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(54) Title: SUBSTITUTED INDAZOLES AND RELATED HETEROCYCLES

(57) Abstract: The present invention relates to substituted indazoles and related heterocycles. These compounds are useful for the prevention and/or treatment of hyperproliferative, inflammatory and degenerative disorders and diseases. Thus, this invention is also concerned with the use of the compounds of the present invention for the prevention and/or treatment of hyperproliferative, inflammatory and degenerative disorders and diseases as well as pharmaceutical composition, medicaments and kits comprising the substituted indazoles and related heterocycles of the present invention and processes for manufacturing those compounds.



Substituted indazoles and related heterocycles

Field of the invention

5 The present invention relates to substituted indazoles and related heterocycles. These compounds are useful for the prevention and/or treatment of hyperproliferative, inflammatory and degenerative disorders and diseases. Thus, this invention is also concerned with the use of the compounds of the present invention for the prevention and/or treatment of
10 hyperproliferative, inflammatory and degenerative disorders and diseases as well as pharmaceutical compositions, medicaments and kits comprising the substituted indazoles and related heterocycles of the present invention and processes for manufacturing those compounds.

15 Background of the invention

CDK8, along with its closely related isoform CDK19, is an oncogenic transcription-regulating kinase. In contrast to some other members of the CDK family (such as CDK1, CDK2, and CDK4/6), CDK8 plays no direct role
20 in cell cycle progression. CDK8 knockout in embryonic stem cells prevents embryonic development, due to its essential role in the pluripotent stem cell phenotype but CDK8 depletion does not inhibit the growth of normal cells.

CDK8 is a cyclin dependent kinase that has a conserved function in
25 transcription as part of the Mediator complex (Taatjes, D. J., Trends Biochem Sci 35, 315-322 (2010)). CDK8 has been shown to regulate several signaling pathways that are key regulators of both ES pluripotency and cancer. CDK8 activates the Wnt pathway by promoting expression of β -Catenin target genes (Firestein, R. et al., Nature 455, 547-551 (2008)) or by inhibiting E2F1,
30 a potent inhibitor of β -Catenin transcriptional activity (Morris, E. J. et al., Nature 455, 552-556 (2008)). CDK8 promotes Notch target gene expression by phosphorylating the Notch intracellular domain, activating Notch enhancer

complexes at target genes (Fryer C. J. et al., Mol Cell 16:509-20 (2004)).
CDK8 phosphorylation of SMAD proteins leads to activation of TGF- β /BMP
target genes followed by degradation of the SMAD proteins to limit the target
gene expression (Alarcon, C. et al., Cell 139, 757-769 (2009)).

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The role of CDK8 in cancer is due to its unique function as a regulator of
several transcriptional programs involved in carcinogenesis. CDK8 has been
identified as an oncogene in melanoma (Kapoor A. et al., Nature 468:1105-9
(2010)) and colon cancer (Firestein R. et al., Nature 455:547-51 (2008);
10 Morris E. J. et al., Nature 455:552-6 (2008)), the CDK8 gene being amplified
in about 50% of the latter cancers. Higher expression of CDK8 has been
associated with worse prognosis in colon, breast and ovarian cancer (Porter
D. C. et al., Proc. Nat. Ac. Sci. 109: 13799-13804 (2012)). The known
cancer-relevant activities of CDK8 include positive regulation of the Wnt/ β -
15 catenin pathway, growth factor-induced transcription and TGF β signaling.
CDK8 was also shown to maintain the pluripotent phenotype of embryonic
stem cells and has been associated with the cancer stem cell phenotype.
DNA-damaging chemotherapeutic drugs induce TNF α , an activator of the
transcription factor NF κ B, in endothelial cells and in other cancer-associated
20 stromal elements. Stroma-derived TNF α acts on tumor cells, where it
induces NF κ B-mediated production of related tumor-promoting cytokines
CXCL1 and CXCL2. CXCL1/2 attract myeloid cells to the tumor, by binding to
CXCR2 receptor on the myeloid cell surface. Myeloid cells then secrete small
calcium-binding proteins 5100A8 and A9 that are associated with chronic
25 inflammation and cancer. 5100A8/9 act on tumor cells, promoting both their
metastasis and survival of chemotherapy.

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As CDK8 is a regulator of the Wnt/ β -catenin signalling pathway it may be
associated with disorders and diseases where activation of the Wnt/ β -catenin
pathway plays a role. Thus, the treatment of several disorders and diseases
by inhibiting the Wnt/ β -catenin signalling has been suggested and discussed

(Moon R.T. et al., Nature Reviews Genetics 5:689-699 (2004); Chien A.J. et al., J Investig. Dermatology 129:1614-1627 (2009)); among these diseases are hyperproliferative, inflammatory or degenerative disorders, in particular several cancer diseases (Giles R.H. et al., Biochim Biophys Acta 1653:1-24 (2003); Luu H.H. et al., Current Cancer Drug Targets 4:653-671 (2004)).

WO 2006/010595 A1, WO 2008/003396 A1 and WO 2008/155001 A1 all disclose specific 6-hydroxy substituted indazole derivatives as HSP90 modulators but are silent about any CDK8 inhibitory activity.

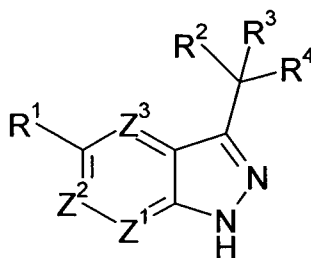
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Description of the invention

It is an object of the present invention to provide CDK8 inhibitors that inhibitors may be useful for the prevention and/or treatment of medical conditions, disorders and/or diseases that are affected by CDK8 activity. It is a particular object of the present invention to provide such inhibitors for the treatment of hyperproliferative, inflammatory or degenerative disorders, in particular cancer diseases.

20 This object has surprisingly been solved by providing a compound according to formula (I):

25



(I)

30 or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios,

wherein

- Z^1 denotes CH, CF or N;
 Z^2 denotes CR^5 or N;
 Z^3 denotes CH, CF or N;
 5 R^1 denotes $-C(=O)-R^6$, $-NHR^7$, $-SO_2R^8$, Hetar¹ or Hetcyc¹;
 R^2 and R^3 denote independently from each other H, Hal, straight-chain or branched C_{1-3} -alkyl, or form, together with the carbon atom to which they are attached to, a saturated C_{3-5} -cycloalkyl that may be unsubstituted or mono-substituted with C_{1-3} -alkyl;
 10 R^4 denotes Ar^4 or Hetar⁴;
 R^5 denotes H, F or $-LA^5$;
 R^6 denotes $-NHR^{6a}$ or Hetcyc⁶;
 R^7 denotes H, $-C(=O)-LA^{7a}$, $-SO_2-LA^{7b}$, LA^{7c} or Hetar⁷;
 R^8 denotes $-NHR^{8a}$ or Hetcyc⁸;
 15 Hetar¹ denotes a mono-, bi- or tricyclic aromatic ring system with 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 ring atoms wherein 1, 2, 3, 4 or 5 of said ring atoms is/are a hetero atom(s) selected from N, O and/or S and the remaining ring atoms are carbon atoms wherein that aromatic ring system may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from LA^{1c} , $-O-LA^{1d}$,
 20 $-NR^{1a}R^{1b}$; preferably, Hetar¹ is connected to its pendant group via one of its ring carbon atoms;
 Hetcyc¹ denotes a saturated or partially unsaturated heterocycle
 25 with 3, 4, 5, 6, 7 ring atoms wherein 1, 2 or 3 of said ring atoms is/are a hetero atom(s) selected from N, O and/or S and the remaining ring atoms are carbon atoms, wherein that heterocycle may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from straight-chain or branched C_{1-6} -alkyl, straight-chain or branched $-O-C_{1-6}$ -alkyl, Hal or oxo ($=O$); preferably, at least one of hetero atoms is
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nitrogen and more preferably the heterocycle is connected to its pendant group via this nitrogen atom;

