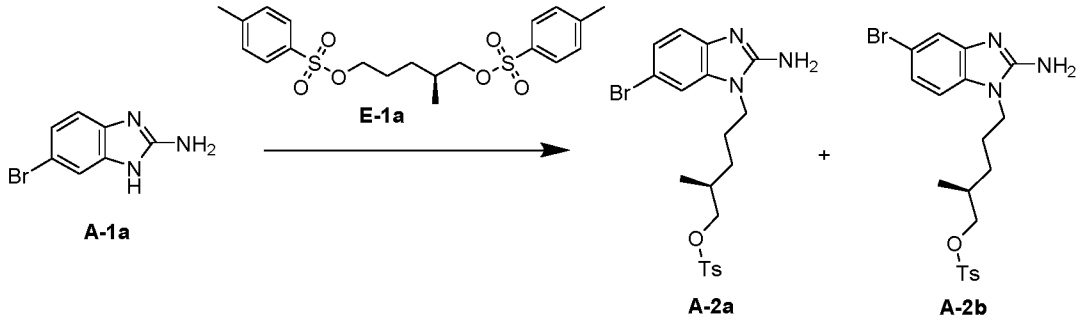
#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
A-4a		$(M+H)^+$ = 290; $t_{Ret.}$ = 0.9	VAB
A-4b		$(M+H)^+$ = 478	VAB
A-4c		$(M+H)^+$ = 378	VAB
A-4d		$(M+H)^+$ = 490; $t_{Ret.}$ = 1.10	VAB
A-4e		$(M+H)^+$ = 290; $t_{Ret.}$ = 0.85	VAB
A-4f		$(M+H)^+$ = 478	VAB

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
A-4g		$(M+H)^+$ = 440; $t_{Ret.}$ = 1.19	VAB
A-4h		$(M+H)^+$ = 336; $t_{Ret.}$ = 1.41	LCMS3, basisch_1
A-4i		$(M+H)^+$ = 440	VAB
A-4j			
A-4k		$(M+H)^+$ = 220; $t_{Ret.}$ = xxx	VAB
A-4l		$(M+H)^+$ = 234;	VAB
A-4m		$(M+H)^+$ = 206;	VAB

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
A-4n		$(M+H)^+$ = 248;	VAB

Synthesis of intermediates A-2

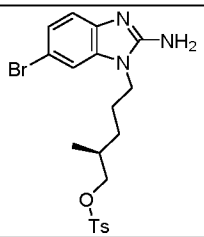
Experimental procedure for the synthesis of **A-2a** and **A-2b**

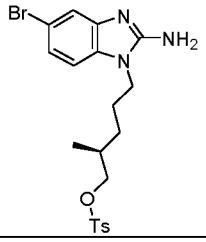


To a stirred solution of **A-1a** (209 mg, 0.94 mmol) and **E-1a** (400 mg, 0.94 mmol) in AcCN (3.0 mL) is added 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (0.2 mL, 1.59 mmol) and the reaction mixture is stirred at rt for 16 h. After filtration of the reaction mixture and washing with AcCN the solvent of the filtrate is evaporated under reduced pressure. The residue is purified by reversed phase chromatography (method: prep. HPLC1) to afford the regioisomers **A-2a** and **A-2b** in a 1:1 mixture.

The following intermediates **A-2** (table 5) are available in an analogous manner starting from different building blocks **A-1** and **E-1**.

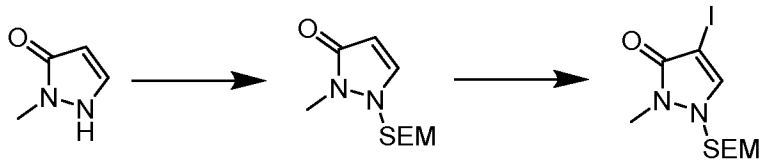
Table 5:

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
A-2a		$(M+H)^+$ = 466; $t_{Ret.}$ = 1.4	LCMS3, basisch_1

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
A-2b		$(M+H)^+$ = 466; $t_{Ret.}$ = 1.4	LCMS3, basisch_1

Synthesis of intermediates B-7

Experimental procedure for the synthesis of **B-7a:**



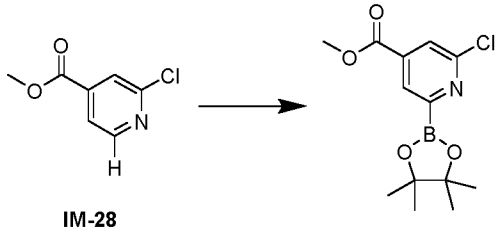
IM-26 **IM-27** **B-7a**

Starting material **IM-26** (25.0 g, 0.247 mol) and K_2CO_3 (75.0 g, 0.543 mol) are dissolved in AcCN (1.0 L) and the solution is cooled to 0 °C. SEM-Cl (75.0 g, 0.432 mol) is added dropwise under stirring. The reaction mixture is stirred at rt for 1 h. After filtration and purification by normal phase chromatography (DCM/MeOH/NH_3 94.5:5:0.5) the desired product **IM-27** (HPLC-MS: $(M+H)^+$ = 229, $t_{Ret.}$ = 1.0 min, method LCMS3, basisch_1) is obtained.

Starting material **IM-27** (38.0 g, 0.133 mol) is dissolved in AcCN (570 mL) and the solution is cooled to 0 °C. Then *N*-iodosuccinimide (32.2 g, 0.136 mol) is cautiously added under stirring. Stirring is continued at 0 °C for 2 h. After that another portion of *N*-iodosuccinimide (3.2 g, 0.014 mol) is added and stirring is continued at 0 °C for another 30 min. Afterwards the reaction mixture is slowly warmed to rt and water is added. Extraction is performed using DCM. The organic layer is dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography (cyclohexane/EtOAc) to afford the desired product **B-7a** (HPLC-MS: $(M+H)^+$ = 355, $t_{Ret.}$ = 1.2 min, method LCMS3, basisch_1).

Synthesis of intermediates F-2

Experimental procedure for the synthesis of **F-2a:**

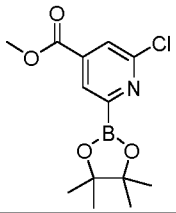
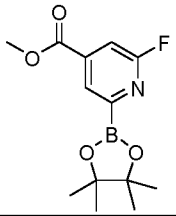


IM-28 **F-2a**

Bis(pinacolato)diboron (273.3 g, 1.076 mol) is suspended in MTBE (2.5 L) and the mixture is heated to 70 °C. The volume of the reaction mixture is reduced by 1/3 by distillation and the mixture is cooled down to 20 °C. Then (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (8.9 g, 0.013 mol) and 4,4'-di-*tert*-butyl-2,2'-bipyridyl (7.2 g, 0.027 mol) are added and the reaction mixture is stirred at rt for 15 min. After that the reaction mixture is cannulated to a melt of **IM-28** (157.0 g, 0.897 mol) and the reaction mixture is stirred at rt for 90 h. Then the solvent is removed under reduced pressure. The crude product oil is stirred in *n*-hexane (1.0 L) at rt for 16 h. The precipitated product is filtered and rinsed with *n*-hexane. Drying in at rt for 16 h affords **F-2a**.

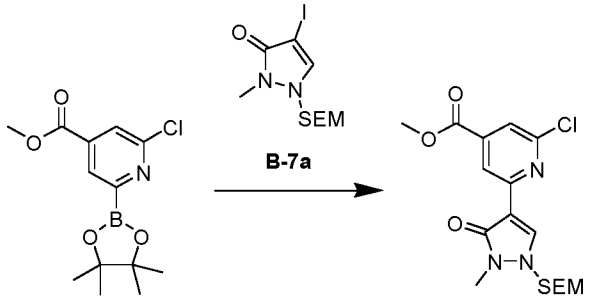
The following intermediates **F-2** (table 6) are available in an analogous manner starting from different precursors.

Table 6:

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
F-2a		$(M+H)^+$ = 298	VAB
F-2b		$(M+H)^+$ = 282	VAB

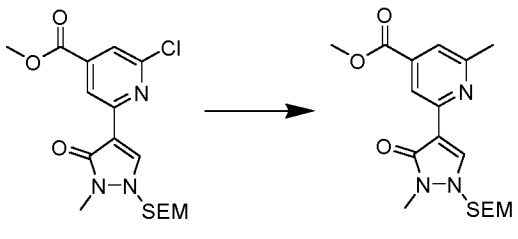
Synthesis of intermediates B-8

Experimental procedure for the synthesis of **B-8a:**



B-7a (4.0 g, 10.60 mmol), **F-2a** (4.2 g, 12.72 mmol), tris(dibenzylideneacetone)-dipalladium(0) (243 mg, 0.27 mmol), di(1-adamantyl)-*n*-butylphosphine (285 mg, 0.80 mmol) and Cs_2CO_3 (10.4 g, 31.81 mmol) are suspended in toluene (48 mL) and water (12 mL). The reaction mixture is stirred at 65 °C for 5 h. Then the reaction mixture is cooled to rt and extracted with EtOAc. The organic layer is dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. The crude product is dissolved in toluene (30 mL) and hexane (300 mL) are added slowly while stirring to cause precipitation of the product. After filtration and washing of the precipitate (1 x 5 mL toluene/hexane 1:10, 2 x 5 mL hexane) drying *in vacuo* yields product **B-8a**.

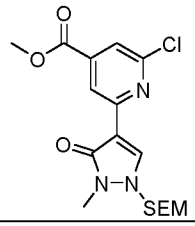
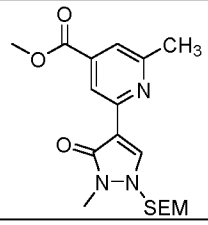
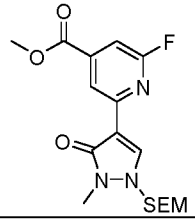
Experimental procedure for the synthesis of **B-8b:**



To a solution of **B-8a** (990 mg, 2.14 mmol) in dioxane (20 mL) are added trimethylboroxine (805 mg, 6.41 mmol), tris(dibenzylideneacetone)dipalladium(0) (49 mg, 0.05 mmol), butyl-di-1-adamantylphosphine (61 mg, 0.16 mmol) and Cs_2CO_3 (2.1 g, 6.41 mmol). The reaction mixture is stirred at 65 °C for 16 h. After filtration and concentration of the reaction mixture under reduced pressure water is added to the residue. Extraction is performed using DCM. The combined organic layers are dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography (DCM/MeOH 95:5) to yield **B-8b**.

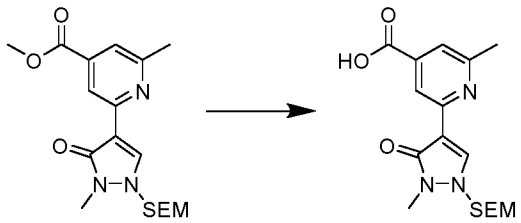
The following intermediates **B-8** (table 7) are available in an analogous manner starting from different building blocks **F-2** and **B-7**.

Table 7:

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
B-8a		$(M+H)^+$ = 398/400; $t_{Ret.}$ = 1.65	LCMS3, basisch_1
B-8b		$(M+H)^+$ = 420; $t_{Ret.}$ = 1.6	LCMS3, basisch_1
B-8c		$(M+H)^+$ = 382; $t_{Ret.}$ = 1.55	LCMS3, basisch_1

Synthesis of intermediates B-3

Experimental procedure for the synthesis of **B-3a**:



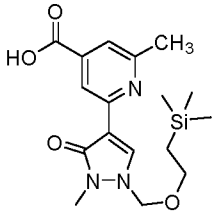
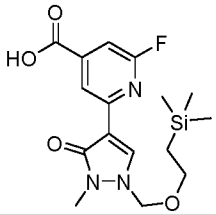
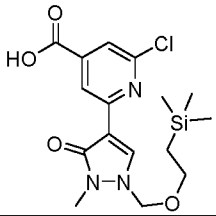
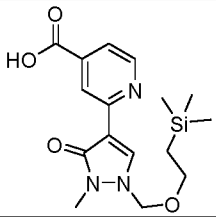
B-8b **B-3a**

B-8b (114.6 g, 0.256 mol) is dissolved in THF (360 mL). Then a solution of NaOH (11.3 g, 0.281 mol) in water (180 mL) is added and the reaction mixture is stirred at rt for 30 min. After that the reaction mixture is acidified to pH 5 using a 6 N aqueous solution of HCl. Filtration of the formed slurry and washing with water affords the crude product, which is dried under vacuum at 50 °C. The crude product is redissolved in EtOAc (200 mL) and stirred at 60 °C for 1 h. After cooling down to room temperature *n*-heptane (150 mL) is

added dropwise. Stirring at rt is continued for 3 h. Then filtration followed by washing of the solid with heptane and drying under vacuum at 50 °C affords product **B-3a**.

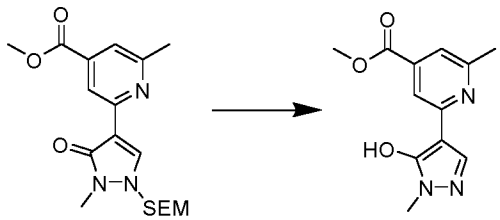
The following intermediates **B-3** (table 8) are available in an analogous manner starting from different building blocks **B-8**.

Table 8:

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
B-3a		$(M+H)^+$ = 364	LCMS3, basisch_1
B-3b		$(M+H)^+$ = 368	LCMS3, basisch_1
B-3c		$(M+H)^+$ = 384/386	LCMS3, basisch_1
B-3d		$(M+H)^+$ = 350	LCMS3, basisch_1

Synthesis of intermediates B-1

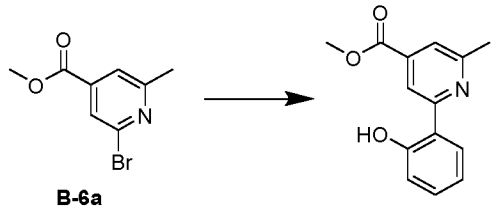
Experimental procedure for the synthesis of **B-1a:**



B-8b **B-1a**

To a stirred solution of **B-8b** (400 mg, 0.91 mmol) in 1,4-dioxane (2.4 mL) is added a 4 M solution of HCl in 1,4-dioxane (2.3 mL, 9.09 mmol). The reaction mixture is stirred at rt for 6 h. Then the precipitated product is filtered and washed with 1,4-dioxane (10 mL) and DCM (10 mL). After drying *in vacuo* the HCl salt form of the product is obtained. This intermediate is washed with a saturated aqueous solution of Na_2CO_3 and extraction is done using DCM to afford product **B-1a**.

Experimental procedure for the synthesis of **B-1b:**

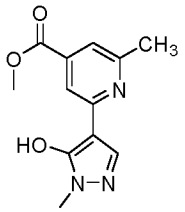


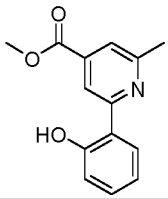
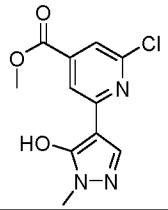
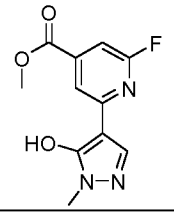
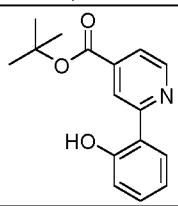
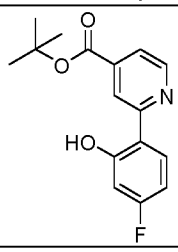
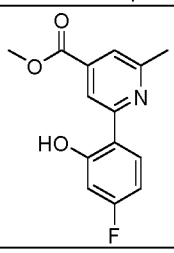
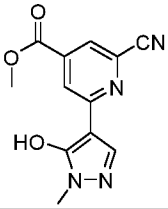
B-6a **B-1b**

To a stirred solution of **B-6a** (100 mg, 0.43 mmol) in dioxane (3 mL) are added 2 M aqueous solution of K_2CO_3 (0.3 mL, 0.65 mmol) and Pd dppf (18 mg, 0.02 mmol). The reaction mixture is stirred under microwave irradiation at 90 °C for 1 h. After filtration of the reaction mixture and washing with MeOH the solvent of the filtrate is evaporated under reduced pressure. The residue is resolved in water and extraction is done using DCM. The combined organic layers are dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. Purification is done by normal phase chromatography (DCM/MeOH 50:1) to afford product **B-1b**.

The following intermediates **B-1** (table 9) are available in an analogous manner starting from different building blocks **B-6** and **B-8**, respectively.

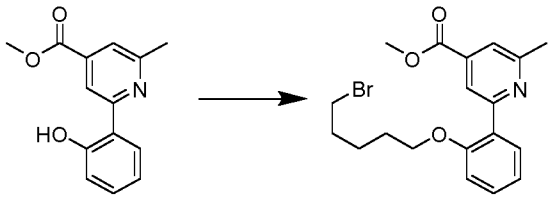
Table 9:

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
B-1a		$(M+H)^+$ = 248	LCMS3, basisch_1

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
B-1b		$(M+H)^+$ = 244; $t_{Ret.}$ = 1.3	LCMS3, basisch_1
B-1c		$(M+H)^+$ = 268	LCMSBAS1
B-1d		$(M+H)^+$ = 252	LCMSBAS1
B-1e		$(M+H)^+$ = 272; $t_{Ret.}$ = 1.51	LCMSBAS1
B-1f		$(M+H)^+$ = 290; $t_{Ret.}$ = 1.57	LCMSBAS1
B-1g		$(M+H)^+$ = 262; $t_{Ret.}$ = 1.38	LCMSBAS1
B-1h		$(M+H)^+$ = 259	LCMS3, basisch_1

Synthesis of intermediates B-2

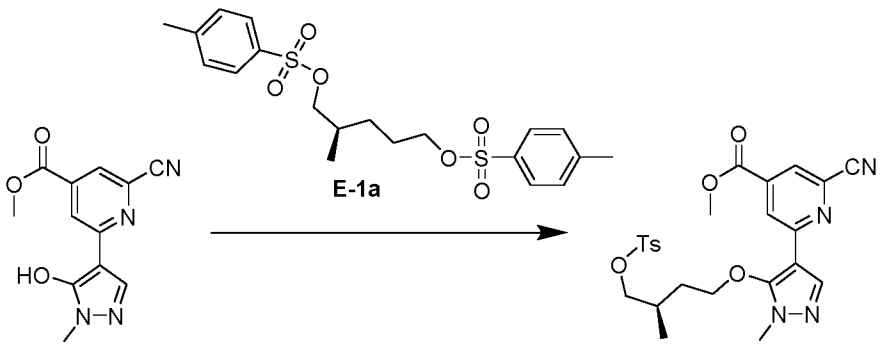
Experimental procedure for the synthesis of **B-2a**:



B-1b **B-2a**

To a stirred solution of **B-1b** (89 mg, 0.366 mmol) in AcCN (5 mL) is added 1,5-dibromopentane (**E-1b**). The reaction mixture is stirred at 110 °C for 8 h and afterwards the solvent is evaporated under reduced pressure. The residue is resolved in water and extracted with DCM. The organic layer is dried over $MgSO_4$, filtered and the solvent is removed under vacuum. The crude product is purified by normal phase chromatography (cyclohexane/EtOAc 7:3) to obtain product **B-2a**.

Experimental procedure for the synthesis of **B-2p**:

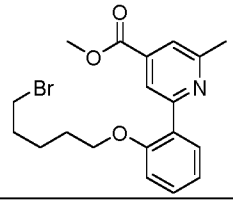
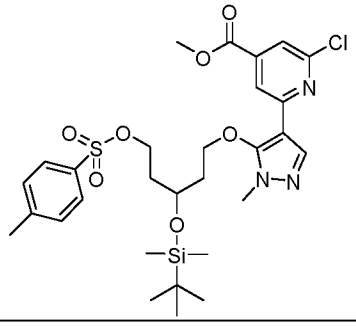
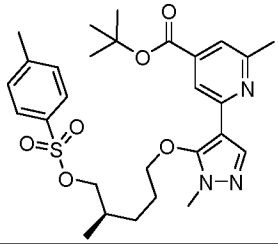
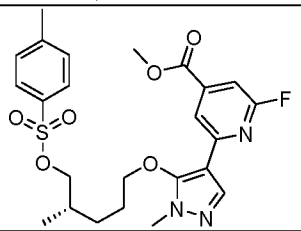
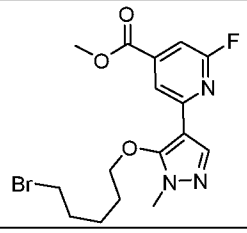
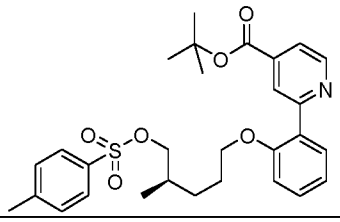


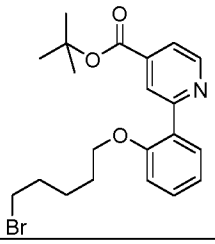
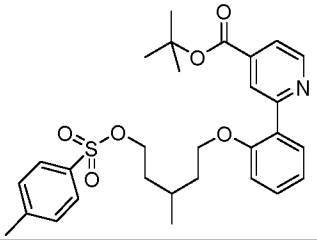
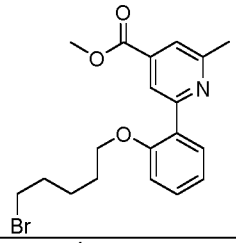
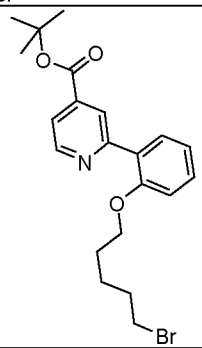
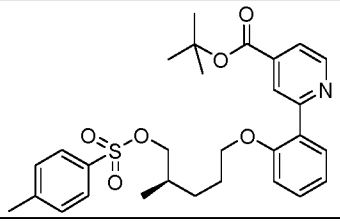
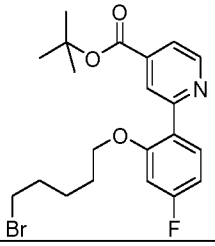
B-1h **E-1a** **B-2p**

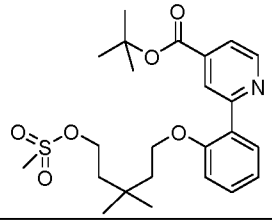
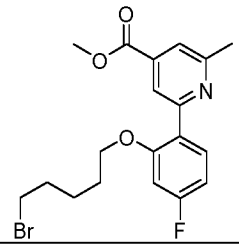
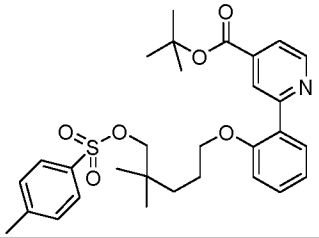
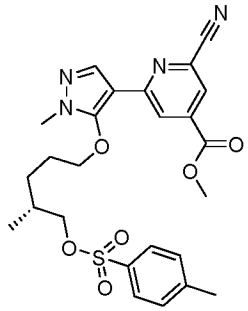
To a stirred solution of **B-1h** (1500 mg, 5.81 mmol) in AcCN (30 mL) and DMF (30 mL) is added K_2CO_3 (1.20 g, 8.71 mmol) and cooled down to 0 °C. To this reaction mixture is added a solution of **E-1a** (5.0 g, 11.6 mmol) and the mixture is stirred at this temperature for 16 h.The solvents are evaporated under reduced pressure and water is added and the mixture is extracted with DCM. The collected organic phase is dried over Na_2SO_4 and the solvents are evaporated under reduced pressure. The crude product is purified by flash chromatography with DCM:MeOH (50:1) yielding **B-2p**.

The following intermediates **B-2** (table 10) are available in an analogous manner starting from different building blocks **B-1** and **E-1**.

Table 10:

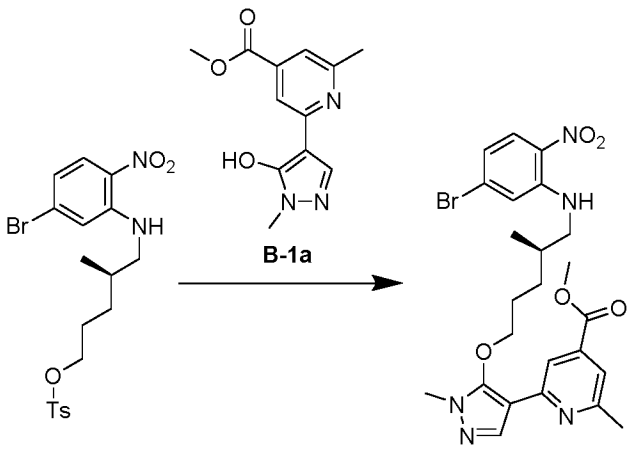
#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
B-2a		$(M+H)^+$ = 410.2/412.2; $t_{Ret.}$ = 0.96	4_BAS_PN
B-2b		$(M+H)^+$ = 638.2 $t_{Ret.}$ = 1.05	2_FEC_PN
B-2c		$(M+H)^+$ = 544.0 $t_{Ret.}$ = 1.80	LCMS3, basisch1
B-2d		$(M+H)^+$ = 506 $t_{Ret.}$ = 1.51	LCMS3, basisch1
B-2e		$(M+H)^+$ = 400.0 $t_{Ret.}$ = 1.43	LCMS3, basisch1
B-2f		$(M+H)^+$ = 526.0 $t_{Ret.}$ = 1.04	LCMSBAS1

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
B-2g		$(M+H)^+$ = 420.0/422.0 $t_{Ret.}$ = 1.74	LCMSBAS1
B-2h		$(M+H)^+$ = 526.2 $t_{Ret.}$ = 1.02	4_BAS_PN
B-2i		$(M+H)^+$ = 392 $t_{Ret.}$ = 1.59	LCMSBAS1
B-2j		$(M+H)^+$ = 420/422 $t_{Ret.}$ = 1.69	LCMSBAS1
B-2k		$(M+H)^+$ = 526 $t_{Ret.}$ = 1.04	LCMSBAS1
B-2l		$(M+H)^+$ = 438 $t_{Ret.}$ = 1.72	LCMSBAS1

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
B-2m		$(M+H)^+$ = 464 $t_{Ret.}$ = 1.58	LCMSBAS1
B-2n		$(M+H)^+$ = 410 $t_{Ret.}$ = 1.60	LCMSBAS1
B-2o		$(M+H)^+$ = 540.2 $t_{Ret.}$ = 1.04	4_BAS_PN
B-2p		$(M+H)^+$ = 513; $t_{Ret.}$ = 1.55	LCMS3, basisch1

Synthesis of intermediates C-3

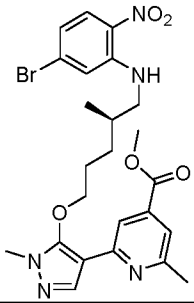
Experimental procedure for the synthesis of **C-3a**:

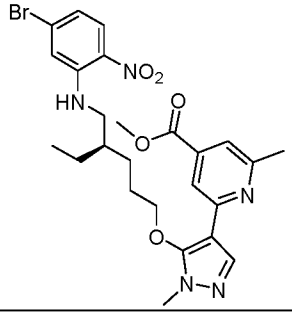
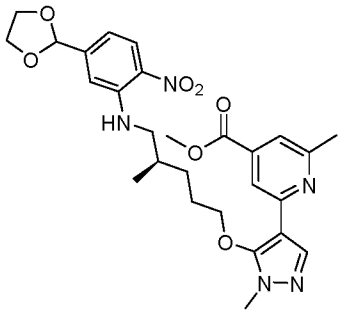
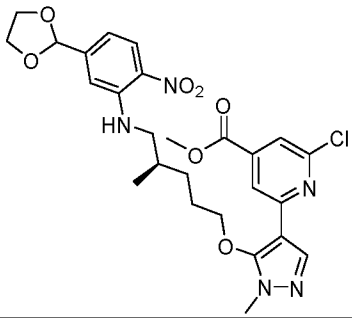
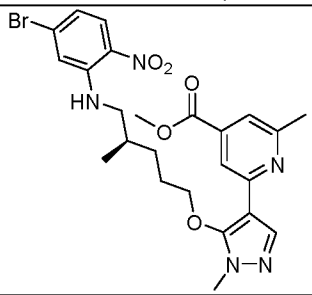
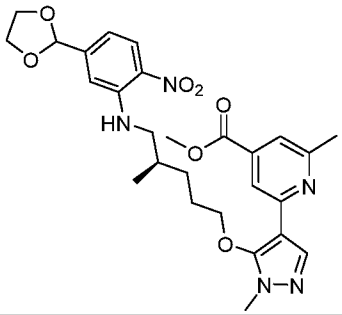


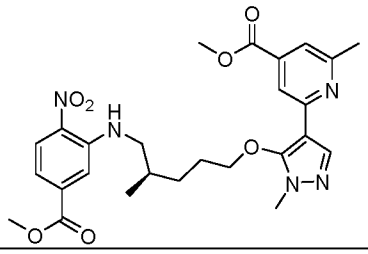
The starting materials **A-3a** (3.1 g, 7.34 mmol), **B-1a** (2.3 g, 8.84 mmol) and K_2CO_3 (3.1 g, 22.01 mmol) are dissolved in AcCN (208 mL) and the reaction mixture is stirred under reflux for 12 h. Then the reaction mixture is filtered and washed with AcCN. The solvent is evaporated from the filtrate under reduced pressure. The residue is purified by normal phase chromatography (cyclohexane/EtOAc) to afford product **C-3a**.

The following intermediates **C-3** (table 11) are available in an analogous manner starting from different building blocks **A-3** and **B-1**.

Table 11:

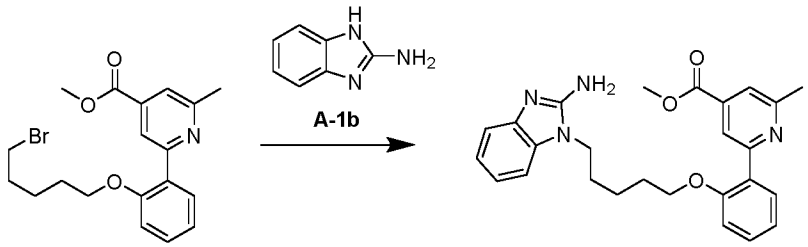
#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-3a		$(M+H)^+$ = 546; $t_{Ret.}$ = 1.8	LCMS3, basisch_1

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-3b		$(M+H)^+$ = 560/562; $t_{Ret.}$ = 1.24	VAB
C-3c		$(M+H)^+$ = 543; $t_{Ret.}$ = 1.07	VAB
C-3d		$(M+H)^+$ = 560/562; $t_{Ret.}$ = 1.12	VAB
C-3e		$(M+H)^+$ = 546/548; $t_{Ret.}$ = 1.17	VAB
C-3f		$(M+H)^+$ = 543; $t_{Ret.}$ = 1.07	VAB

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-3g		$(M+H)^+$ = 526.3; $t_{Ret.}$ = 1.11	VAB

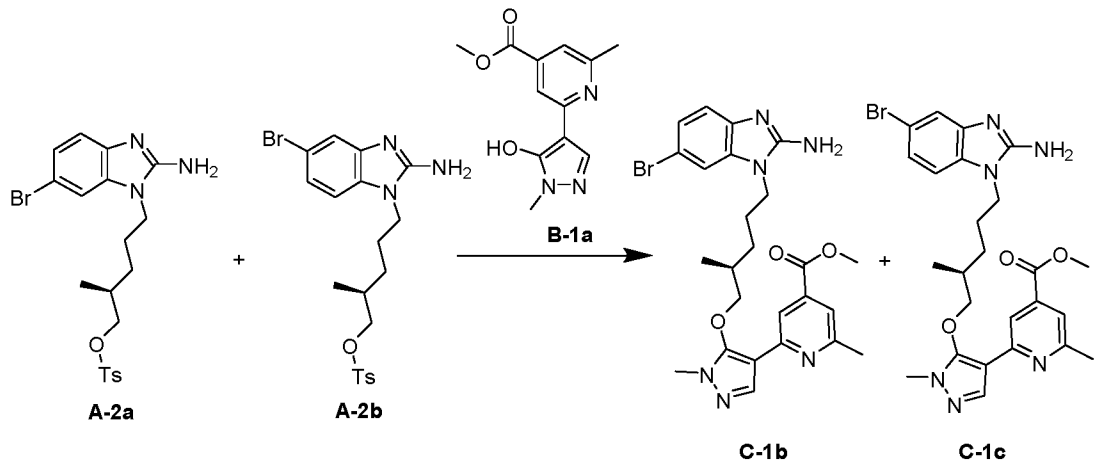
Synthesis of intermediates C-1 and C-4

Experimental procedure for the synthesis of **C-1a:**



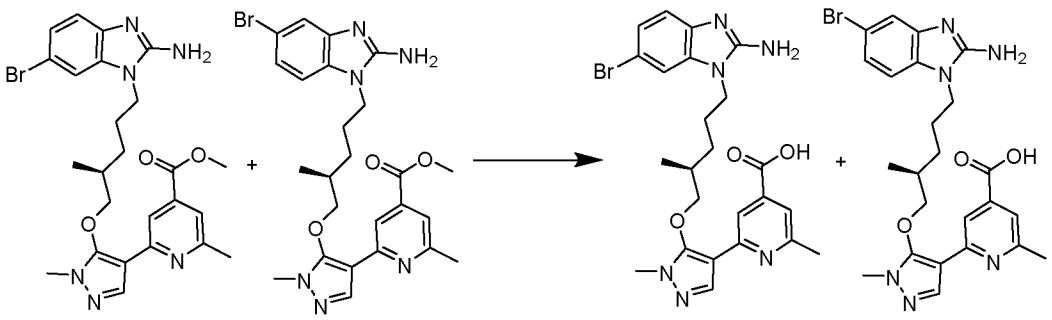
To a stirred solution of the starting material **B-2a** (60 mg, 0.15 mmol) in AcCN (1 mL) is added a suspension of K_2CO_3 (40 mg, 0.30 mmol) and **A-1b** (30 mg, 0.22 mmol) in AcCN (1 mL). The reaction mixture is stirred at 90 °C for 16 h, afterwards filtered and concentrated under vacuum. The residue is redissolved in water and extracted with DCM. The organic layer is dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by normal phase chromatography (DCM/MeOH 50:1) to yield the desired product **C-1a**.