Ar⁴ denotes a mono- or bicyclic aromatic ring system with 6, 7, 8, 9, 10 ring carbon atoms wherein that aromatic ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from R^{4a}, R^{4b}, R^{4c};

Hetar⁴ denotes a mono-, bi- or tricyclic aromatic ring system with 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 ring atoms wherein 1, 2, 3, 4 or 5 of said ring atoms is/are a hetero atom(s) selected from N, O and/or S and the remaining ring atoms are carbon atoms wherein that aromatic ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from R^{4d}, R^{4e}, R^{4f};

R^{1a}, R^{1b} denote independently from each other H, straight-chain or branched C₁₋₈-alkyl, or

R^{1a} and R^{1b} form together with the nitrogen atom to which they are attached to a 3-, 4-, 5-, 6- or 7-membered heterocycle that may contain another hetero atom selected from N and O;

R^{4a}, R^{4b}, R^{4c} denote independently from each other H, Hal, Hetar^{4a}, Hetcyc^{4a}, Ar^{4a}, CA^{4a}, straight-chain or branched C₁₋₆-alkyl or -O-C₁₋₆-alkyl which C₁₋₆-alkyl or -O-C₁₋₆-alkyl may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, OH, or

two of R^{4a}, R^{4b}, R^{4c} form together a divalent alkylene chain with 2, 3, 4, 5 chain carbon atoms that alkylene chain may be unsubstituted or substituted with straight-chain or branched C₁₋₄-alkyl wherein 1 or 2 non-adjacent methylene groups of that alkylene chain may be replaced by NH, O and/or S;

R^{4d}, R^{4e}, R^{4f} denote independently from each other H, Hal, Hetar^{4b}, Hetcyc^{4b}, Ar^{4b}, CA^{4b}, straight-chain or branched C₁₋₆-alkyl or -O-C₁₋₆-alkyl which C₁₋₆-alkyl or -O-C₁₋₆-alkyl may be

unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, OH;

5 LA^{1c} denotes a straight-chain or branched C₁₋₈-alkyl which may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, OH, -NR^{1c1}R^{1c2}, and in which C₁₋₈-alkyl 1 or 2 non-terminal and non-adjacent -CH₂- groups may be replaced by -O-, -S-, and/or 1 or 2 non-terminal and non-adjacent -CH₂-, -CH- groups may be replaced by -NH-, -N-;

10 LA^{1d} denotes a straight-chain or branched C₁₋₈-alkyl which may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, OH, -NR^{1d1}R^{1d2}, and in which C₁₋₈-alkyl 1 or 2 non-terminal and non-adjacent -CH₂- groups may be replaced by -O-, -S-, and/or 1 or 2 non-terminal and non-adjacent -CH₂-, -CH- groups may be replaced by -NH-, -N-;

15 LA⁵, LA^{7a}, LA^{7b} denote independently from each other a straight-chain or branched C₁₋₈-alkyl which may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal;

20 LA^{7c} denotes a straight-chain or branched C₁₋₈-alkyl which may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, -NH₂, -NH-C(=O)-C₁₋₆-alkyl, wherein such C₁₋₆-alkyl group may be straight-chain or branched;

25 R^{6a} denotes H, LA^{6a}, CA^{6a}, Hetar^{6a}, -Ar^{6a}, -C₁₋₄-alkyl-Ar^{6a};

30 Hetcyc⁶ denotes saturated or partially unsaturated heterocycle with 3, 4, 5, 6, 7 ring atoms wherein 1, 2 or 3 of said ring atoms is/are a hetero atom(s) selected from N, O and/or S and the remaining ring atoms are carbon atoms wherein that heterocycle may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from straight-chain

or branched C₁₋₆-alkyl, straight-chain or branched -O-C₁₋₆-alkyl, Hal, OH, Ar^{6b}; preferably, at least one of the hetero atoms is nitrogen and more preferably the heterocycle is connected to its pendant group via this nitrogen atom;

- 5 R^{8a} denotes CA^{8a} or LA^{8a};
- Hetcyc⁸, Hetcyc^{4a}, Hetcyc^{4b} each denote independently from each other saturated or partially unsaturated heterocycle with 3, 4, 5, 6, 7 ring atoms wherein 1, 2 or 3 of said ring atoms is/are a hetero atom(s) selected from N, O and/or S and the remaining
- 10 ring atoms are carbon atoms wherein that heterocycle may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from straight-chain or branched C₁₋₆-alkyl, straight-chain or branched -O-C₁₋₆-alkyl, Hal or OH;
- 15 Ar^{4a} denotes a mono- or bicyclic aromatic ring system with 6, 7, 8, 9, 10 ring carbon atoms wherein that aromatic ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from R^{4a1}, R^{4a2}, R^{4a3};
- 20 CA^{4a}, CA^{4b}, CA^{6a}, CA^{8a} each denote independently from each other saturated or partially unsaturated cycloalkyl with 3, 4, 5, 6, 7 ring carbon atoms which cycloalkyl may be unsubstituted or substituted with a substituent selected from C₁₋₄-alkyl, -O-C₁₋₄-alkyl or OH;
- 25 Hetar⁷, Hetar^{4a}, Hetar^{4b}, Hetar^{6a} each denote independently from each other a mono-, bi- or tricyclic aromatic ring system with 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 ring atoms wherein 1, 2, 3 or 4 of said ring atoms is/are a hetero atom(s) selected from N, O and/or S and the remaining ring atoms are carbon atoms wherein
- 30 that aromatic ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from C₁₋₄-alkyl, -O-C₁₋₄-alkyl, Hal, wherein that

straight-chain or branched C₁₋₄-alkyl group may be unsubstituted or mono-substituted with –OH or –O-C₁₋₄-alkyl;

5 Ar^{4b} denotes a mono- or bicyclic aromatic ring system with 6, 7, 8, 9, 10 ring carbon atoms wherein that aromatic ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from R^{4d1}, R^{4d2}, R^{4d3};

10 LA^{6a} denotes straight-chain or branched C₁₋₈-alkyl which may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, OH, –NR^{6a1}R^{6a2}, and in which C₁₋₈-alkyl 1 or 2 non-terminal and non-adjacent –CH₂– groups may be replaced by –O–, –S–, and/or 1 or 2 non-terminal and non-adjacent –CH₂–, –CH– groups may be replaced by –NH–, –N–;

15 Ar^{6a} denotes a mono-, bi- or tricyclic aromatic ring system with 6, 7, 8, 9, 10, 11, 12, 13, 14 ring carbon atoms wherein that aromatic ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from R^{6a3}, R^{6a4}, R^{6a5};

20 Ar^{6b} denotes a mono-, bi- or tricyclic aromatic ring system with 6, 7, 8, 9, 10, 11, 12, 13, 14 ring carbon atoms wherein that aromatic ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from R^{6b1}, R^{6b2}, R^{6b3};

25 LA^{8a} denotes straight-chain or branched C₁₋₈-alkyl which may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal;

30 R^{1c1}, R^{1c2}, R^{1d1}, R^{1d2}, R^{6a1}, R^{6a2} denote independently from each other H, straight-chain or branched C₁₋₈-alkyl, or each R^{1c1} and R^{1c2}; R^{1d1} and R^{1d2}; R^{6a1} and R^{6a2} independently from the other pairs of substituents form together with the nitrogen atom to which they are attached to a 3-, 4-, 5-, 6- or 7-membered

heterocycle that may contain another hetero atom selected from N and O;

R^{4a1} , R^{4a2} , R^{4a3} , R^{4d1} , R^{4d2} , R^{4d3} , R^{6a3} , R^{6a4} , R^{6a5} , R^{6b1} , R^{6b2} , R^{6b3} each denote independently from each other H, Hal, straight-chain or branched C₁₋₆-alkyl, straight-chain or branched –O-C₁₋₆-alkyl which C₁₋₆-alkyl or –O-C₁₋₆-alkyl may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, OH;

Hal denotes F, Cl, Br or I.