Experimental procedure for the synthesis of **C-1b** and **C-1c**



A 1:1 mixture of the regioisomers **A-2a** and **A-2b** (132 mg, 0.28 mmol), starting material **B-1a** (70 mg, 0.28 mmol) and K_2CO_3 (59 mg, 0.43 mmol) are dissolved in AcCN (1 mL). The reaction mixture is stirred at 80 °C for 48 h. Then the reaction mixture is filtered and the precipitate is washed with AcCN. The solvent is evaporated under reduced pressure. The crude product is purified by reversed phase chromatography (method: prep. HPLC1) to obtain the 1:1 mixture of the ester-regioisomeres **C-1b** and **C-1c**.

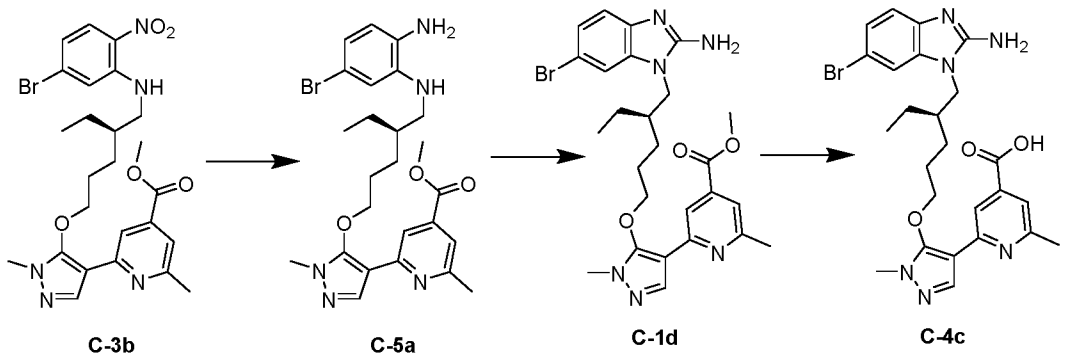
Experimental procedure for the synthesis of **C-4a** and **C-4b**



C-1b **C-1c** **C-4a** **C-4b**

Intermediates **C-1b** and **C-1c** obtained are dissolved in THF (2 mL), aqueous LiOH solution (0.5 mL; 50 mg, 2.1 mmol) is added and the mixture is stirred for 4 h at 50 °C. The organic solvents are evaporated and the aqueous phase adjusted to a pH value of 6-7. The precipitate is collected and dried yielding **C-4a** and **C-4b**.

Experimental procedure for the synthesis of **C-1d** and **C-4c**:



C-3b **C-5a** **C-1d** **C-4c**

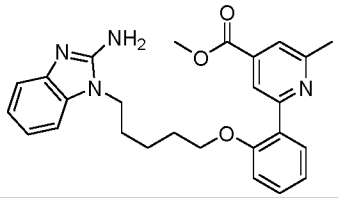
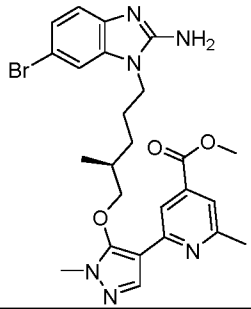
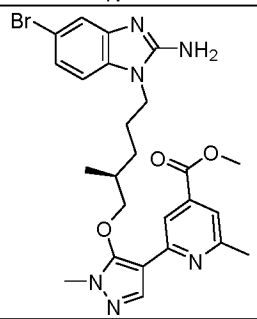
The starting material **C-3b** (3.0 g, 5.36 mmol) is dissolved in a mixture of THF (1000 mL) and cyclohexane (1000 mL). Then aqueous slurry of a RANEY-Nickel sponge (50 %) is added and the reaction mixture is stirred under a pressure of 5 bar hydrogen for 6 h. After that the reaction mixture is filtered and the solvent is evaporated under reduced pressure. The crude product **C-5a** is dissolved in toluene, again evaporated to dryness and used for

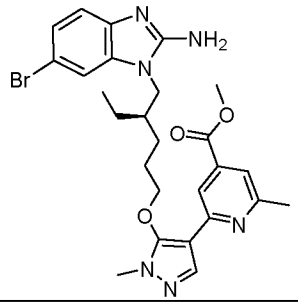
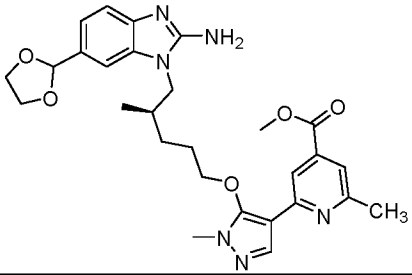
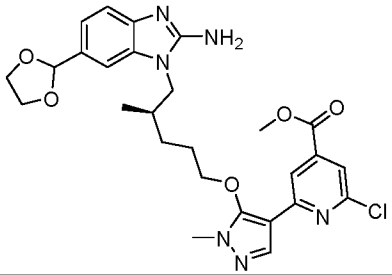
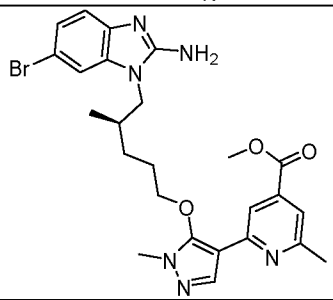
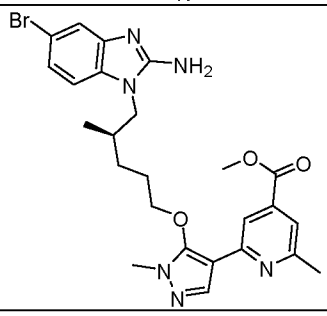
the subsequent reaction without further purification.

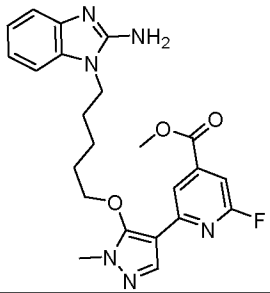
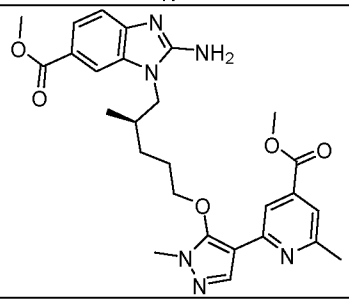
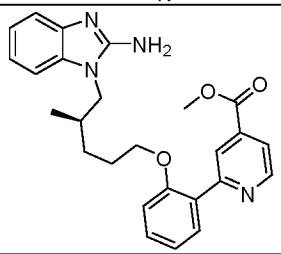
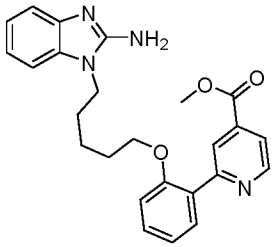
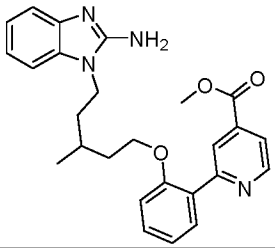
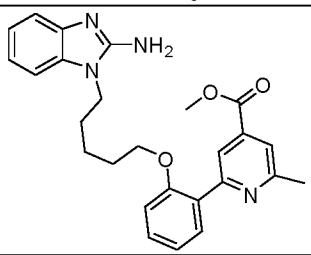
The intermediate product **C-5a** (2.7 g, 5.23 mmol) is dissolved in *tert*-butanol (20 mL). Then 3 M cyanic bromide in DCM (2.6 mL, 7.84 mmol) is added and the reaction mixture is stirred at 50 °C for 3 h. After that the reaction mixture is diluted with DCM and the reaction is quenched with a aqueous solution of $NaHCO_3$. After extraction with DCM, drying of the organic layer over $MgSO_4$ and filtration the solvent is evaporated under reduced pressure. The crude product is purified by reversed phase chromatography (method: prep. HPLC1) yielding the ester **C-1d**, which is dissolved in THF and treated with an aqueous 1 M NaOH solution (400 µL). After 1 h the solvents are evaporated yielding product **C-4c**.

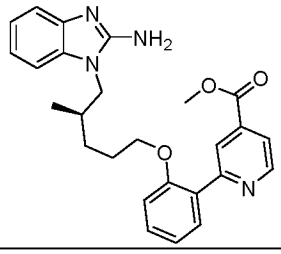
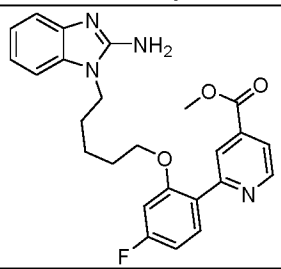
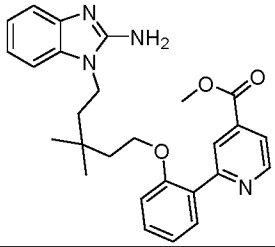
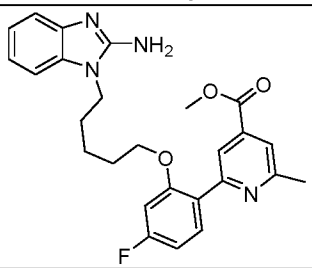
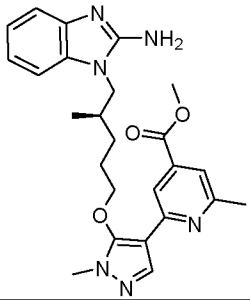
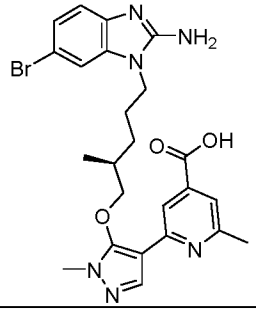
The following intermediates **C-1** and **C-4** (table 12) are available in an analogous manner starting from different building blocks **A-1**, **A-2**, **B-1, B-2** and **C-3**.

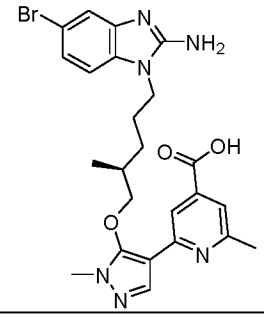
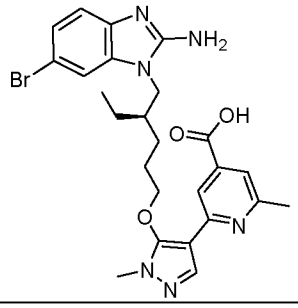
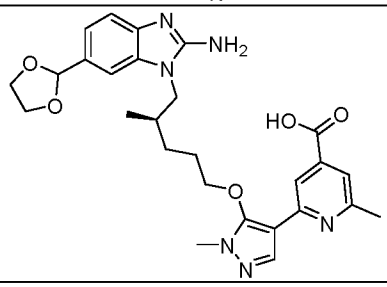
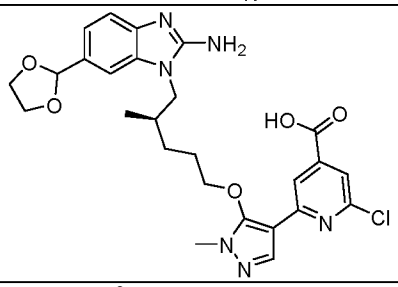
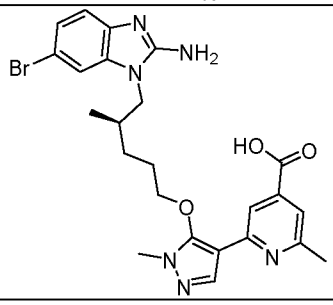
Table 12:

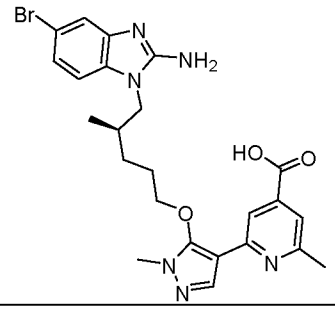
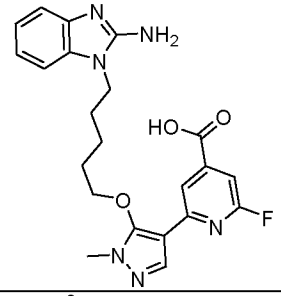
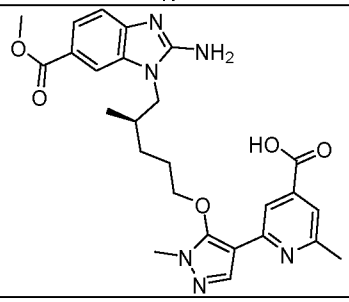
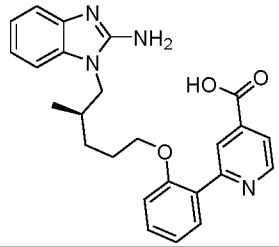
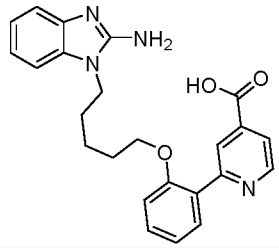
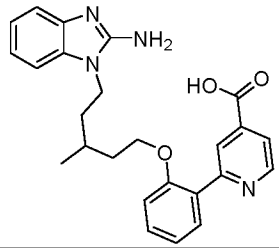
#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-1a		$(M+H)^+$ = 455; $t_{Ret.}$ = 0.77	4_Bas_PN
C-1b			
C-1c			

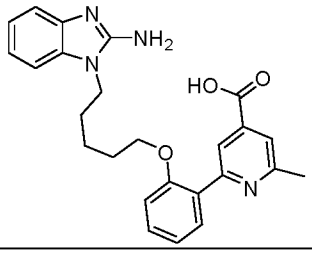
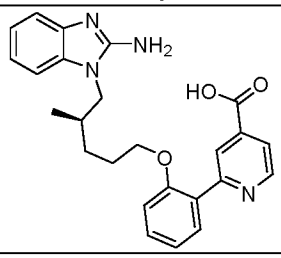
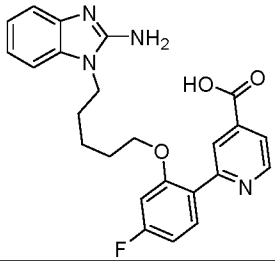
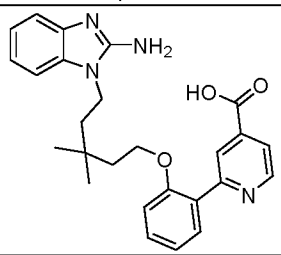
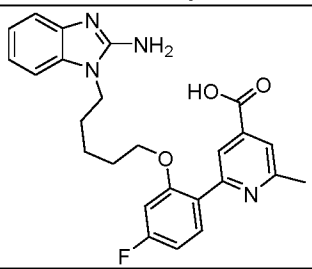
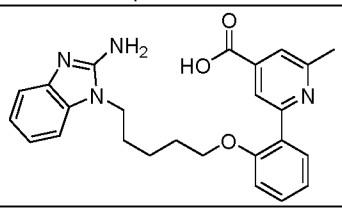
#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-1d			
C-1e			
C-1f			
C-1g			
C-1h			

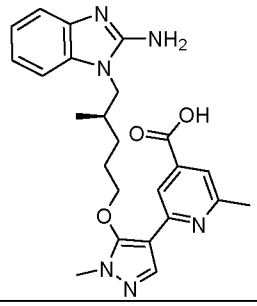
#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-1i			
C-1j		$(M+H)^+$ =521.3 $t_{Ret.}$ =0.901	VAB
C-1k			
C-1l			
C-1m			
C-1n			

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-1o			
C-1p			
C-1q			
C-1r			
C-1s			
C-4a		$(M+H)^+$ = 527; $t_{Ret.}$ =0.95	LCMS3, basisch_1

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-4b		$(M+H)^+$ = 527; $t_{Ret.}$ =0.95	LCMS3, basisch_1
C-4c		$(M+H)^+$ = 541/543 $t_{Ret.}$ = 0.74	VAB
C-4d		$(M+H)^+$ = 521 $t_{Ret.}$ = 0.61	VAB
C-4e		$(M+H)^+$ = 523 $t_{Ret.}$ = 1.41	LCMS3, basisch_1
C-4f		$(M+H)^+$ = 527/529	LCMS3, basisch_1

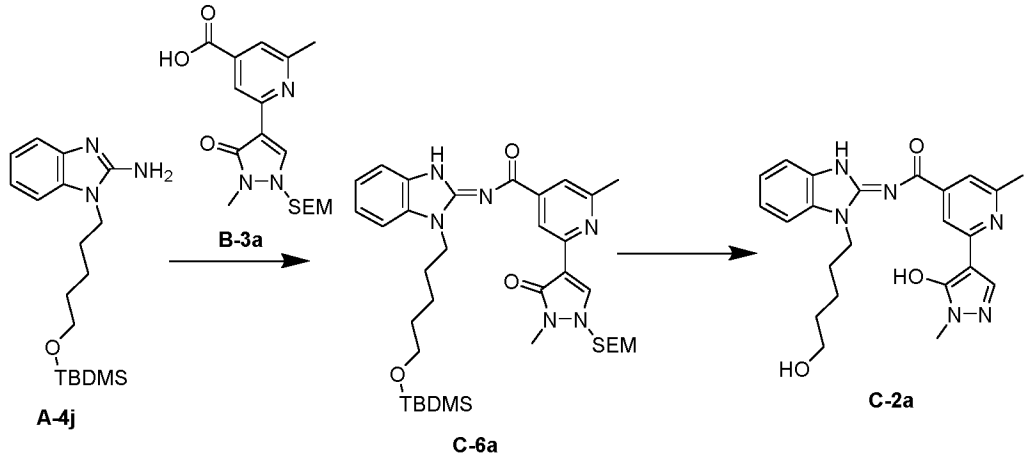
#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-4g		$(M+H)^+$ = 527/529	LCMS3, basisch_1
C-4h		$(M+H)^+$ =439.0 $t_{Ret.}$ =0.31	4_BAS_PN
C-4i			
C-4j		$(M+H)^+$ =431.2 $t_{Ret.}$ =0.44	4_BAS_PN
C-4k		$(M+H)^+$ =417.2 $t_{Ret.}$ =0.44	4_BAS_PN
C-4l		$(M+H)^+$ =431.2 $t_{Ret.}$ =0.42	4_BAS_PN

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-4m		$(M+H)^+$ =431.2 $t_{Ret.}$ =0.42	4_BAS_PN
C-4n		$(M+H)^+$ =431.2 $t_{Ret.}$ =0.44	4_BAS_PN
C-4o		$(M+H)^+$ =435.2 $t_{Ret.}$ =0.42	4_BAS_PN
C-4p		$(M+H)^+$ =445.2 $t_{Ret.}$ =0.43	4_BAS_PN
C-4q		$(M+H)^+$ =449.2 $t_{Ret.}$ =0.42	4_BAS_PN
C-4r			

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-4s			

Synthesis of intermediates C-2

Experimental procedure for the synthesis of **C-2a**:

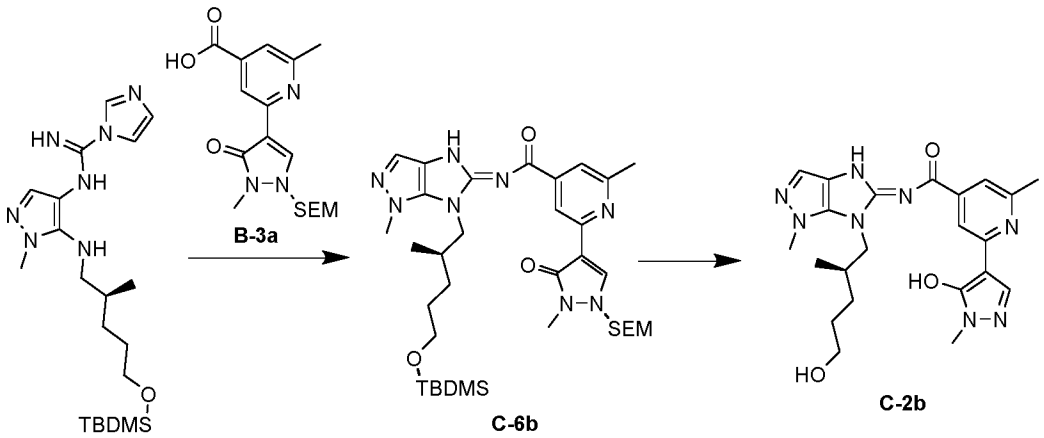


Starting material **B-3a** (1.2 g, 3.42 mmol) is dissolved in 1,4-dioxane (33 mL). TEA (2.9 mL) and HATU (1.6 g, 4.12 mmol) are added to the solution, which is stirred at rt for 20 min. Then **A-4j** (1.1 g, 3.42 mmol) is added and the reaction mixture is stirred at rt for 48 h. After that extraction is done using DCM/water. The organic layer is dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure to obtain the crude intermediate product **C-6a**, which is used for further synthesis without any additional purification step.

The crude intermediate product **C-6a** (512 mg, 0.42 mmol) is dissolved in EtOH (10 mL) and a 4 M solution of HCl in 1,4-dioxane (5.0 mL, 20.00 mmol) is added to the solution. The reaction mixture is stirred at rt for 16 h. Then a saturated aqueous solution of $NaHCO_3$ is added and the reaction mixture is extracted twice with DCM. The combined organic layers are dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by reversed phase chromatography (prep. HPLC1)

to afford product **C-2a**.

Experimental procedure for the synthesis of **C-2b**:



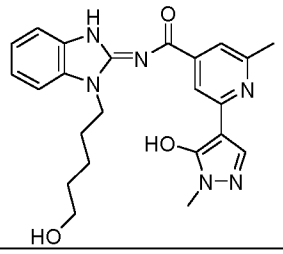
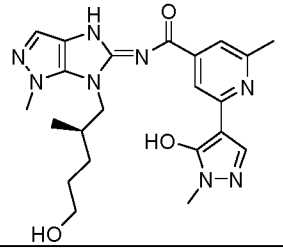
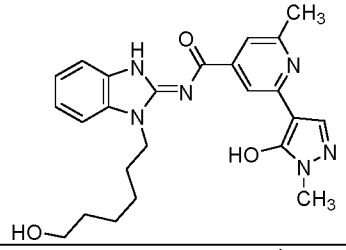
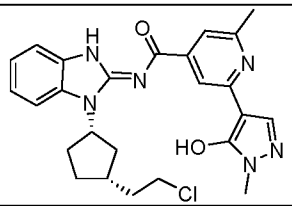
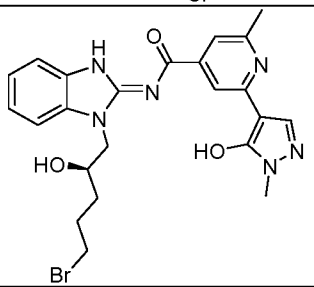
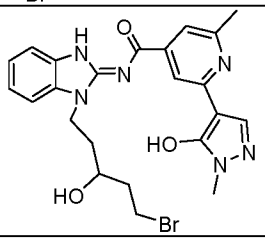
Starting material **B-3a** (1.0 g, 2.75 mmol), HATU (1.1 g, 2.84 mmol) and DIPEA (2.0 mL, 11.76 mmol) are dissolved in 1,4-dioxane (20 mL) and the reaction mixture is stirred at 55 °C for 30 min. Then **A-5a** (1.0 g, 2.38 mmol) is added to the reaction mixture and stirring is continued at 55 °C for 1 h followed by stirring at rt for 48 h. After that the reaction mixture is concentrated under reduced pressure and the residue is purified by reversed phase chromatography (method: prep. HPLC1) to obtain the intermediate product **C-6b**.

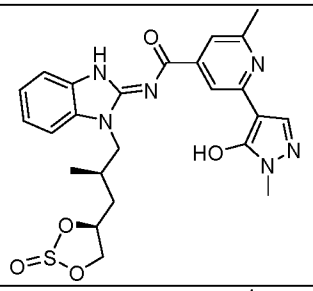
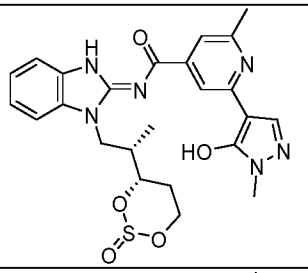
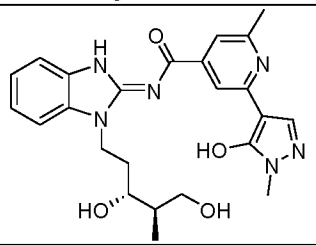
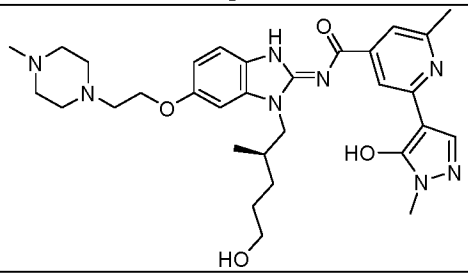
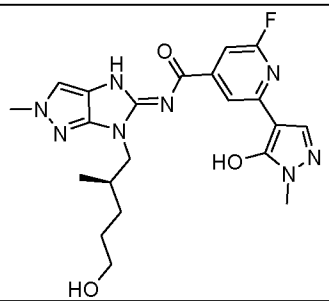
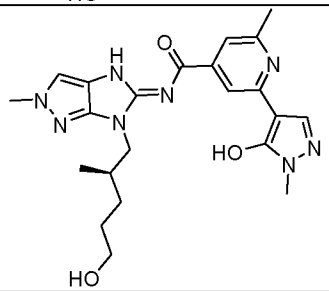
The intermediate product **C-6b** (633 mg, 0.91 mmol) is dissolved in THF (20 mL) and a 1 M solution of TBAF in THF (3.5 mL, 3.50 mmol) is added to the solution. The reaction mixture is stirred at rt for 72 h. Stirring is continued at 50 °C for 72 h. After that acetone is added to the reaction mixture and the solvent is evaporated under reduced pressure. The solid is suspended in AcCN and the solid material is collected by filtration yielding the product **C-2b**.

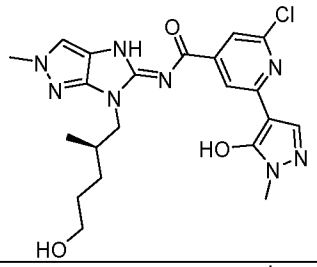
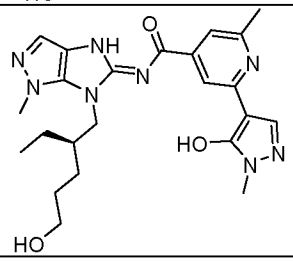
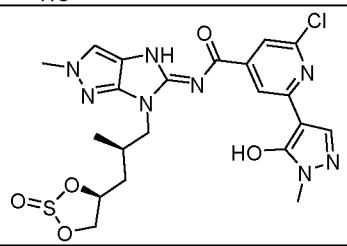
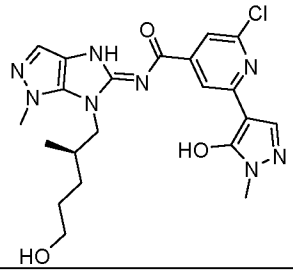
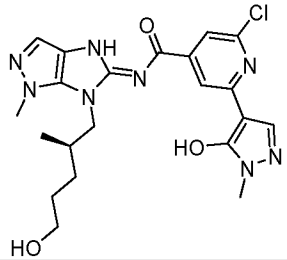
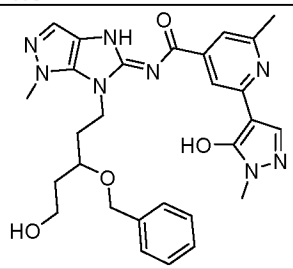
The following intermediates **C-2** (table 13) are available in an analogous manner starting from different building blocks **A-4**, **A-5** and **B-3**.

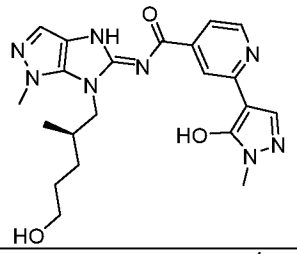
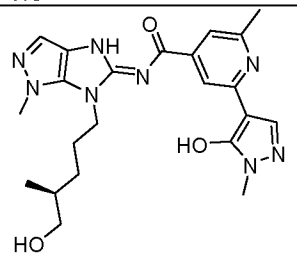
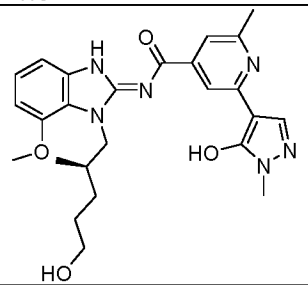
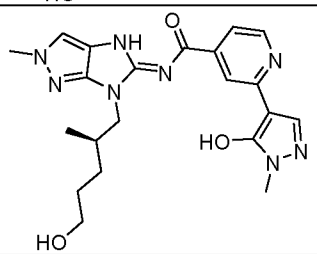
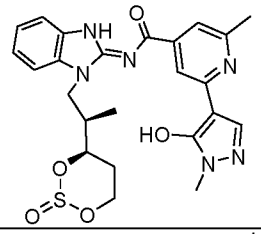
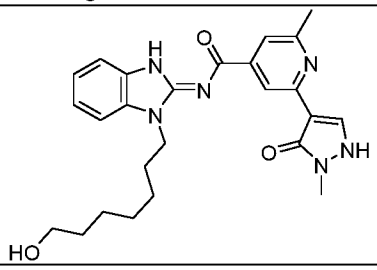
Table 13:

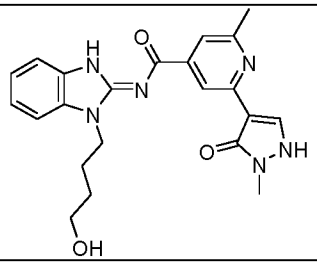
#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-2a		$(M+H)^+$ = 435; $t_{Ret.}$ = 0.8	VAB
C-2b		$(M+H)^+$ = 453; $t_{Ret.}$ = 0.6	VAB
C-2c		$(M+H)^+$ = 499; $t_{Ret.}$ = 0.79	VAB
C-2d		$(M+H)^+$ = 461; $t_{Ret.}$ = 1.08	LCMS3, basisch1
C-2e		$(M+H)^+$ = 513/515; $t_{Ret.}$ = 0.86	VAB
C-2f		$(M+H)^+$ = 513; $t_{Ret.}$ = 1.08	LCMS3, basisch1

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-2g		$(M+H)^+$ = 511; $t_{Ret.}$ = 0.89	VAB
C-2h		$(M+H)^+$ = 511.2; $t_{Ret.}$ = 0.53	4_BAS_PN.M
C-2i		$(M+H)^+$ = 447; $t_{Ret.}$ = 1.15	LCMS3, basisch1
C-2j		$(M+H)^+$ = 591; $t_{Ret.}$ = 0.88	LCMS3, basisch1
C-2k		$(M+H)^+$ = 457.0 $t_{Ret.}$ = 0.79	LCMS3, basisch1
C-2l		$(M+H)^+$ = 453; $t_{Ret.}$ = 0.633	VAB