In general, all residues which occur more than once may be identical or different, i.e. are independent of one another. Above and below, the residues and parameters have the meanings indicated for formula (I), unless expressly indicated otherwise. Accordingly, the invention relates, in particular, to the compounds of formula (I) in which at least one of the said residues has one of the preferred meanings indicated below.

Any of those preferred or particular embodiments of the present invention as specified below and in the claims do not only refer to the specified compounds of formula (I) but to derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, too, unless indicated otherwise.

In one particular embodiment the compounds of the present invention are compounds of formula (I)

wherein

Z^1 denotes CH or N;

Z^2 denotes CR⁵;

Z^3 denotes CH or N;

wherein, if Z^1 denotes N, then Z^3 denotes CH, and if Z^3 denotes N, then Z^1 denotes CH;

R^2 and R^3 denote independently from each other H, F, or form, together with the carbon atom to which they are attached to, a cyclopropyl ring;

5 $Hetar^1$ denotes a mono-cyclic aromatic ring system with 5 or 6 ring atoms wherein 1 or 2 of said ring atoms is/are nitrogen atom(s) wherein that aromatic ring system may be unsubstituted or mono-substituted with a substituent selected from LA^{1c} , - $NR^{1a}R^{1b}$;

10 $Hetcyc^1$ denotes a saturated heterocycle with 4, 5, 6 ring atoms wherein 1 of said ring atoms is a nitrogen atom or 2 of said ring atoms are either one nitrogen and one oxygen atom or two nitrogen atoms, wherein that heterocycle may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from straight-chain or
15 branched C_{1-6} -alkyl or oxo (=O);

Ar^4 denotes phenyl that may be unsubstituted or mono-, di-substituted with substituents that are independently from each other selected from R^{4a} , R^{4b} ;

20 $Hetar^4$ denotes a mono- or bi-cyclic aromatic ring system with 5, 6, 9, 10 ring atoms wherein 1 of said ring atoms is a nitrogen atom or 2 of said ring atoms are two nitrogen atoms wherein that aromatic ring system may be unsubstituted or mono-substituted with a substituent R^{4d} ;

25 R^5 denotes H;

R^{1a} , R^{1b} denote H;

LA^{1c} denotes a straight-chain or branched C_{1-4} -alkyl which may be unsubstituted or substituted with 1 substituent being OH;

30 R^{4a} , R^{4b} denote independently from each other H, $Hetar^{4a}$, straight-chain or branched C_{1-4} -alkyl or $-O-C_{1-4}$ -alkyl which C_{1-4} -alkyl or $-O-C_{1-4}$ -alkyl may be unsubstituted or substituted with 1, 2, or 3 substituents independently from each other selected from Hal;

R^{4d} denotes straight-chain or branched C_{1-4} -alkyl;

- LA^{7a}, LA^{7b} denote independently from each other a straight-chain or branched C₁₋₄-alkyl;
- R^{6a} denotes H, LA^{6a}, CA^{6a}, Hetar^{6a}, -CH₂-Ar^{6a};
- 5 Hetcyc⁶ denotes saturated heterocycle with 4, 5, 6 ring atoms wherein 1 of said ring atoms is a nitrogen atom or 2 of said ring atoms are either one nitrogen and one oxygen atom or two nitrogen atoms wherein that heterocycle may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from straight-chain or branched C₁₋₄-alkyl, straight-chain or branched -O-C₁₋₄-alkyl, F, Cl, OH, Ar^{6b};
- 10 Hetcyc⁸ denotes saturated heterocycle with 4, 5, 6 ring atoms wherein 1 of said ring atoms is a nitrogen atom or 2 of said ring atoms are either one nitrogen and one oxygen atom or two nitrogen atoms wherein that heterocycle may be unsubstituted or mono-substituted with -O-C₁₋₄-alkyl;
- 15 CA^{6a} denotes saturated cycloalkyl with 3, 5, 6 ring carbon atoms which cycloalkyl may be unsubstituted or substituted with a substituent being OH;
- 20 Hetar⁷, Hetar^{4a}, Hetar^{6a} denote a mono-cyclic aromatic ring system with 5 or 6 ring atoms wherein 1 of said ring atoms is a nitrogen atom or 2 of said ring atoms are nitrogen atoms wherein that aromatic ring system may be unsubstituted or mono-substituted with a substituent being C₁₋₄-alkyl;
- 25 Ar^{6a} denotes phenyl that may be unsubstituted or mono-substituted with R^{6a3};
- Ar^{6b} denotes phenyl that may be unsubstituted or mono-substituted with R^{6b1};
- LA^{6a} denotes straight-chain or branched C₁₋₄-alkyl;
- 30 R^{6a3} denotes straight-chain or branched -O-C₁₋₄-alkyl which -O-C₁₋₄-alkyl may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from F, Cl;
- R^{6b1} denotes H, F, Cl;

while R¹, R⁴, R⁶, R⁷, R⁸, R^{8a}, LA^{7c}, CA^{8a}, LA^{8a} are as defined above or in claim 1 hereinafter.

Another particular embodiment of the present invention are compounds
5 according to formula (I),

wherein

Z¹, Z² and Z³ all denote CH; and

R² and R³ both denote H.

It particularly preferred for this embodiment that

10 Hetar¹ denotes a mono-cyclic aromatic ring system with 5 ring atoms wherein 2 of said ring atoms are nitrogen atoms wherein that aromatic ring system may be mono-substituted with LA^{1c}, or denotes a mono-cyclic aromatic ring system with 6 ring atoms wherein 1 of said ring atoms is a nitrogen atom wherein that
15 aromatic ring system may be mono-substituted with NH₂;

Hetcyc¹ denotes -N-morpholinyl, N-piperdiny, N-pyrrolidin-2-one, 3-methyl-pyrrolidin-2-one;

Ar⁴ denotes phenyl that may be unsubstituted or mono-substituted with a substituent selected from methyl, methoxy, Hetar^{4a} or di-
20 substituted with methoxy;

Hetar⁴ denotes N-methyl-benzimidazole, N-methylindazole;

R⁵ denotes H;

LA^{1c} denotes methyl, ethyl, 2-hydroxyethyl;

R^{6a} denotes H, LA^{6a}, CA^{6a}, Hetar^{6a}, -Ar^{6a}, -CH₂-Ar^{6a};

25 Hetcyc⁶ denotes N-azetidiny which may be unsubstituted or mono-substituted with a substituent selected from OH, methoxy, F, Cl or di-substituted with substituents selected from F, Cl; N-pyrrolidinyl which may be unsubstituted or mono-substituted with a substituent selected from OH, phenyl, p-chlorophenyl or di-
30 substituted with substituents selected from F, Cl; N-morpholinyl, N-piperazinyl, N-piperidinyl which may be unsubstituted or mono-

substituted with a substituent selected from OH, F, Cl or di-substituted with substituents selected from F, Cl;

LA^{7a} and LA^{7b} both denote methyl;

LA^{7c} denotes $-\text{CH}_2\text{-CH}_2\text{-NH-C(=O)-CH}_3$;

5 R^{8a} denotes cyclopropyl;

Hetcyc⁸ denotes N-azetidiny which may be unsubstituted or mono-substituted with a substituent selected from OH, methoxy;

CA^{6a} denotes cyclopropyl or cyclohexyl which may be unsubstituted or mono-substituted with OH;