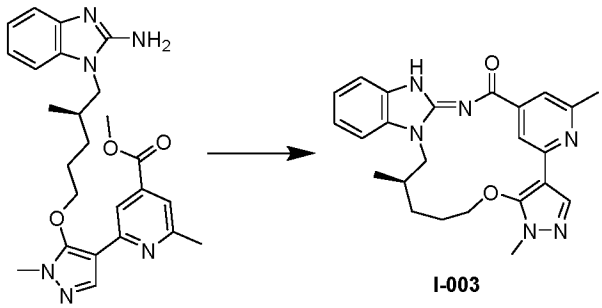
#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-2m		$(M+H)^+$ = 473.0; $t_{Ret.}$ = 0.84	LCMS3, basisch1
C-2n		$(M+H)^+$ = 467; $t_{Ret.}$ = 0.669	VAB
C-2o		$t_{Ret.}$ = 0.76	2_FEC_PN.M
C-2p		$(M+H)^+$ = 473; $t_{Ret.}$ = 0.8	LCMS3, basisch1
C-2q		$(M+H)^+$ = 473.2; $t_{Ret.}$ = 0.31	4_BAS_PN
C-2r		$(M+H)^+$ = 545; $t_{Ret.}$ = 0.67	VAB

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-2s		$(M+H)^+$ = 439; $t_{Ret.}$ = 0.72	LCMS3, basisch1
C-2t		$(M+H)^+$ = 453.2; $t_{Ret.}$ = 0.611	VAB
C-2u		$(M+H)^+$ = 609.3; $t_{Ret.}$ = 1.1	VAB
C-2v		$(M+H)^+$ = 438.0; $t_{Ret.}$ = 0.78	LCMS3, basisch1
C-2w		$(M+H)^+$ = 511.1; $t_{Ret.}$ = 0.817	VAB
C-2x		$(M+H)^+$ = 463.0; $t_{Ret.}$ = 1.10	LCMS3, basisch1

#	structure	MS $(M+H)^+$; $t_{Ret.}$ HPLC [min]	HPLC-MS method
C-2y		$(M+H)^+$ = 421; $t_{Ret.}$ = 0.72	VAB

Preparation of compounds (I) according to the invention

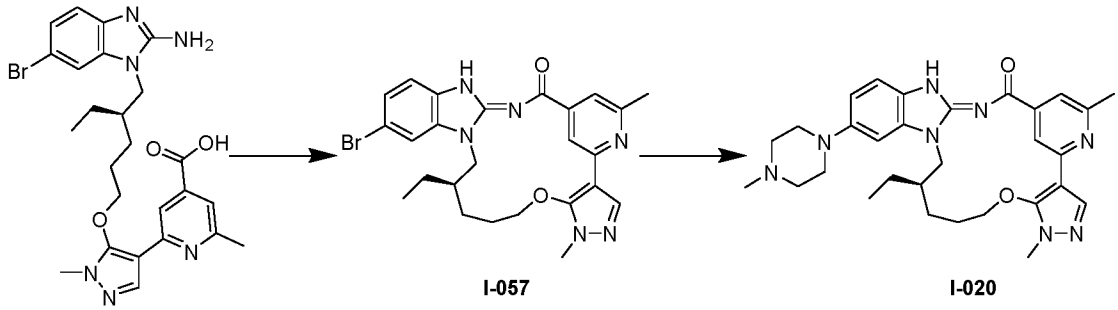
Experimental procedure for the synthesis of **I-003** (method A)



C-1s **I-003**

Starting material **C-1s** (34 mg, 0.07 mmol) is dissolved in DMSO (0.8 mL), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (0.02 mL, 0.13 mmol) is added and the reaction mixture is stirred at 80 °C for 48 h. Then the reaction mixture is filtered and purification is done by reversed phase chromatography (method: prep. HPLC1) to afford product **I-003**.

Experimental procedure for the synthesis of **I-057** and **I-020** (method A')



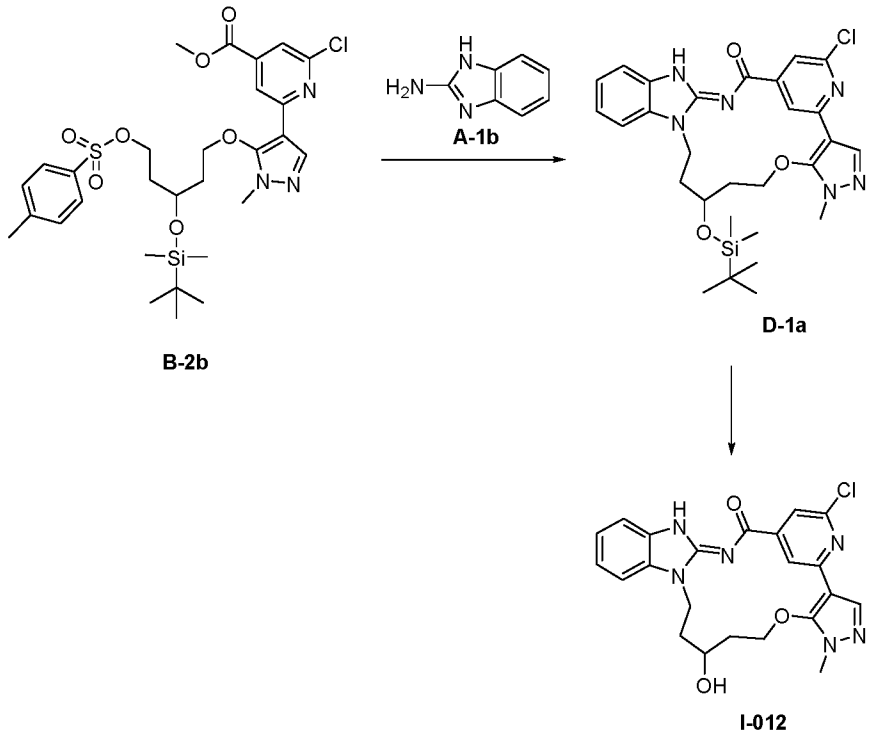
C-4c **I-057** **I-020**

C-4c (227 mg, 0.421 mmol) and DIPEA (0.37 mL, 2.10 mmol) are dissolved in dioxane (5 mL) and the reaction mixture is stirred at 25 °C for 10 min. Then HATU (240 mg, 0.63 mmol) is added and stirring of the reaction mixture at 25 °C is continued for 2 h. The solvent is evaporated under reduced pressure and the crude product is purified by normal phase chromatography (EtOAc/MeOH 90:10) to afford **I-057**.

I-057 (50 mg; 0.096 mmol) is dissolved in dioxane (750 µL) and *N*-methylpiperazine (0.042 mL; 0.38 mmol) and methansulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)paladium(II) (8.6 mg; 0.01 mmol) is added. The reaction mixture is flushed with argon and LiHMDS (0.28 mL; 0.28 mmol) is slowly added at rt. Then the reaction mixture is stirred at 65 °C for 30 min. The solvents are evaporated under reduced pressure and the crude product is purified by

reversed phase chromatography (method: prep. HPLC1) to yield product **I-020**.

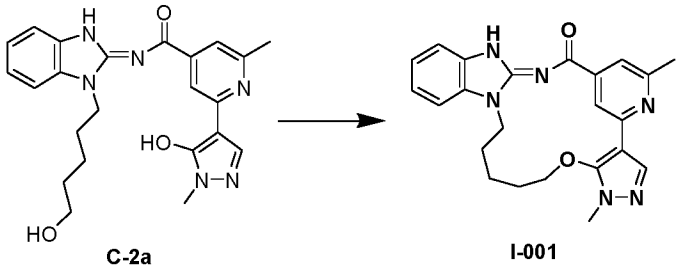
Experimental procedure for the synthesis of **I-012** (method A)



B-2b (1200 mg, 1.88 mmol) is dissolved in AcCN (10 mL) and K_2CO_3 (393 mg, 2.82 mmol) and **A-1b** (275 mg, 2.07 mol) are added. The reaction mixture is stirred at 100 °C for 4 d. The solvents are evaporated under reduced pressure and water is added and the mixture is extracted with DCM. The collected organic phase is dried over Na_2SO_4 and the solvents are evaporated under reduced preasure. The crude product is purified by column chromatography (40 g SiO_2, cyclohexane/EtOAc 1:1) yielding **D-1a** (HPLC-MS: $(M+H)^+$ = 567.0 , $t_{Ret.}$ = 1.86 min, method LCMS3, basisch_1).

Intermediate **D-1a** is dissolved in THF (2 mL) and TBAF (1 M in THF; 0.200 mL; 0.200 mmol;) is added. The reaction mixture is stirred at 25 °C for 18 h. The solvents are evaporated under reduced pressure and water is added and the mixture is extracted with DCM. The collected organic phase is dried over Na_2SO_4 and the solvents are evaporated under reduced pressure. The crude product is purified by reversed phase chromatography (method: prep. HPLC1) to yield product **I-012**.

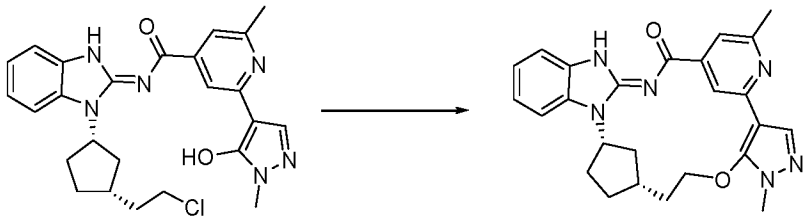
Experimental procedure for the synthesis of **I-001** (synthesis method B)



C-2a **I-001**

C-2a (50 mg, 0.12 mmol) is dissolved in THF (4.0 mL) and triphenylphosphine (130 mg, 0.47 mmol) is added to the solution. After the reaction mixture has been stirred at rt for 20 min diisopropyl azodicarboxylate (0.1 mL, 0.48 mmol) is added to the reaction mixture. Then the reaction is stirred at rt for 1 h. After that extraction is done using DCM/water. The organic layer is dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. The crude product is purified by reversed phase chromatography (method: prep. HPLC1) to yield product **I-001**.

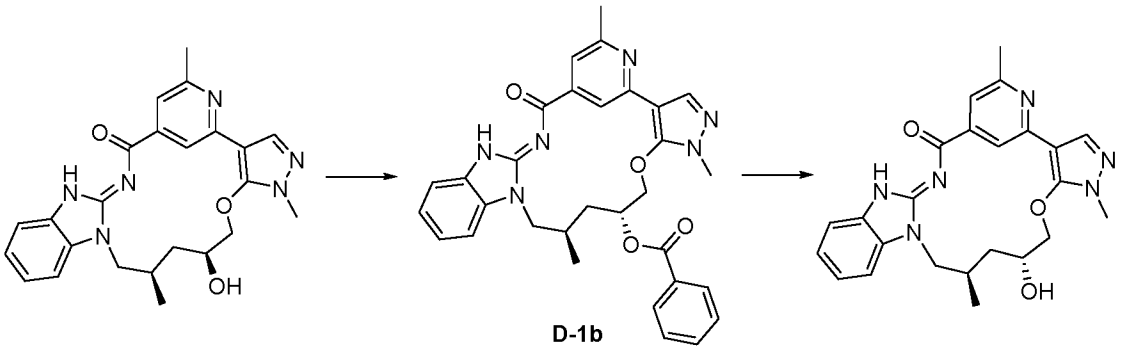
Experimental procedure for the synthesis of **I-006** (synthesis method B)



C-2d **I-006**

C-2d (25 mg, 0.052 mmol) is dissolved in dry AcCN (3 mL) and K_2CO_3 (43 mg, 0.31 mmol) is added. The mixture is stirred at 90 °C for 16 h. The reaction mixture is filtered off and is purified by reverse phase chromatography (prep. HPLC1 method) yielding **I-006**.

Experimental procedure for the synthesis of **I-014**

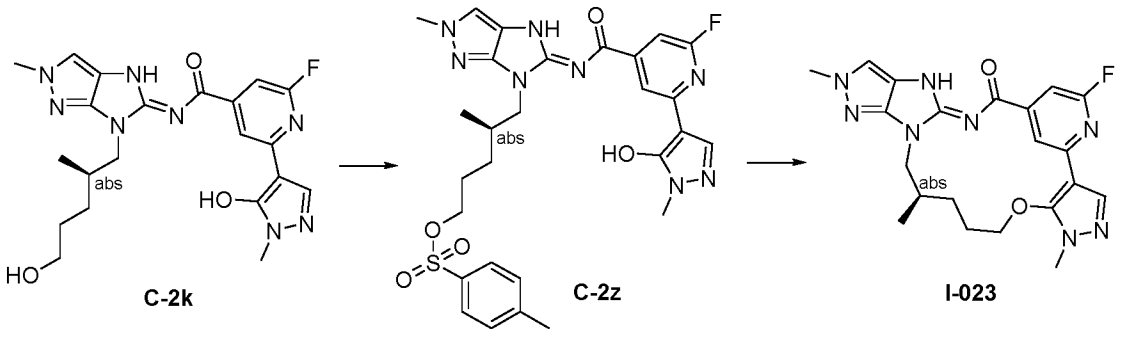


I-013 **D-1b** **I-014**

I-013 (50 mg, 0.11 mmol), benzoic acid (30 mg, 0.24 mmol) and triphenylphosphine (100 mg, 0,36 mmol) are dissolved in THF (5 mL) and diisopropyl azodicarboxylate (0.09 mL, 0.43 mmol) is added. The reaction mixture is shaken at rt for 16 h. The solvents are evaporated under reduced pressure and the crude product is purified using prep. HPLC1 method yielding intermediate **D-1b** (HPLC-MS: $(M+H)^+$ = 551, $t_{Ret.}$ = 0.83 min, method VAB).

Intermediate **D-1b** (43 mg, 0.074 mmol) is dissolved in 1,4-dioxan (0.5 mL) and LiOH (1 M solution, 0.5 mL) is added. The reaction is shaken at 25 °C for 3 h. The solvents are evaporated under reduced pressure and the crude product is purified using prep. HPLC1 method yielding **I-014**.

Experimental procedure for the synthesis of **I-023** (synthesis method B)



C-2k **C-2z** **I-023**

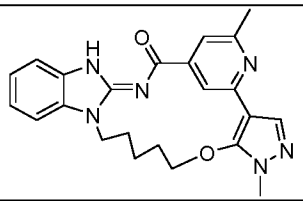
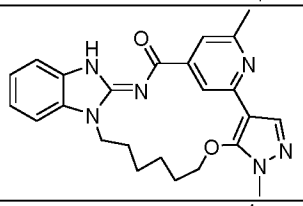
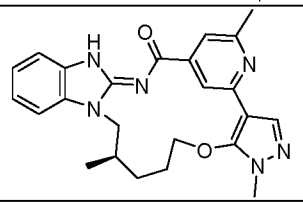
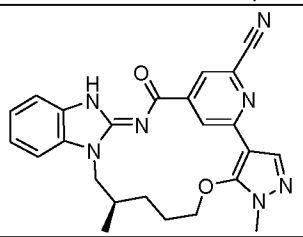
C-2k (160 mg, 0.35mmol) is dissolved in dry AcCN, K_2CO_3 (97 mg, 0.70 mmol) is added. Then *p*-toluensulfonyl chloride (80 mg, 0.42 mmol) is added. The reaction mixture is stirred at rt for 18 h. The solvents are evaporated under reduced pressure and water is added and the mixture is extracted with DCM. The collected organic phase is dried over

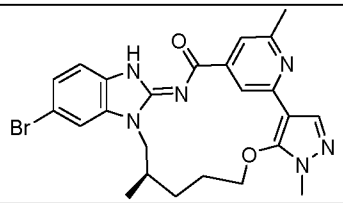
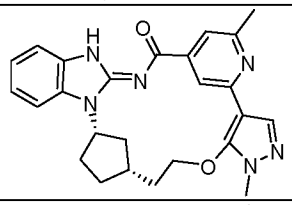
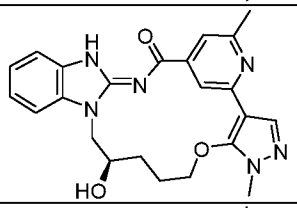
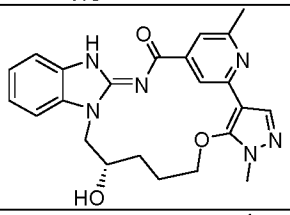
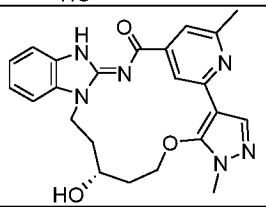
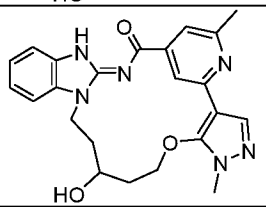
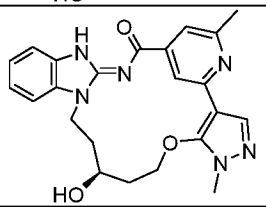
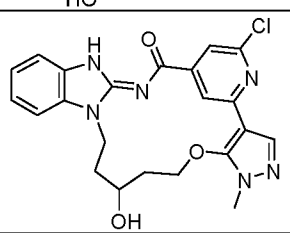
Na_2SO_4 and the solvents are evaporated under reduced pressure yielding intermediate **C-2z** (HPLC-MS: $(M+H)^+$ = 611, $t_{Ret.}$ = 0.65 min, method 2_FEC_PN).

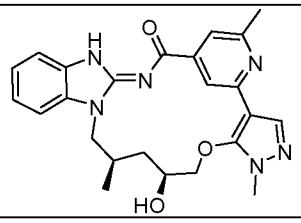
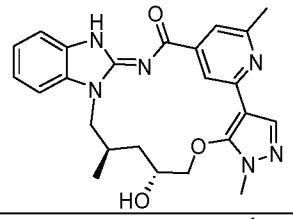
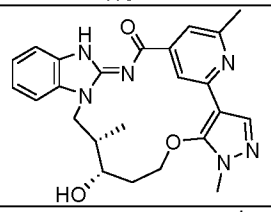
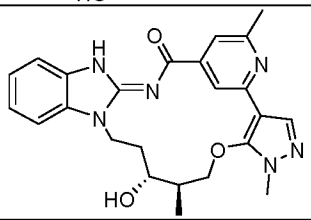
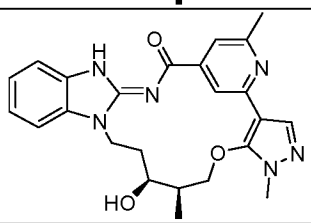
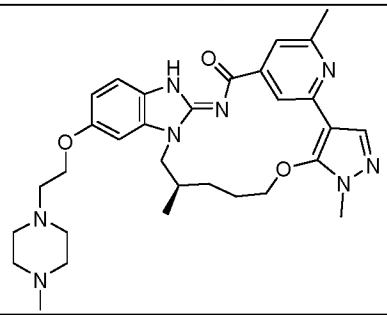
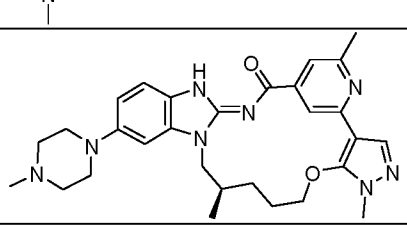
Intermediate **C-2z** (90 mg, 0.15 mmol) is dissolved in dry THF and K_2CO_3 (41 mg, 0.30 mmol) is added. The reaction mixture is stirred at 90 °C for 3 d. The solvents are evaporated under reduced pressure and water is added and the mixture is extracted with DCM. The collected organic phase is dried over Na_2SO_4 and the solvents are evaporated under reduced pressure. The crude producte is purified by flash chromatography with DCM:MeOH (10:1) yielding **I-023**.

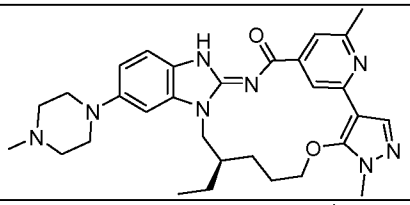
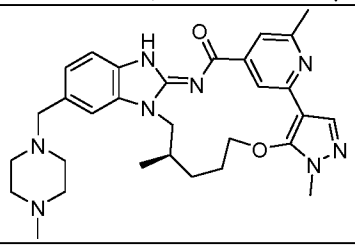
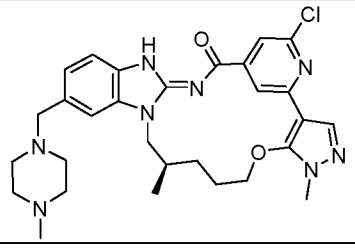
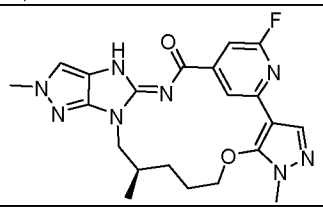
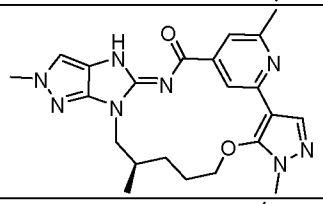
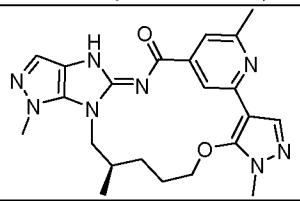
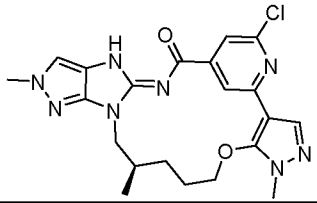
The following compounds **(I)** (table 14) are available in an analogous manner starting from different building blocks **A-1**, **B-2**, **C-1** and **C-2** or by derivatization of compounds **(I)** initially obtained.

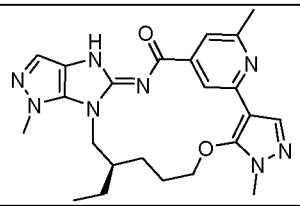
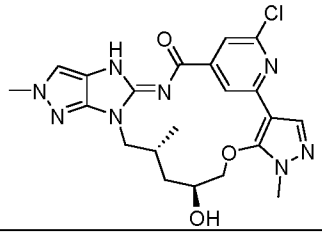
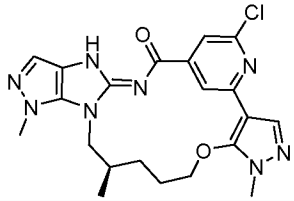
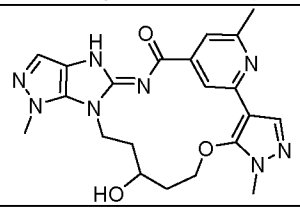
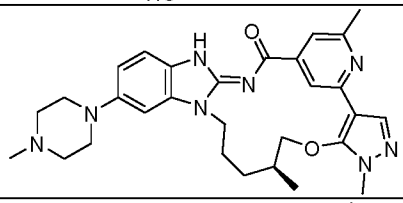
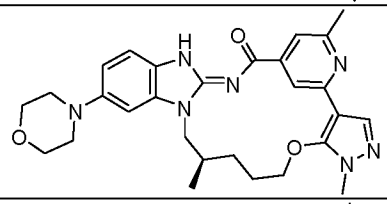
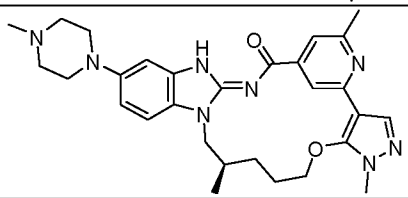
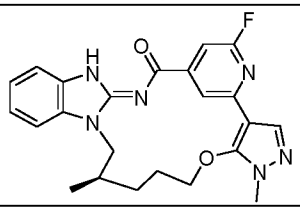
Table 14:

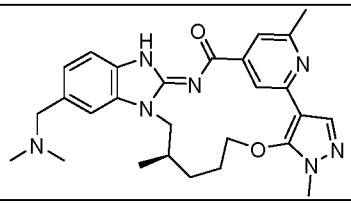
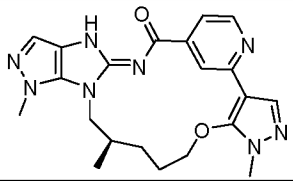
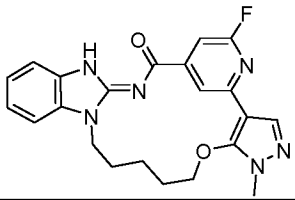
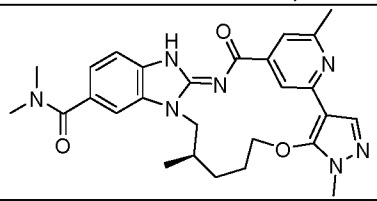
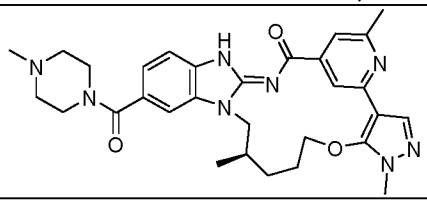
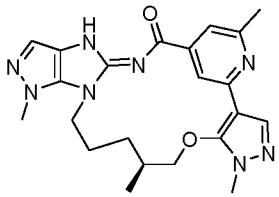
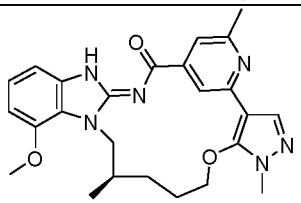
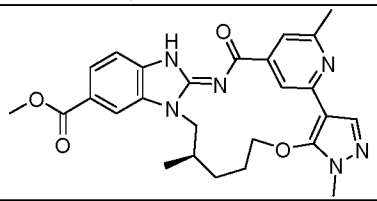
#	structure	method	IC_{50} [nM]	MS $(M+H)^+$ t_{Ret} HPLC [min]	HPLC-MS method
I-001		B	1.2	$(M+H)^+$ = 417, $t_{Ret.}$ = 1.3	LCMS3, basisch_1
I-002		B	4.2	$(M+H)^+$ = 431, $t_{Ret.}$ = 1.4	LCMS3, basisch_1
I-003		A	0.8	$(M+H)^+$ = 431, $t_{Ret.}$ = 1.4	LCMS3, basisch_1
I-004		C	1.3	$(M+H)^+$ = 442, $t_{Ret.}$ = 1.5	LCMS3, basisch_1

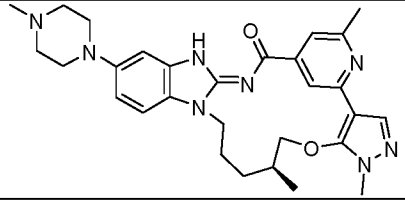
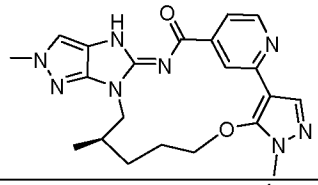
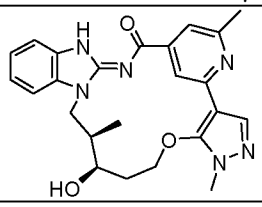
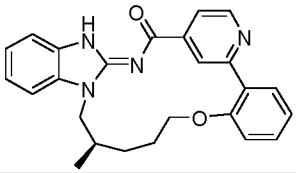
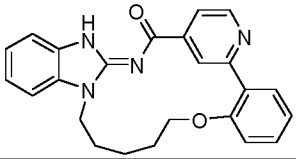
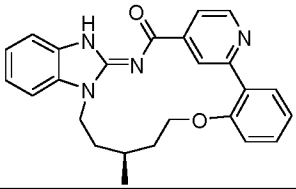
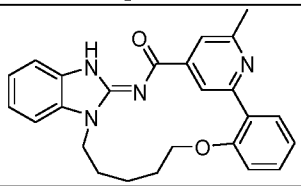
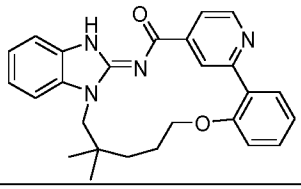
#	structure	method	IC_{50} [nM]	MS $(M+H)^+$ t_{Ret} HPLC [min]	HPLC-MS method
I-005		A'	4	$(M+H)^+$ = 509, $t_{Ret.}$ = 1.49	LCMS3, basisch_1
I-006		B	17	$(M+H)^+$ = 443, $t_{Ret.}$ = 1.4	LCMS3, basisch_1
I-007		B	1.1	$(M+H)^+$ = 433, $t_{Ret.}$ = 1.1	LCMS3, basisch_1
I-008			7.4	$(M+H)^+$ = 433, $t_{Ret.}$ = 1.1	LCMS3, basisch_1
I-009		B	1.0	$(M+H)^+$ = 433, $t_{Ret.}$ = 1.1	LCMS3, basisch_1
I-010		B	1.2	$(M+H)^+$ = 433, $t_{Ret.}$ = 1.1	LCMS3, basisch_1
I-011		B	6.5	$(M+H)^+$ = 433, $t_{Ret.}$ = 1.1	LCMS3, basisch_1
I-012		C	5.2	$(M+H)^+$ = 453, $t_{Ret.}$ = 1.2	LCMS3, basisch_1

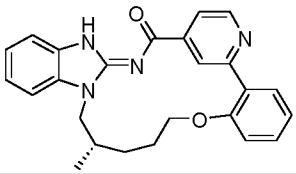
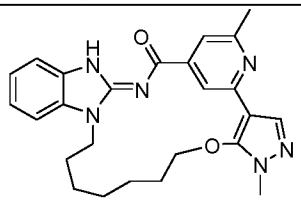
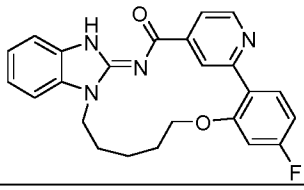
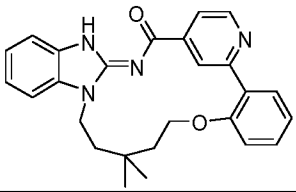
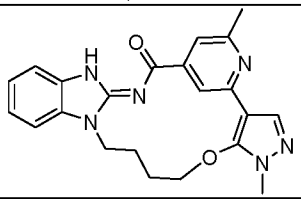
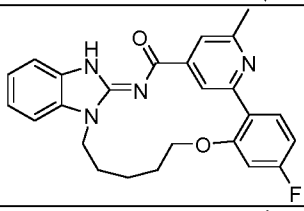
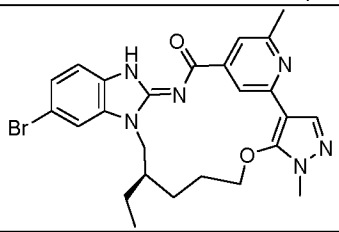
#	structure	method	IC_{50} [nM]	MS $(M+H)^+$ t_{Ret} HPLC [min]	HPLC-MS method
I-013		B	0.7	$(M+H)^+$ = 447, $t_{Ret.}$ = 1.2	LCMS3, basisch_1
I-014			4.2	$(M+H)^+$ = 447, $t_{Ret.}$ = 1.2	LCMS3, basisch_1
I-015		B	0.6	$(M+H)^+$ = 447, $t_{Ret.}$ = 1.2	LCMS3, basisch_1
I-016		B	0.8	$(M+H)^+$ = 447, $t_{Ret.}$ = 1.2	LCMS3, basisch_1
I-017			8.9	$(M+H)^+$ = 447, $t_{Ret.}$ = 1.2	LCMS3, basisch_1
I-018		B	0.5	$(M+H)^+$ = 573, $t_{Ret.}$ = 1.23	LCMS3, basisch_1
I-019		A	0.6	$(M+H)^+$ = 529, $t_{Ret.}$ = 0.43	LCMS3, basisch_1

#	structure	method	IC_{50} [nM]	MS $(M+H)^+$ t_{Ret} HPLC [min]	HPLC-MS method
I-020		A	0.6	$(M+H)^+$ = 543, $t_{Ret.}$ = 1.37	LCMS1, basisch_1
I-021		A	0.6	$(M+H)^+$ = 543, $t_{Ret.}$ = 1.24	LCMS3, basisch_1
I-022		A	0.8	$(M+H)^+$ = 563, $t_{Ret.}$ = 1.41	LCMS3, basisch_1
I-023		B	0.5	$(M+H)^+$ = 439, $t_{Ret.}$ = 1.22	LCMS3, basisch_1
I-024		B	0.6	$(M+H)^+$ = 435, $t_{Ret.}$ = 1.14	LCMS3, basisch_1
I-025		B	0.8	$(M+H)^+$ = 435, $t_{Ret.}$ = 1.1	LCMS3, basisch_1
I-026		B	1.5	$(M+H)^+$ = 455, $t_{Ret.}$ = 1.28	LCMS3, basisch_1