10 Hetar⁷ denotes pyridyl, pyrid-4-yl;

Hetar^{4a} is defined as above or in any of claim 1 or 2 hereinafter;

Hetar^{6a} denotes N-methyl-pyrazin-3-yl;

Ar^{6a} denotes o-(2,2,2-trifluoroethoxy)-phenyl;

LA^{6a} denotes methyl

15 R¹, R⁴, R⁶, R⁷, R⁸ are as defined above or in claim 1 hereinafter.

Still another particular embodiment of the present invention are compounds of formula (I),

wherein

20 R¹ denotes $-\text{C(=O)-R}^6$ or Hetar¹.

Further preferred compounds of formula (I) are those being defined as follows:

R¹ denotes $-\text{C(=O)-R}^6$ or Hetar¹;

25 Hetar¹ denotes a mono-cyclic aromatic ring system with 5 or 6 ring atoms wherein 1 or 2 of said ring atoms is/are nitrogen atom(s) wherein that aromatic ring system may be unsubstituted or mono-substituted with a substituent selected from methyl, ethyl, 2-hydroxyethyl;

30 R⁶ denotes $-\text{NHR}^{6a}$ or Hetcyc⁶;

R^{6a} denotes H, LA^{6a} or CA^{6a};

- LA^{6a} denotes straight-chain or branched C₁₋₄-alkyl which may be unsubstituted or substituted with 1 substituent being OH, and in which C₁₋₄-alkyl 1 non-terminal -CH₂- group may be replaced by -O-;
- 5 CA^{6a} denotes saturated cycloalkyl with 3 or 6 ring carbon atoms which cycloalkyl may be unsubstituted or substituted with a substituent being OH;
- 10 Hetcyc⁶ denotes saturated heterocycle with 4, 5, 6 ring atoms wherein 1 of said ring atoms is a nitrogen atom or 2 of said ring atoms are either one nitrogen and one oxygen atom or two nitrogen atoms wherein that heterocycle may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from straight-chain or branched C₁₋₄-alkyl, straight-chain or branched -O-C₁₋₄-alkyl, F, OH, and
- 15 wherein that heterocycle is attached to the carbonyl C-atom of the -C(=O)-R⁶ moiety via a ring nitrogen atom.

Still another particular embodiment of the present invention are compounds of formula (I),

- 20 wherein
- R⁴ denotes N-methyl-benzimidazole, N-methylindazole or phenyl that may be unsubstituted or mono-substituted with a substituent selected from methyl, N-methylpyrazole, N-(2-hydroxy-2-methylpropyl)pyrazole, or N-methylindazole.
- 25 Further preferred compounds of formula (I) with R⁴ as being defined above are those having the specified meanings of those other particular embodiments described above.

- Particular embodiments of the present invention are those compounds of
- 30 formula (I), in which

R¹ denotes -C(=O)-R⁶, -NHR⁷, -SO₂R⁸, Hetar¹ or Hetcyc¹;

- 5 R^6 denotes $-NH_2$, $-NH$ -methyl, $-NH$ -cyclopropyl, $-NH-(CH_2)_2-OH$, $-NH-(CH_2)_3-OH$, $-NH-(CH_2)_4-OH$, $-NH-(CH_2)_5-OH$, $-NH-(CH_2)_2-OCH_3$, $-NH-(CH_2)_2-NH_2$, $-NH-(CH_2)_2-N(CH_3)_2$, $-NH$ -(1-methyl-1H-pyrazol-4-yl), $-NH$ -(4-hydroxycyclohexyl), $-NH$ -(*trans*-4-hydroxycyclohexyl), $-NH$ -(*cis*-4-hydroxycyclohexyl), $-NH$ -(2-(2,2,2-trifluoroethoxy)-benzyl), 3,3-difluoro-pyrrolidin-1-yl, 3,3-difluoro-piperidin-1-yl, 4,4-difluoro-piperidin-1-yl, piperazin-1-yl, pyrrolidin-1-yl, 3-hydroxy-pyrrolidin-1-yl, (*R*)-3-hydroxy-pyrrolidin-1-yl, (*S*)-3-hydroxy-pyrrolidin-1-yl, 2-(4-chlorophenyl)-pyrrolidin-1-yl, (*R*)-2-(4-chlorophenyl)-pyrrolidin-1-yl, (*S*)-2-(4-chlorophenyl)-pyrrolidin-1-yl, 4,4-difluoro-piperidin-1-yl, N-morpholin-4-yl, 3-hydroxy-azetidiny, 3-methoxy-azetidiny, 3,3-difluoro-azetidiny;
- 10 R^7 denotes $-C(=O)-CH_3$, SO_2CH_3 ;
- 15 R^8 denotes NH -cyclopropyl, 3-methoxy-azetidiny;
- Hetar¹ denotes 1-methyl-1H-pyrazol-3-yl, 1-methyl-1H-pyrazol-4-yl, 1-methyl-1H-imidazol-2-yl, 1-methyl-1H-imidazol-4-yl, 1-(2-hydroxyethyl)-1H-imidazol-2-yl, 1-(2-hydroxyethyl)-1H-imidazol-4-yl, 2-amino-pyridin-4-yl, 4-amino-pyridin-2-yl;
- 20 Hetcyc¹ denotes pyrrolidin-2-one, 3-methyl-pyrrolidin-2-one, (*R*)-3-methyl-pyrrolidin-2-one, (*S*)-3-methyl-pyrrolidin-2-one, morpholin-4-yl, piperazin-1-yl;
- and/or
- 25 R^4 denotes 3,4-dimethoxyphenyl, 3-methylphenyl, 4-(1-methyl-1H-pyrazol-4-yl)-phenyl, 4-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]-phenyl, 1-methyl-1H-indazol-5-yl, 1-methyl-1H-indazol-6-yl.

Particularly preferred embodiments of the present invention is a compound, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including

30 mixtures thereof in all ratios, that is selected from the group consisting of:

- (1) 3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid methylamide
- (2) 3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid
cyclopropylamide
- (3) 3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid (2-methoxy-ethyl)-amide
- (4) (3,3-Difluoro-pyrrolidin-1-yl)-[3-(3-methyl-benzyl)-1H-indazol-5-yl]-methanone
- (5) 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid amide
- (6) 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid cyclopropylamide
- (7) 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid methylamide
- (8) 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid (2-methoxy-ethyl)-amide
- (9) [3-(3-Methyl-benzyl)-1H-indazol-5-yl]-piperazin-1-yl-methanone
- (10) 3-(1-Methyl-1H-indazol-6-ylmethyl)-1H-indazole-5-carboxylic acid
methylamide
- (11) (3,3-Difluoro-pyrrolidin-1-yl)-[3-(3,4-dimethoxy-benzyl)-1H-indazol-5-yl]-methanone
- (12) 3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid amide
- (13) [3-(3,4-Dimethoxy-benzyl)-1H-indazol-5-yl]-((R)-3-hydroxy-pyrrolidin-1-yl)-methanone
- (14) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid
methylamide
- (15) (3,3-Difluoro-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone
- (16) (3,3-Difluoro-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- (17) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic
acid cyclopropylamide
- (18) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic
acid (2-methoxy-ethyl)-amide
- (19) [3-(3,4-Dimethoxy-benzyl)-1H-indazol-5-yl]-((S)-3-hydroxy-pyrrolidin-1-yl)-methanone