#	structure	method	IC_{50} [nM]	MS $(M+H)^+$ t_{Ret} HPLC [min]	HPLC-MS method
I-027		B	1.5	$(M+H)^+$ = 515, $t_{Ret.}$ = 1.04	LCMS3, basisch_1
I-028		B	3.5	$(M+H)^+$ = 471, $t_{Ret.}$ = 1.08	LCMS3, basisch_1
I-029		B	7.5	$(M+2H)^+$ = 455, $t_{Ret.}$ = 1.22	LCMS3, basisch_1
I-030		B	28	$(M+H)^+$ = 437, $t_{Ret.}$ = 0.89	LCMS3, basisch_1
I-031		A	0.5	$(M+H)^+$ = 529, $t_{Ret.}$ = 1.29	LCMS3, basisch_1
I-032		A	0.6	$(M+H)^+$ = 516, $t_{Ret.}$ = 1.27	LCMS3, basisch_1
I-033		A	0.6	$(M+H)^+$ = 529, $t_{Ret.}$ = 1.30	LCMS3, basisch_1
I-034		A'	0.7	$(M+H)^+$ = 435, $t_{Ret.}$ = 1.42	LCMS3, basisch_1

#	structure	method	IC_{50} [nM]	MS $(M+H)^+$ t_{Ret} HPLC [min]	HPLC-MS method
I-035		A	0.7	$(M+H)^+$ = 488, $t_{Ret.}$ = 1.33	LCMS3, basisch_1
I-036		B	0.7	$(M+H)^+$ = 421, $t_{Ret.}$ = 1.06	LCMS3, basisch_1
I-037		A	1.2	$(M+H)^+$ = 421, $t_{Ret.}$ = 1.38	LCMS3, basisch_1
I-038		A	1.3	$(M+H)^+$ = 502, $t_{Ret.}$ = 1.16	LCMS3, basisch_1
I-039		A	1.6	$(M+H)^+$ = 557, $t_{Ret.}$ = 1.12	LCMS3, basisch_1
I-040		B	1.7	$(M+H)^+$ = 435, $t_{Ret.}$ = 1.10	LCMS3, basisch_1
I-041		B	1.9	$(M+H)^+$ = 461, $t_{Ret.}$ = 1.44	LCMS3, basisch_1
I-042		A'	2.3	$(M+H)^+$ = 489, $t_{Ret.}$ = 1.39	LCMS3, basisch_1

#	structure	method	IC_{50} [nM]	MS $(M+H)^+$ t_{Ret} HPLC [min]	HPLC-MS method
I-043		A	2.3	$(M+H)^+$ = 529, $t_{Ret.}$ = 1.31	LCMS3, basisch_1
I-044		B	3.4	$(M+H)^+$ = 421, $t_{Ret.}$ = 1.14	LCMS3, basisch_1
I-045		B	3.6	$(M+H)^+$ = 447, $t_{Ret.}$ = 1.14	LCMS3, basisch_1
I-046		A	4.1	$(M+H)^+$ = 413, $t_{Ret.}$ = 1.53	LCMS3, basisch_1
I-047		A	6.2	$(M+H)^+$ = 399, $t_{Ret.}$ = 1.46	LCMS3, basisch_1
I-048		A	15	$(M+H)^+$ = 413, $t_{Ret.}$ = 0.77	LCMSBAS1
I-049		A	16	$(M+H)^+$ = 413, $t_{Ret.}$ = 1.48	LCMSBAS1
I-050		A'	17	$(M+H)^+$ = 427, $t_{Ret.}$ = 1.53	LCMSBAS1

#	structure	method	IC_{50} [nM]	MS $(M+H)^+$ t_{Ret} HPLC [min]	HPLC-MS method
I-051		A	20	$(M+H)^+$ = 413, $t_{Ret.}$ = 1.53	LCMSBAS1
I-052		B	23	$(M+H)^+$ = 445, $t_{Ret.}$ = 1.44	LCMS3, basisch_1
I-053		A	24	$(M+H)^+$ = 417, $t_{Ret.}$ = 1.45	LCMSBAS1
I-054		A	25	$(M+H)^+$ = 427, $t_{Ret.}$ = 1.51	LCMSBAS1
I-055		B	66	$(M+H)^+$ = 403, $t_{Ret.}$ = 1.18	LCMS3, basisch_1
I-056		A	69	$(M+H)^+$ = 431, $t_{Ret.}$ = 1.53	LCMSBAS1
I-057		A´		$(M+H)^+$ = 523/525, $t_{Ret.}$ = 1.12	VAB

The following Examples describe the biological activity of the compounds according to the invention, without restricting the invention to these Examples:

Biochemical EGFR inhibition assays

Initially, the inhibitory effect of compounds according to the invention is measured in biochemical assays which measure the phosphorylation activity of EGFR enzyme forms on poly-GT substrate in the presence of different concentrations of ATP (5 µM and 100 µM final assay concentration).

The following enzyme forms of EGFR are representative examples that can be used in these assays at the given concentrations:

EGFR *wt* (Life technologies; PV4190); final assay concentration 1.5 nM

EGFR (d746-750 T790M C797S) (SignalChem; E10-12UG); final assay concentration 15 nM

EGFR (mutated) 695-1022, T790M, C797S, L858R (in house prep); final assay concentration 3 nM

Test compounds dissolved in DMSO are dispensed onto assay plates (Proxiplate 384 PLUS, white, PerkinElmer; 6008289) using an Access Labcyte Workstation with the Labcyte Echo 55x. For the chosen highest assay concentration of 100 µM, 150 nL of compound solution is transferred from a 10 mM DMSO compound stock solution. A series of eleven fivefold dilutions per compound is transferred to the assay plate, compound dilutions are tested in duplicates. DMSO is added as backfill to a total volume of 150 nL. The assay runs on a fully automated robotic system.

5 µL of EGFR enzyme form in assay buffer (50 mM HEPES pH 7.3, 10 mM $MgCl_2$, 1 mM EGTA, 0.01 % Tween 20, 2 mM DTT) are dispensed into columns 1-23, than 5 µL of ATP and ULight-poly-GT substrate (PerkinElmer; TRF0100-M) mix in assay buffer is added to all wells (final assay concentration of the ULight-poly-GT substrate 200 nM). Each of the different EGFR enzyme form assays is available at low ATP (final assay concentration 5 µM) and high ATP levels (final assay concentration 100 µM). After 90 minutes incubation at room temperature 5 µL EDTA (final assay concentration 50 mM) and LANCE Eu-anti-P-Tyr (PT66) antibody (PerkinElmer, AD0069) (final assay concentration 6 nM) mix are added to stop the reaction and start the binding of the antibody. After additional 60 minutes incubation at room temperature the signal is measured in a PerkinElmer Envision HTS Multilabel Reader using the TR-FRET LANCE Ultra specs of PerkinElmer (used

wavelengths: excitation 320 nm, emission 1 665 nm, emission 2 615 nm). Each plate contains 16 wells of a negative control (diluted DMSO instead of test compound; w EGFR enzyme form; column 23) and 16 wells of a positive control (diluted DMSO instead of test compound; w/o EGFR enzyme form; column 24). Negative and positive control values are used for normalization and IC_{50} values are calculated and analysed using a 4 parametric logistic model.

These biochemical EGFR enzyme form compound dose-response assays quantify the kinase activity *via* phosphorylation of a tagged poly-GT substrate. The results of the assay are provided as IC_{50} values. The lower the reported IC_{50} values for a given compound, the more potent the compound inhibits the kinase activity of the EGFR enzyme on poly-GT substrate.

Table 15 contains IC_{50} data of compounds according to the invention generated in the corresponding biochemcial assays as described above:

Table 15:

	Del_TM_CS (5 µM ATP) [nM]	Del_TM_CS (100 µM ATP) [nM]	LR_TM_CS (5 µM ATP [nM]	LR_TM_CS (100 µM ATP) [nM]	*wt* (5 µM ATP) [nM]	*wt* (100 µM ATP) [nM]
I-001				6		> 100000
I-003				3		900
I-005				16		> 100000
I-021				2		90
I-037	0.2		0.3	3	13	> 100000
I-046	1.3		1.8	16	18	> 100000

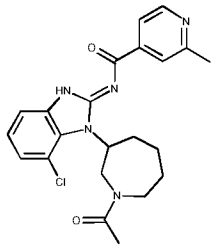
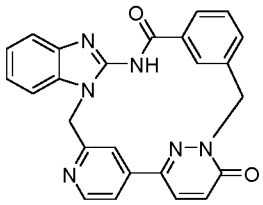
Ba/F3 cell model generation and proliferation assays

Ba/F3 cells were ordered from DSMZ (ACC300, Lot17) and grown in RPMI-1640 (ATCC 30-2001) + 10 % FCS + 10 ng/ml IL-3 at 37 °C in 5 % CO_2 atmosphere. Plasmids containing EGFR mutants were obtained from GeneScript. To generate EGFR-dependent Ba/F3 models, Ba/F3 cells were transduced with retroviruses containing vectors that harbor EGFR isoforms. Platinum-E cells (Cell Biolabs) were used for retrovirus packaging. Retrovirus was added to Ba/F3 cells. To ensure infection, 4 µg/mL polybrene was added and cells were spinfected. Infection efficiency was confirmed by measuring GFP-positive

cells using a cell analyzer. Cells with an infection efficiency of 10 % to 20 % were further cultivated and puromycin selection with 1 µg/mL was initiated. As a control, parental Ba/F3 cells were used to show selection status. Selection was considered successful when parental Ba/F3 cells cultures died. To evaluate the transforming potential of EGFR mutations, the growth medium was no longer supplemented with IL-3. Ba/F3 cells harboring the empty vector were used as a control. A switch from IL-3 to EGF was performed for Ba/F3 cells with the wildtype EGFR known for its dependency on EGF ligand. Approximately ten days before conducting the experiments, puromycin was left out. For proliferation assays (data in table 13), Ba/F3 cells were seeded into 96-well plates at 5 x 10^3 cells / 100 µL in growth media. Compounds were added by using a HP D3000 Digital Dispenser. All treatments were performed in technical triplicates. Treated cells were incubated for 72 h at 37 °C with 5 % CO_2. CellTiter-Glo® Luminescent Cell Viability Assay (Promega) was performed and chemoluminescence was measured by using the multilabel Plate Reader VICTOR X4. The raw data were imported into and analyzed with the Boehringer Ingelheim proprietary software MegaLab (curve fitting based on the program PRISM, GraphPad Inc.).

Table 16: Viability IC_{50} values in nM of Ba/F3 cell lines driven by the indicated EGFR alleles and treated with the indicated compounds (average data of two independent biological experiments with three technical replicates are shown).

cell model / drug	IC_{50} EGFR-indep. + IL-3 [nM]	IC_{50} EGFR *wt* + EGFR [nM]	IC_{50} EGFR del19 [nM]
erlotinib	> 5000	38.9	2.0
gefitinib	> 5000	37.0	1.8
afatinib	1055.7	0.60	0.02
dacomitinib	977.9	0.64	0.01
osimertinib	960.3	26.7	0.5
nazartinib	> 5000	95.1	1.1
nazartinib w/o warhead	5026.1	1625.0	3435.7

cell model / drug	IC_{50} EGFR-indep. + IL-3 [nM]	IC_{50} EGFR *wt* + EGFR [nM]	IC_{50} EGFR del19 [nM]
			
Exp. WO 2014/121942	3500	2800	-
			
I-021	1100	190	1

cell model / drug	IC_{50} EGFR del19 T790M [nM]	IC_{50} EGFR del19 C797S [nM]	IC_{50} EGFR del19 T790M C797S [nM]
erlotinib	1039.8	3.0	3562.5
gefitinib	852.7	2.6	2091.2
afatinib	31.2	1.9	807.3
dacomitinib	56.3	1.6	1170.3
osimertinib	1.6	628.4	729.6
nazartinib	4.1	744.8	455.2
nazartinib w/o warhead	2523.9	3518.7	2229.8
Exp. WO 2014/121942	-	-	770
I-021	0.3	0.5	0.2

cell model / drug	IC_{50} EGFR L858R [nM]	IC_{50} EGFR L858R T790M [nM]	IC_{50} EGFR L858R C797S [nM]
erlotinib	4.6	> 5000	11.1

cell model / drug	IC_{50} EGFR L858R [nM]	IC_{50} EGFR L858R T790M [nM]	IC_{50} EGFR L858R C797S [nM]
gefitinib	5.8	3399.6	11.5
afatinib	0.02	34.8	7.2
dacomitinib	0.03	61.4	6.9
osimertinib	1.1	1.9	768.7
nazartinib	5.1	7.3	1985.2
nazartinib w/o warhead	2706.3	2935.4	3615.9
Exp. WO 2014/121942	-	-	-
I-021	7	0.9	4

cell model / drug	IC_{50} EGFR L858R T790M C797S [nM]
erlotinib	> 5000
gefitinib	> 5000
afatinib	1145.4
dacomitinib	1602.4
osimertinib	1082.3
nazartinib	758.8
nazartinib w/o warhead	3545.5
Exp. WO 2014/121942	2200
I-021	0.4

pEGFR assay

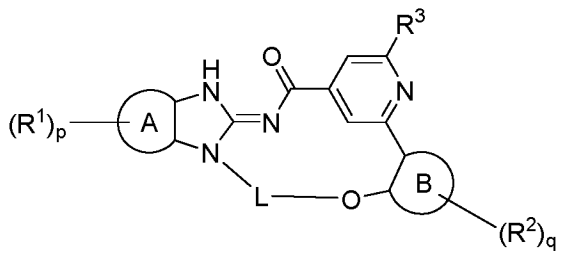
This assay quantifies the phosphorylation of EGFR at Tyr1068 and was used to measure the inhibitory effect of compounds on the transgenic EGFR del19 T790M C797S protein in Ba/F3 cells. Murine Ba/F3 cells were grown in RPMI-1640 (ATCC 30-2001) + 10 % FCS + 10 ng/mL IL-3 at 37 °C in 5 % CO_2 atmosphere and transduced with a retroviral vector encoding EGFR del19 T790M C797S. Transduced cells were selected using puromycin. Following selection, IL-3 was withdrawn and IL-3 independent cells cultured. p-EGFR

Tyr1068 was determined using the AlphaScreen Surefire pEGF Receptor (Tyr1068) Assay (PerkinElmer, TGRERS). For the assay, Ba/F3 EGFR del19 T790M C797S cells were seeded in DMEM medium with 10 % FCS. 60 nL compound dilutions were added to each well of Greiner TC 384 plates using the Echo platform. Subsequently, 60.000 cells/well in 60 µL were added. Cells were incubated with compound for 4 h at 37 °C. Following centrifugation and removal of the medium supernatant, 20 µL of 1.6-fold lysis buffer from TGR/Perkin Elmer kit with protease inhibitors was added. The mixture was incubated at room temperature with shaking (700 rpm) for 20 min. After centrifugation, 4 µL of the lysate were transferred to Proxiplates. 5 µL of Acceptor Mix (Activation Buffer diluted 1:25 in combined Reaction Buffer 1 and Reaction Buffer 2 (TGRERS Assay Kit, PerkinElmer) plus 1:50 of Protein A Acceptor Beads 6760137) were added to each well. Plates were shaken for 1 min (1400 rpm) and incubated for 2 h at room temperature in the dark. 3 µL of donor mix (AlphaScreen Streptavidin-coated Donor Beads (6760002, PerkinElmer) 1:50 diluted in Dilution Buffer (TGRERS Assay Kit, PerkinElmer) were added to each well. Plates were shaken for 1 min (1400 rpm) and incubated for 2 h at room temperature in the dark. Plates were subsequently analyzed using an Envision reader platform. Results were computed in the following way: The ratio of the value of the test compound and the value of the negative control (DMSO) was calculated. IC_{50} values are computed from these values in the MEGASTAR IC_{50} application using a 4 parametric logistic model.

This cellular phospho-EGFR (pEGFR) compound dose-response assay quantifies the phosphorylation of EGFR at Tyr1068 in Ba/F3 cells expressing the EGFR variant del19 T790M C797S. The results of the assay are provided as IC_{50} values (see table 14). The lower the reported pEGFR IC_{50} values for a given compound, the more potent the compound inhibits the EGFR del19 T790M C797S target protein in Ba/F3 cells.