- (20) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid amide
- (21) {3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-piperazin-1-yl-methanone
- 5 (22) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (1-methyl-1H-pyrazol-4-yl)-amide
- (23) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid amide
- (24) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid cyclopropylamide
- 10 (25) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (2-methoxy-ethyl)-amide
- (26) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (1-methyl-1H-pyrazol-4-yl)-amide
- 15 (27) 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid (4-hydroxy-cyclohexyl)-amide
- (28) (3,3-Difluoro-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone
- (29) 3-(1-Methyl-1H-indazol-6-ylmethyl)-1H-indazole-5-carboxylic acid cyclopropylamide
- 20 (30) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (4-hydroxy-cyclohexyl)-amide
- (31) ((S)-3-Hydroxy-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- 25 (32) ((R)-3-Hydroxy-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone
- (33) ((S)-3-Hydroxy-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone
- (34) ((R)-3-Hydroxy-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- 30 (35) [(R)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone

- (36) [(R)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3-methyl-benzyl)-1H-indazol-5-yl]-methanone
- (37) [(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone
- 5 (38) [(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3-methyl-benzyl)-1H-indazol-5-yl]-methanone
- (39) 3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid 2-(2,2,2-trifluoro-ethoxy)-benzylamide
- 10 (40) [(R)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3,4-dimethoxy-benzyl)-1H-indazol-5-yl]-methanone
- (41) [(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3,4-dimethoxy-benzyl)-1H-indazol-5-yl]-methanone
- (42) 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid 2-(2,2,2-trifluoro-ethoxy)-benzylamide
- 15 (43) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-pyrazolo[4,3-b]pyridine-5-carboxylic acid methylamide
- (44) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid methylamide
- (45) (3,3-Difluoro-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-ethanone
- 20 (46) (3,3-Difluoro-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-pyrazolo[4,3-b]pyridin-5-yl]-ethanone
- (47) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-pyrazolo[4,3-b]pyridine-5-carboxylic acid methylamide
- 25 (48) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid methylamide
- (49) (3,3-Difluoro-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}-methanone
- (50) (3,3-Difluoro-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-pyrazolo[4,3-b]pyridin-5-yl}-methanone
- 30 (51) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (2-amino-ethyl)-amide

- (52) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (2-dimethylamino-ethyl)-amide
- (53) N-(4-hydroxybutyl)-3-{[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-1H-indazole-5-carboxamide
- 5 (54) N-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-acetamide
- (55) N-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanesulfonamide
- (56) 1-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyrrolidin-2-one
- 10 (57) (S)-3-Methyl-1-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyrrolidin-2-one
- (58) (R)-3-Methyl-1-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyrrolidin-2-one
- 15 (59) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-5-morpholin-4-yl-1H-indazole
- (60) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-5-piperazin-1-yl-1H-indazole
- (61) 5-[(4,4-difluoropiperidin-1-yl)carbonyl]-3-{[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-1H-indazole
- 20 (62) 5-[(3,3-difluoropiperidin-1-yl)carbonyl]-3-{[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-1H-indazole
- (63) 3-{[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-5-[(morpholin-4-yl)carbonyl]-1H-indazole
- 25 (64) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-sulfonic acid cyclopropylamide
- (65) 5-(3-Methoxy-azetidine-1-sulfonyl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole
- (66) (3-Methoxy-azetidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone
- 30 (67) (3-Hydroxy-azetidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone

- (68) (3,3-Difluoro-azetidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone
- (69) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (2-hydroxy-ethyl)-amide
- 5 (70) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (2-amino-ethyl)-amide
- (71) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (2-dimethylamino-ethyl)-amide
- (72) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (3-hydroxy-propyl)-amide
- 10 (73) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (4-hydroxy-butyl)-amide
- (74) N-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-acetamide
- 15 (75) N-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanesulfonamide
- (76) 1-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-pyrrolidin-2-one
- (77) (S)-3-Methyl-1-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-pyrrolidin-2-one
- 20 (78) (R)-3-Methyl-1-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-pyrrolidin-2-one
- (79) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid methylamide
- 25 (80) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (4-hydroxy-cyclohexyl)-amide
- (81) (3-Methoxy-azetidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- (82) (3-Hydroxy-azetidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- 30 (83) (3,3-Difluoro-azetidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone

- (84) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (2-hydroxy-ethyl)-amide
- (85) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (3-hydroxy-propyl)-amide
- 5 (86) {3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyrrolidin-1-yl-methanone
- (87) {3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-piperidin-1-yl-methanone
- (88) 3-(1-Methyl-1H-indazol-6-ylmethyl)-1H-indazole-5-carboxylic acid
10 2-(2,2,2-trifluoro-ethoxy)-benzylamide
- (89) 5-(1-Methyl-1H-pyrazol-3-yl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole
- (90) 4-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyridin-2-ylamine
- 15 (91) [(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- (92) 3-{[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-N-{[2-(2,2,2-trifluoroethoxy)phenyl]methyl}-1H-indazole-5-carboxamide
- (93) [3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-piperazin-1-yl-methanone
20
- (94) 5-(1-Methyl-1H-imidazol-2-yl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole
- (95) 2-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyridin-4-ylamine
- 25 (96) 5-(1-Methyl-1H-imidazol-4-yl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole
- (97) 2-(2-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-imidazol-1-yl)-ethanol
- (98) 4-[3-[(1-methylindazol-5-yl)methyl]-1H-indazol-5-yl]morpholine
- 30 (99) 1-methyl-5-[[5-(1-methylpyrazol-3-yl)-1H-indazol-3-yl]methyl]indazole

- (100) ((S)-3-Hydroxy-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone
- (101) ((R)-3-Hydroxy-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone
- 5 (102) [(R)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- (103) N-{2-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-ylamino]-ethyl}-acetamide
- (104) [3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-pyridin-4-yl-amine
- 10 (105) 1-methyl-5-[[5-(1-methylimidazol-4-yl)-1H-indazol-3-yl]methyl]indazole
- (106) 1-methyl-5-[[5-(1-methylimidazol-2-yl)-1H-indazol-3-yl]methyl]indazole
- 15 (107) 2-{2-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-imidazol-1-yl}-ethanol
- (108) {3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyridin-4-yl-amine
- (109) (3,3-Difluoro-pyrrolidin-1-yl)-(3-{4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazol-5-yl)-methanone
- 20 (110) (3-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazol-5-yl)-pyrrolidin-1-yl-methanone
- (111) (3,3-Difluoro-azetidin-1-yl)-(3-{4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazol-5-yl)-methanone
- 25 (112) 3-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazole-5-carboxylic acid methylamide
- (113) N-(2-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-ylamino}-ethyl)-acetamide
- 30 (114) 2-{4-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-imidazol-1-yl}-ethanol.

As used herein, the following definitions shall apply unless otherwise indicated:

- 5 The term “aliphatic” or “aliphatic group”, as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as
- 10 “carbocycle” “cycloaliphatic” or “cycloalkyl”), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-8 or 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other
- 15 embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, “cycloaliphatic” (or “carbocycle” or “cycloalkyl”) refers to a monocyclic C₃-C₇ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single
- 20 point of attachment to the rest of the molecule. Exemplary aliphatic groups are linear or branched, substituted or unsubstituted C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.
- 25 In particular, the term “C₁₋₃-alkyl” refers to alkyl groups having 1, 2 or 3 carbon atoms. Exemplary C₁₋₃-alkyl groups are methyl, ethyl, propyl and isopropyl. The term “C₁₋₄-alkyl” refers to alkyl groups having 1, 2, 3 or 4 carbon atoms. Exemplary C₁₋₄-alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl. The term “C₁₋₆-alkyl” refers to alkyl
- 30 groups having 1, 2, 3, 4, 5 or 6 carbon atoms. Exemplary C₁₋₆-alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, n-pentyl, 2-pentyl, n-hexyl, 2-hexyl, n-septyl, 2-septyl, n-octyl, 2-octyl, 2,2,4-

trimethylpentyl. Each of these alkyl groups may be straight-chain or – except for C₁-alkyl and C₂-alkyl – branched and may be unsubstituted or substituted with 1, 2 or 3 substituents that may be the same or different and are, if not specified differently elsewhere in this specification, selected from the group comprising halogen, hydroxy, alkoxy, unsubstituted or mono- or di-substituted amino.