Claims

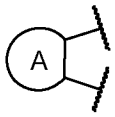
1. A compound of formula **(I)**



(I)

,

wherein



is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

p is selected from the group consisting of 0, 1, 2 and 3;

each $\mathbf{R^1}$ is independently selected from the group consisting of $\mathbf{R^{a1}}$ and $\mathbf{R^{b1}}$;

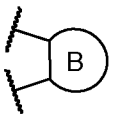
$\mathbf{R^{a1}}$ is selected from the group consisting of $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{4\text{-}10}$cycloalkenyl, 3-10 membered heterocyclyl, $C_{6\text{-}10}$aryl and 5-10 membered heteroaryl, wherein the $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{4\text{-}10}$cycloalkenyl, 3-10 membered heterocyclyl, $C_{6\text{-}10}$aryl and 5-10 membered heteroaryl are all optionally substituted by one or more, identical or different $\mathbf{R^{b1}}$ and/or $\mathbf{R^{c1}}$;

each $\mathbf{R^{b1}}$ is independently selected from the group consisting of $-OR^{c1}$, $-NR^{c1}R^{c1}$, halogen, -CN, $-C(O)R^{c1}$, $-C(O)OR^{c1}$, $-C(O)NR^{c1}R^{c1}$, $-S(O)_2R^{c1}$, $-S(O)_2NR^{c1}R^{c1}$, $-NHC(O)R^{c1}$, $-N(C_{1\text{-}4}alkyl)C(O)R^{c1}$, $-NHC(O)OR^{c1}$, $-N(C_{1\text{-}4}alkyl)C(O)OR^{c1}$ and the bivalent substituent =O;

each $\mathbf{R^{c1}}$ is independently selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{4\text{-}10}$cycloalkenyl, 3-10 membered heterocyclyl, $C_{6\text{-}10}$aryl and 5-10 membered heteroaryl, wherein the $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{4\text{-}10}$cycloalkenyl, 3-10 membered heterocyclyl, $C_{6\text{-}10}$aryl and 5-10 membered heteroaryl are all optionally substituted by one or more, identical or different $\mathbf{R^{d1}}$ and/or $\mathbf{R^{e1}}$;

each $\mathbf{R^{d1}}$ is independently selected from the group consisting of $-OR^{e1}$, $-NR^{e1}R^{e1}$, halogen, -CN, $-C(O)R^{e1}$, $-C(O)OR^{e1}$, $-C(O)NR^{e1}R^{e1}$, $-S(O)_2R^{e1}$, $-S(O)_2NR^{e1}R^{e1}$, $-NHC(O)R^{e1}$, $-N(C_{1-4}alkyl)C(O)R^{e1}$, $-NHC(O)OR^{e1}$, $-N(C_{1-4}alkyl)C(O)OR^{e1}$ and the bivalent substituent =O;

each $\mathbf{R^{e1}}$ is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}cycloalkenyl, 3-10 membered heterocyclyl optionally substituted with C_{1-4} alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, C_{6-10}aryl, 5-10 membered heteroaryl and $(C_{1-4}alkyl)_2$amino-C_{1-4}alkyl;



is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

q is selected from the group consisting of 0, 1 and 2;

each $\mathbf{R^2}$ is independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}haloalkyl, -CN, C_{1-4}alkoxy, C_{1-4}haloalkoxy and halogen;

$\mathbf{R^3}$ is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{2-4}alkenyl, C_{2-4}alkinyl, halogen, -CN, $-NH_2$, $-NH(C_{1-4}alkyl)$ and $-N(C_{1-4}alkyl)_2$; and

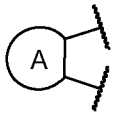
L is selected from the group consisting of straight chain C_{3-7}alkylene, straight chain C_{3-7}alkenylene and straight chain C_{3-7}alkynylene, wherein one or two methylene groups $-CH_2-$ in such straight chain C_{3-7}alkylene, straight chain C_{3-7}alkenylene and straight chain C_{3-7}alkynylene are optionally and independently replaced by a group/atom selected from oxygen, -NH- and $-N(C_{1-4}alkyl)-$;

wherein such straight chain can be optionally substituted on carbon by one or more, identical or different substituent(s) selected from the group consisting of C_{1-4}alkyl, halogen and hydroxy;

wherein one carbon atom, two carbon atoms or one carbon atom and one nitrogen atom in such straight chain can be optionally bridged with C_{1-5}alkylene, wherein one methylene group $-CH_2-$ in such bridging C_{1-5}alkylene can be optionally replaced by oxygen, to form a C_{3-6}carbocycle or 3-6 membered nitrogen- and/or oxygen-containing heterocycle;

or a salt thereof.

2. The compound or salt according to claim 1, wherein



is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

p is selected from the group consisting of 1, 2 and 3;

each $\mathbf{R^1}$ is independently selected from the group consisting of $\mathbf{R^{a1}}$ and $\mathbf{R^{b1}}$;

$\mathbf{R^{a1}}$ is selected from the group consisting of C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted by one or more, identical or different $\mathbf{R^{b1}}$ and/or $\mathbf{R^{c1}}$;

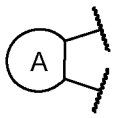
each $\mathbf{R^{b1}}$ is independently selected from the group consisting of $-OR^{c1}$, $-NR^{c1}R^{c1}$, halogen, -CN, $-C(O)R^{c1}$, $-C(O)OR^{c1}$, $-C(O)NR^{c1}R^{c1}$ and the bivalent substituent =O;

each $\mathbf{R^{c1}}$ is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl, C_{6-10}aryl and 5-10 membered heteroaryl are all optionally substituted by one or more, identical or different $\mathbf{R^{d1}}$ and/or $\mathbf{R^{e1}}$;

each $\mathbf{R^{d1}}$ is independently selected from the group consisting of $-OR^{e1}$, $-NR^{e1}R^{e1}$, halogen, -CN, $-C(O)R^{e1}$, $-C(O)OR^{e1}$, $-C(O)NR^{e1}R^{e1}$ and the bivalent substituent =O;

each $\mathbf{R^{e1}}$ is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl optionally substituted with C_{1-4} alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, C_{6-10}aryl, 5-10 membered heteroaryl and $(C_{1-4}alkyl)_2$amino-C_{1-4}alkyl.

3. The compound or salt according to any one of claim 1 and 2, wherein



is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

p is selected from the group consisting of 1, 2 and 3;

each R^1 is independently selected from the group consisting of R^{a1} and R^{b1};

R^{a1} is selected from the group consisting of C_{1-6}alkyl and 3-10 membered heterocyclyl, wherein the C_{1-6}alkyl and 3-10 membered heterocyclyl are all optionally substituted by one or more, identical or different R^{b1} and/or R^{c1};

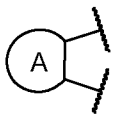
each R^{b1} is independently selected from the group consisting of $-OR^{c1}$, $-NR^{c1}R^{c1}$, halogen, -CN, $-C(O)R^{c1}$, $-C(O)OR^{c1}$, $-C(O)NR^{c1}R^{c1}$ and the bivalent substituent =O;

each R^{c1} is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl and 3-10 membered heterocyclyl, wherein the C_{1-6}alkyl, C_{3-10}cycloalkyl, and 3-10 membered heterocyclyl are all optionally substituted by one or more, identical or different R^{d1} and/or R^{e1};

each R^{d1} is independently selected from the group consisting of $-OR^{e1}$, $-NR^{e1}R^{e1}$, halogen, -CN, $-C(O)R^{e1}$, $-C(O)OR^{e1}$, $-C(O)NR^{e1}R^{e1}$ and the bivalent substituent =O;

each R^{e1} is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, 3-10 membered heterocyclyl optionally substituted with C_{1-4} alkyl, C_{1-4}alkoxy-C_{1-4}alkyl and $(C_{1-4}alkyl)_2$amino-C_{1-4}alkyl.

4. The compound or salt according to claim 1, wherein

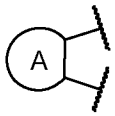


is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

p is selected from the group consisting of 1, 2 and 3;

each R^1 is selected from the group consisting of halogen, C_{1-4}alkyl, C_{1-4}alkoxy, heterocyclyl-C_{1-4}alkoxy with a 5-7 membered heterocyclyl which is optionally substituted with C_{1-4}alkyl, heterocyclyl-C_{1-4}alkyl with a 5-7 membered heterocyclyl which is optionally substituted with C_{1-4}alkyl, 5-7 membered heterocyclyl optionally substituted with C_{1-4}alkyl, $(C_{1-4}alkyl)_2N$-C_{1-4}alkyl, $-C(O)N(C_{1-4}alkyl)_2$, -C(O)-heterocyclyl with a 5-7 membered heterocyclyl optionally substituted with C_{1-4}alkyl and $-C(O)O-C_{1-4}$alkyl.

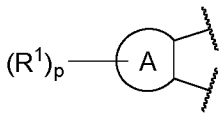
5. The compound or salt according to claim 1, wherein



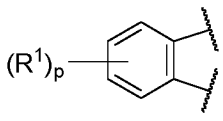
is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

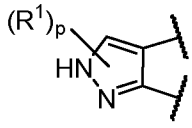
p is 0.

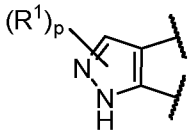
6. The compound or salt according to claim 1, wherein



is selected from the group consisting of



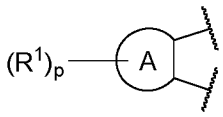
, 

and 

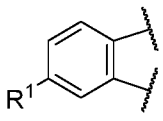
, wherein

R^1 and **p** are defined as in any one of claims 1 to 4.

7. The compound or salt according to claim 1, wherein



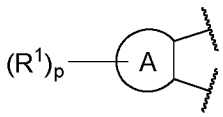
is



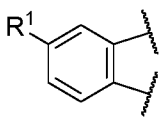
, wherein

R^1 is defined as in any one of claims 1 to 4.

8. The compound or salt according to claim 1, wherein



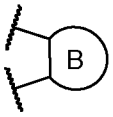
is



, wherein

R^1 is defined as in any one of claims 1 to 4.

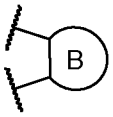
9. The compound or salt according to any one of claims 1 to 8, wherein



is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

q is 0.

10. The compound or salt according to any one of claims 1 to 8, wherein

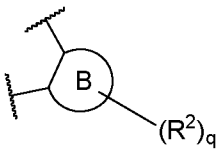


is selected from the group consisting of phenylene and 5-6 membered heteroarylene;

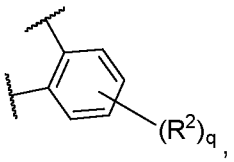
q is 1;

$\mathbf{R^2}$ is selected from the group consisting of $C_{1\text{-}4}$alkyl and halogen.

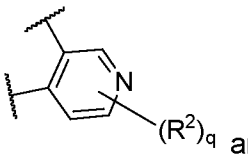
11. The compound or salt according to any one of claims 1 to 8, wherein



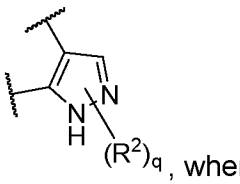
is selected from the group consisting of



,



and



, wherein

$\mathbf{R^2}$ and **q** are defined as in any one of claims 1, 9 or 10.

12. The compound or salt according to any one of claims 1 to 12, wherein

$\mathbf{R^3}$ is selected from the group consisting of hydrogen, $C_{1\text{-}4}$alkyl, halogen and -CN.

13. The compound or salt according to any one of claims 1 to 12, wherein

L is straight chain $C_{3\text{-}7}$alkylene, wherein one or two methylene groups $-CH_2-$ in such straight chain $C_{3\text{-}7}$alkylene are optionally and independently replaced by a group/atom selected from oxygen, -NH- and -N($C_{1\text{-}4}$alkyl)-;

wherein such straight chain can be optionally substituted on carbon by one or more, identical or different substituent(s) selected from the group consisting of C_{1-4}alkyl, halogen and hydroxy;

wherein one carbon atom, two carbon atoms or one carbon atom and one nitrogen atom in such straight chain can be optionally bridged with C_{1-5}alkylene, wherein one methylene group -CH_2- in such bridging C_{1-5}alkylene can be optionally replaced by oxygen, to form a C_{3-6}carbocycle or 3-6 membered nitrogen- and/or oxygen-containing heterocycle;

14. The compound or salt according to any one of claims 1 to 13, wherein

L is straight chain C_{3-7}alkylene,

wherein the straight chain C_{3-7}alkylene can be optionally substituted by one or more, identical or different substituent(s) selected from the group consisting of C_{1-4}alkyl, halogen and hydroxy;

wherein one carbon atom or two carbon atoms in the straight chain C_{3-7}alkylene can be optionally bridged with C_{1-5}alkylene to form a C_{3-6}carbocycle.

15. The compound or salt according to any one of claims 1 to 14, wherein

L is selected from the group consistig of straight chain C_4alkylene, straight chain C_5alkylene, straight chain C_6alkylene and straight chain C_7alkylene,

wherein the straight chain C_4alkylene, straight chain C_5alkylene, straight chain C_6alkylene and straight chain C_7alkylene can be optionally substituted by one or more, identical or different substituent(s) selected from the group consisting of C_{1-4}alkyl, halogen and hydroxy;

wherein one carbon atom or two carbon atoms in such straight chain C_4alkylene, straight chain C_5alkylene, straight chain C_6alkylene and straight chain C_7alkylene can be optionally bridged with C_{1-5}alkylene to form a C_{3-6}carbocycle.

16. The compound according to any one of claims 1 to 15 – or a pharmaceutically acceptable salt thereof – for use as a medicament.

17. The compound according to any one of claims 1 to 15 – or a pharmaceutically acceptable salt thereof – for use in the treatment and/or prevention of a disease and/or condition wherein the inhibition of mutant EGFR is of therapeutic benefit.

18. The compound according to any one of claims 1 to 15 – or a pharmaceutically acceptable salt thereof – for use in the treatment and/or prevention of cancer.

19. The compound – or a pharmaceutically acceptable salt thereof – for use according to any one of claim 16 to 18, wherein said compound is administered before, after or together with at least one other pharmacologically active substance.

20. The compound – or a pharmaceutically acceptable salt thereof – for use according to any one of claim 16 to 18, wherein said compound is administered in combination with at least one other pharmacologically active substance.

21. A method for the treatment and/or prevention of a disease and/or condition wherein the inhibition of mutant EGFR is of therapeutic benefit comprising administering a therapeutically effective amount of a compound of any one of claim 1 to 15 – or a pharmaceutically acceptable salt thereof – to a human being.

22. A method for the treatment and/or prevention of cancer comprising administering a therapeutically effective amount of any one of claim 1 to 15 – or a pharmaceutically acceptable salt thereof – to a human being.

23. The method according to any one of claim 21 and 22, wherein the compound – or the pharmaceutically acceptable salt thereof – is administered before, after or together with at least one other pharmacologically active substance.

24. The method according to any one of claim 21 and 22, wherein the compound – or the pharmaceutically acceptable salt thereof – is administered in combination with a therapeutically effective amount of at least one other pharmacologically active substance.

25. The compound – or the pharmaceutically acceptable salt thereof – for use according to any one of claim 18 to 20, or the method according to any one of claim 22 to 24, wherein the cancer is selected from the group consisting of lung cancer, brain cancers, colorectal cancer, bladder cancer, urothelial cancer, breast cancer, prostate cancer, ovarian cancer, head and neck cancer, pancreatic cancer, gastric cancer and mesothelioma, including metastasis (in particular brain metastasis) of all cancers listed.

26. A pharmaceutical composition comprising a compound according to any one of claim 1 to 15 – or a pharmaceutically acceptable salt thereof – and one or more pharmaceutically acceptable excipient(s).

27. A pharmaceutical preparation comprising a compound according to any one of claim 1 to 15 – or a pharmaceutically acceptable salt thereof – and at least one (preferably one) other pharmacologically active substance.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/067451

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 C07D487/22 C07D498/22 A61K31/439
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)
A61P C07D

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/184757 A1 (IRM LLC [US]; LELAIS GERALD [US] ET AL.) 12 December 2013 (2013-12-12) cited in the application claims 1, 3, 21, 22; examples 17.70, 17.76	1-27
A	WO 2013/184766 A1 (IRM LLC [US]; LELAIS GERALD [US] ET AL.) 12 December 2013 (2013-12-12) cited in the application claims 1, 16; examples 2-15 to 2-18	1-27
X	WO 2014/121942 A1 (MERCK PATENT GMBH [DE]) 14 August 2014 (2014-08-14) cited in the application claims 1, 11; example 18	1-27

☐ Further documents are listed in the continuation of Box C.

☒ 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

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"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
23 July 2020	05/08/2020

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	Miniejew, Catherine

INTERNATIONAL SEARCH REPORT

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