In some instances the C₁₋₃-alkyl, C₁₋₄-alkyl, C₁₋₆-alkyl, C₁₋₈-alkyl groups may also comprise those residues in which 1 or 2 of non-terminal and non-adjacent –CH₂- (methylene) groups are replaced by –O-, –S- and/or 1 or 2 non-terminal and non-adjacent –CH₂- or –CH- groups are replaced by –NH- or –N-. These replacements yield, for instance, alkyl group like –CH₂-CH₂-O-CH₃, –CH₂-CH₂-CH₂-S-CH₃, CH₂-CH₂-NH-CH₂-CH₃, CH₂-CH₂-O-CH₂-CH₂-O-CH₃, CH₂-CH₂-N(CH₃)-CH₂-CH₃, and the like.

The term “C₃₋₅-cycloalkyl” refers to a cycloaliphatic hydrocarbon, as defined above, with 3, 4 or 5 ring carbon atoms. C₃₋₅-cycloalkyl groups may be unsubstituted or substituted with – unless specified differently elsewhere in this specification – 1, 2 or 3 substituents that may be the same or different and are – unless specified differently elsewhere in this specification – selected from the group comprising C₁₋₆-alkyl, O- C₁₋₆-alkyl, halogen, hydroxy, alkoxy, unsubstituted or mono- or di-substituted amino. Exemplary C₃₋₅-cycloalkyl groups are cyclopropyl, 2-methyl-cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl.

The term “alkoxy” refers to alkyl substituents and residues that are connected to another structural moiety via an oxygen atom (-O-). Sometimes, it is also referred to as “O-alkyl” and more specifically as “O-C₁₋₄-alkyl”, “O-C₁₋₆-alkyl”, “O-C₁₋₈-alkyl”. Like the similar alkyl groups, it may be straight-chain or – except for –O-C₁-alkyl and –O-C₂-alkyl – branched and may be unsubstituted or substituted with 1, 2 or 3 substituents that may be the same or different and are, if not specified differently elsewhere in this specification, selected

from the group comprising halogen, unsubstituted or mono- or di-substituted amino. Exemplary alkoxy groups are methoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, n-propoxy, iso-propoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy.

5

The term "alkylene" refers to a divalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, in particular 1, 2, 3, 4 or 5. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced by (or with) a substituent. Suitable substituents include those described herein for a substituted alkyl group. In some instances 1 or 2 non-adjacent methylene groups of the alkylene chain may be replaced by O, S and/or NH or N-C₁₋₄-alkyl. Exemplary alkylene groups are $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-CH_2-NH-CH_2-CH_2-$, $-CH_2-N(CH_3)-CH_2-CH_2-$.

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15

The term "halogen" means F, Cl, Br, or I.

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The term "heteroatom" means one or more of oxygen (O), sulfur (S), or nitrogen (N), including, any oxidized form of nitrogen or sulfur; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidiny) or NR^+ (as in N-substituted pyrrolidiny)).

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The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic and bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term "aryl" is used interchangeably with the term "aryl ring". In certain embodiments of the present invention, "aryl" refers to an "aromatic ring system". More specifically, those aromatic ring systems may be mono-, bi- or tricyclic with 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 ring carbon

- atoms. Even more specifically, those aromatic ring systems may be mono- or bicyclic with 6, 7, 8, 9, 10 ring carbon atoms. Exemplary aryl groups are phenyl, biphenyl, naphthyl, anthracyl and the like, which may be unsubstituted or substituted with one or more identical or different substituents. Also included within the scope of the terms “aryl” or “aromatic ring system”, as they are used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.
- 10 The terms “heteroaryl” and “heteroar-”, used alone or as part of a larger moiety, e.g., “heteroaralkyl”, or “heteroaralkoxy”, refer to groups having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, 1, 2, 3, 4 or 5 heteroatoms. The term “heteroatom” refers to
- 15 nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms “heteroaryl” and “heteroar-”, as
- 20 used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. A
- 25 heteroaryl group is optionally mono-, bi- or tricyclic. The term “heteroaryl” is used interchangeably with the terms “heteroaryl ring”, “heteroaryl group”, or “heteroaromatic”, any of which terms include rings that are unsubstituted or substituted with one or more identical or different substituents. The term
- 30

“heteroaralkyl” refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

- As used herein, the terms “heterocycle”, “heterocyclyl”, “heterocyclic radical”, and “heterocyclic ring” are used interchangeably and refer to a stable 3-, 4-, 5-, 6- or 7-membered monocyclic or 7-, 8-, 9- or 10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably 1, 2, 3 or 4, heteroatoms, as defined herein. When used in reference to a ring atom of a heterocycle, the term “nitrogen” includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 1–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen is N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or ⁺NR (as in *N*-substituted pyrrolidinyl).
- A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms may be unsubstituted or substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, morpholinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms “heterocycle”, “heterocyclyl”, “heterocyclyl ring”, “heterocyclic group”, “heterocyclic moiety”, and “heterocyclic radical”, are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the heterocyclyl ring. A heterocyclyl group is optionally mono- or bicyclic. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are unsubstituted or substituted.

The term “unsaturated”, as used herein, means that a moiety has one or more units of unsaturation.

- 5 As used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.
- 10 As described herein, certain compounds of the invention contain “substituted” or “optionally substituted” moieties. In general, the term “substituted”, whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. “Substituted” applies to one or more hydrogens that are either explicit or
- 15 implicit from the structure. Unless otherwise indicated, a “substituted” or “optionally substituted” group has a suitable substituent at each substitutable position of the group, and when more than one position in any given structure is substituted with more than one substituent selected from a specified group, the substituent is either the same or different at every position. Combinations
- 20 of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable”, as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the
- 25 purposes disclosed herein.

- In the context of the present invention the term “derivative” means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing,
- 30 either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

- The compounds of the present invention can be in the form of a prodrug compound. "Prodrugs" and "prodrug compound" mean a derivative that is converted into a biologically active compound according to the present invention under physiological conditions in the living body, e.g., by oxidation, reduction, hydrolysis or the like, each of which is carried out enzymatically, or without enzyme involvement. Examples of prodrugs are compounds, in which the amino group in a compound of the present invention is acylated, alkylated or phosphorylated, e.g., eicosanoylamino, alanylamino, pivaloyloxymethylamino or in which the hydroxyl group is acylated, alkylated, phosphorylated or converted into the borate, e.g. acetyloxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaryloxy, alanyloxy or in which the carboxyl group is esterified or amidated, or in which a sulfhydryl group forms a disulfide bridge with a carrier molecule, e.g. a peptide, that delivers the drug selectively to a target and/or to the cytosol of a cell. These compounds can be produced from compounds of the present invention according to well-known methods. Other examples of prodrugs are compounds, wherein the carboxylate in a compound of the present invention is for example converted into an alkyl-, aryl-, choline-, amino, acyloxymethylester, linolenoyl-ester.
- The term "solvates" means addition forms of the compounds of the present invention with solvents, preferably pharmaceutically acceptable solvents, that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate, e.g. a mono- or dihydrate. If the solvent is alcohol, the solvate formed is an alcoholate, e.g., a methanolate or ethanolate. If the solvent is an ether, the solvate formed is an etherate, e.g., diethyl etherate.
- The compounds of formula (I) may have one or more centres of chirality. They may accordingly occur in various enantiomeric and diastereomeric forms, as the case may be, and be in racemic or optically active form. The

invention, therefore, also relates to the optically active forms, enantiomers, racemates, diastereomers, collectively: "stereoisomers" for the purpose of the present invention, of these compounds. Since the pharmaceutical activity of the racemates or stereoisomers of the compounds according to the invention may differ, it may be desirable to use a specific stereoisomer, e.g. one specific enantiomer or diastereomer. In these cases, a compound according to the present invention obtained as a racemate - or even intermediates thereof - may be separated into the stereoisomeric (enantiomeric, diastereoisomeric) compounds by chemical or physical measures known to the person skilled in the art. Another approach that may be applied to obtain one or more specific stereoisomers of a compound of the present invention in an enriched or pure form makes use of stereoselective synthetic procedures, e.g. applying starting material in a stereoisomerically enriched or pure form (for instance using the pure or enriched (R)- or (S)-enantiomer of a particular starting material bearing a chiral center) or utilizing chiral reagents or catalysts, in particular enzymes.

Thus, for example, the compounds of the invention which have one or more centers of chirality and which occur as racemates or as mixtures of enantiomers or diastereoisomers can be fractionated or resolved by methods known per se into their optically pure or enriched isomers, i.e. enantiomers or diastereomers. The separation of the compounds of the invention can take place by chromatographic methods, e.g. column separation on chiral or nonchiral phases, or by recrystallization from an optionally optically active solvent or by use of an optically active acid or base or by derivatization with an optically active reagent such as, for example, an optically active alcohol, and subsequent elimination of the radical.

In the context of the present invention the term "tautomer" refers to compounds of the present invention that may exist in tautomeric forms and show tautomerism; for instance, carbonyl compounds may be present in their keto and/or their enol form and show keto-enol tautomerism. Those

tautomers may occur in their individual forms, e.g., the keto or the enol form, or as mixtures thereof and are claimed separately and together as mixtures in any ratio. The same applies for cis/trans isomers, *E/Z* isomers, conformers and the like.

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The compounds of the present invention can be in the form of a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, or a pharmaceutically acceptable solvate of a pharmaceutically acceptable salt.

10 The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable bases or acids, including inorganic bases or acids and organic bases or acids. In cases where the compounds of the present invention contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically acceptable salts. Thus,

15 the compounds of the present invention which contain acidic groups can be present in salt form, and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines

20 such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the present invention which contain one or more basic groups, e.g. groups which can be protonated, can be present in salt form, and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples of suitable acids include hydrogen

25 chloride, hydrogen bromide, hydrogen iodide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, sulfoacetic acid, trifluoroacetic acid, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, carbonic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid,

30 succinic acid, pimelic acid, fumaric acid, malonic acid, maleic acid, malic acid, embonic acid, mandelic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid,

taurocholic acid, glutaric acid, stearic acid, glutamic acid or aspartic acid, and other acids known to the person skilled in the art. The salts which are formed are, inter alia, hydrochlorides, chlorides, hydrobromides, bromides, iodides, sulfates, phosphates, methanesulfonates (mesylates), tosylates, carbonates, bicarbonates, formates, acetates, sulfoacetates, triflates, oxalates, malonates, maleates, succinates, tartrates, malates, embonates, mandelates, fumarates, lactates, citrates, glutarates, stearates, aspartates and glutamates. The stoichiometry of the salts formed from the compounds of the invention may moreover be an integral or non-integral multiple of one.

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If the compounds of the present invention simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts can be obtained by customary methods which are known to a person skilled in the art, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the present invention which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

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Therefore, the following items are also in accordance with the invention:

- (a) all stereoisomers or tautomers of the compounds, including mixtures thereof in all ratios,
- (b) prodrugs of the compounds, or stereoisomers or tautomers of these prodrugs,
- (c) pharmaceutically acceptable salts of the compounds and of the items mentioned under (a) and (b),
- (d) pharmaceutically acceptable solvates of the compounds and of the items mentioned under (a), (b) and (c).

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It should be understood that all references to compounds above and below are meant to include these items, in particular pharmaceutically acceptable solvates of the compounds, or pharmaceutically acceptable solvates of their pharmaceutically acceptable salts.

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Furthermore, the present invention relates to pharmaceutical compositions comprising at least one compound of formula (I), or its derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, as active ingredient, together with a pharmaceutically acceptable carrier.

10

For the purpose of the present invention the term "pharmaceutical composition" refers to a composition or product comprising one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing at least one compound of the present invention and a pharmaceutically acceptable carrier. It may further comprise physiologically acceptable excipients, auxiliaries, adjuvants, diluents and/or additional pharmaceutically active substance other than the compounds of the invention.

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The pharmaceutical compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit

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dosage form and prepared by any of the methods well-known in the art of pharmacy.

A pharmaceutical composition of the present invention may additionally
5 comprise one or more other compounds as active ingredients (drugs), such
as one or more additional compounds of the present invention. In a particular
embodiment the pharmaceutical composition further comprises a second
active ingredient or its derivatives, prodrugs, solvates, tautomers or
10 stereoisomers thereof as well as the physiologically acceptable salts of each
of the foregoing, including mixtures thereof in all ratios, wherein that second
active ingredient is other than a compound of formula (I); preferably, that
second active ingredient is a compound that is useful in the treatment,
prevention, suppression and/or amelioration of medicinal conditions or
15 pathologies for which the compounds of the present invention are useful as
well and which are listed elsewhere hereinbefore or hereinafter. Such
combination of two or more active ingredients or drugs may be safer or more
effective than either drug or active ingredient alone, or the combination is
safer or more effective than would it be expected based on the additive
20 properties of the individual drugs. Such other drug(s) may be administered,
by a route and in an amount commonly used contemporaneously or
sequentially with a compound of the invention. When a compound of the
invention is used contemporaneously with one or more other drugs or active
ingredients, a combination product containing such other drug(s) and the
25 compound of the invention – also referred to as “fixed dose combination” – is
preferred. However, combination therapy also includes therapies in which the
compound of the present invention and one or more other drugs are
administered on different overlapping schedules. It is contemplated that when
used in combination with other active ingredients, the compound of the
30 present invention or the other active ingredient or both may be used
effectively in lower doses than when each is used alone. Accordingly, the
pharmaceutical compositions of the present invention include those that

contain one or more other active ingredients, in addition to a compound of the invention.

5 The compounds of the present invention can be used as medicaments. They exhibit pharmacological activity by inhibiting CDK8 and/or CDK19 kinase. Thus, they are useful for the treatment, prevention, suppression and/or amelioration of medicinal conditions or pathologies that are affected by CDK8 activity and likewise by CDK19 activity. As CDK8 is an activator of the Wnt/ β -catenin pathway, the compounds of the present invention are useful for the
10 treatment, prevention, suppression and/or amelioration of medicinal conditions or pathologies in which Wnt/ β -catenin signaling plays a role. The compounds of the present invention are thus particularly useful for the treatment of a hyperproliferative, inflammatory or degenerative disorder. More specifically, they are useful for the treatment of a disorder or disease
15 selected from the group consisting of brain, lung, colon, epidermoid, squamous cell, bladder, gastric, pancreatic, breast, head & neck, renal, kidney, liver, ovarian, prostate, uterine, oesophageal, testicular, gynecological, thyroid cancer; melanoma, acute myelogenous leukemia, multiple myeloma, chronic myelogenous leukemia, myeloid cell leukemia,
20 Kaposi's sarcoma; multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematoses (SLE) or inflammatory bowel disease; osteoarthritis or Alzheimer's disease. Even more specifically, they are particularly useful for the treatment of the various cancer and tumor diseases listed above, in particular of colon cancer and melanoma.

25 Surprisingly, the compounds of the present invention are inhibiting CDK8 and CDK19 in a selective manner and may not show any significant activity at other pharmacological targets. In particular, they may not inhibit HSP (Heat Shock Protein) 90 considerably. This allows to use the compounds of the
30 present invention in the treatment of diseases or medical conditions where selective inhibition of CDK8 and/or CDK 19 may be beneficial, desired or warranted.

Recent studies (Porter D.C. et al., Proc. Nat. Ac. Sci. 109: 13799-13804 (2012)) have demonstrated the role of CDK8 in damage-induced tumor-promoting paracrine activities. The compounds of the present invention are therefore in particular useful for increasing the efficacy of cancer therapy and may not only be administered in mono-therapy but in combination with and/or addition to other therapeutic agents for treating cancer.

The disclosed compounds of the formula (I) can be administered and/or used in combination with other known therapeutic agents, including anticancer agents. As used herein, the term "anticancer agent" relates to any agent which is administered to a patient with cancer for the purposes of treating the cancer.

The anti-cancer treatment defined above may be applied as a monotherapy or may involve, in addition to the herein disclosed compounds of formula (I), conventional surgery or radiotherapy or medicinal therapy. Such medicinal therapy, e.g. a chemotherapy or a targeted therapy, may include one or more, but preferably one, of the following anti-tumor agents:

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Alkylating agents

such as altretamine, bendamustine, busulfan, carmustine, chlorambucil, chlormethine, cyclophosphamide, dacarbazine, ifosfamide, improsulfan, tosilate, lomustine, melphalan, mitobronitol, mitolactol, nimustine, ranimustine, temozolomide, thiotepa, treosulfan, mechlorethamine, carboquone; apaziquone, fotemustine, glufosfamide, palifosfamide, pipobroman, trofosfamide, uramustine, TH-302⁴, VAL-083⁴;

Platinum Compounds

such as carboplatin, cisplatin, eptaplatin, miriplatine hydrate, oxaliplatin, lobaplatin, nedaplatin, picoplatin, satraplatin;

DNA altering agents

such as amrubicin, bisantrene, decitabine, mitoxantrone, procarbazine, trabectedin, clofarabine;

amsacrine, brostallicin, pixantrone, laromustine^{1,3};

Topoisomerase Inhibitors

- 5 such as etoposide, irinotecan, razoxane, sobuzoxane, teniposide, topotecan; amonafide, belotecan, elliptinium acetate, voreloxin;

Microtubule modifiers

such as cabazitaxel, docetaxel, eribulin, ixabepilone, paclitaxel, vinblastine, vincristine, vinorelbine, vindesine, vinflunine;

- 10 fosbretabulin, tesetaxel;

Antimetabolites

such as asparaginase³, azacitidine, calcium levofolinate, capecitabine, cladribine, cytarabine, enocitabine, floxuridine, fludarabine, fluorouracil, gemcitabine, mercaptopurine, methotrexate, nelarabine, pemetrexed,

- 15 pralatrexate, azathioprine, thioguanine, carmofur; doxifluridine, elacytarabine, raltitrexed, sapacitabine, tegafur^{2,3}, trimetrexate;

Anticancer antibiotics

such as bleomycin, dactinomycin, doxorubicin, epirubicin, idarubicin, levamisole, miltefosine, mitomycin C, romidepsin, streptozocin, valrubicin, zinostatin,

- 20 zorubicin, daunorubicin, plicamycin; aclarubicin, peplomycin, pirarubicin;

Hormones/Antagonists

such as abarelix, abiraterone, bicalutamide, buserelin, calusterone, chlorotrianisene, degarelix, dexamethasone, estradiol, fluocortolone

- 25 fluoxymesterone, flutamide, fulvestrant, goserelin, histrelin, leuprorelin, megestrol, mitotane, nafarelin, nandrolone, nilutamide, octreotide, prednisolone, raloxifene, tamoxifen, thyrotropin alfa, toremifene, trilostane, triptorelin, diethylstilbestrol;

acolbifene, danazol, deslorelin, epitiostanol, orteronel, enzalutamide^{1,3};

- 30 Aromatase inhibitors

such as aminoglutethimide, anastrozole, exemestane, fadrozole, letrozole, testolactone;
formestane;

Small molecule kinase inhibitors

- 5 such as crizotinib, dasatinib, erlotinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, ruxolitinib, sorafenib, sunitinib, vandetanib, vemurafenib, bosutinib, gefitinib, axitinib;
afatinib, alisertib, dabrafenib, dacomitinib, dinaciclib, dovitinib, enzastaurin, nintedanib, lenvatinib, linifanib, linsitinib, masitinib, midostaurin, motesanib,
10 neratinib, orantinib, perifosine, ponatinib, radotinib, rigosertib, tipifarnib, tivantinib, tivozanib, trametinib, pimasertib, brivanib alaninate, cediranib, apatinib⁴, cabozantinib S-malate^{1,3}, ibrutinib^{1,3}, icotinib⁴, buparlisib², cipatinib⁴, cobimetinib^{1,3}, idelalisib^{1,3}, fedratinib¹, XL-647⁴;

Photosensitizers

- 15 such as methoxsalen³;
porfimer sodium, talaporfin, temoporfin;

Antibodies

- such as alemtuzumab, besilesomab, brentuximab vedotin, cetuximab, denosumab, ipilimumab, ofatumumab, panitumumab, rituximab, tositumomab,
20 trastuzumab, bevacizumab, pertuzumab^{2,3};
catumaxomab, elotuzumab, epratuzumab, farletuzumab, mogamulizumab, necitumumab, nimotuzumab, obinutuzumab, ocaratuzumab, oregovomab, ramucirumab, rilotumumab, siltuximab, tocilizumab, zalutumumab, zanolimumab, matuzumab, dalotuzumab^{1,2,3}, onartuzumab^{1,3}, racotumomab¹,
25 tabalumab^{1,3}, EMD-525797⁴, nivolumab^{1,3};

Cytokines

such as aldesleukin, interferon alfa², interferon alfa2a³, interferon alfa2b^{2,3};
celmoleukin, tasonermin, teceleukin, oprelvekin^{1,3}, recombinant interferon beta-1a⁴;

- 30 Drug Conjugates

such as denileukin diftitox, ibritumomab tiuxetan, iobenguane I123, prednimustine, trastuzumab emtansine, estramustine, gemtuzumab, ozogamicin,

aflibercept;

cintredekin besudotox, edotreotide, inotuzumab ozogamicin, naptumomab estafenatox, oportuzumab monatox, technetium (99mTc) arcitumomab^{1,3}, vintafolide^{1,3};

5 Vaccines

such as sipuleucel³; vitespen³, emepepimut-S³, oncoVAX⁴, rindopepimut³, troVax⁴, MGN-1601⁴, MGN-1703⁴;

Miscellaneous

10 alitretinoin, bexarotene, bortezomib, everolimus, ibandronic acid, imiquimod, lenalidomide, lentinan, metirosine, mifamurtide, pamidronic acid, pegaspargase, pentostatin, sipuleucel³, sizofiran, tamibarotene, temsirolimus, thalidomide, tretinoin, vismodegib, zoledronic acid, vorinostat;

celecoxib, cilengitide, entinostat, etanidazole, ganetespib, idronoxil, iniparib, ixazomib, lonidamine, nimorazole, panobinostat, peretinoin, plitidepsin,

15 pomalidomide, procodazol, ridaforolimus, tasquinimod, telotristat, thymalfasin, tirapazamine, tosedostat, trabedersen, ubenimex, valspodar, gendicine⁴, picibanil⁴, reolysin⁴, retaspimycin hydrochloride^{1,3}, trebananib^{2,3}, virulizin⁴, carfilzomib^{1,3}, endostatin⁴, immucothel⁴, belinostat³, MGN-1703⁴;

¹ **Prop. INN (Proposed International Nonproprietary Name)**

20 ² **Rec. INN (Recommended International Nonproprietary Names)**

³ **USAN (United States Adopted Name)**

⁴ **no INN.**

25 Examples of other active substances (ingredients, drugs) that may be administered in combination with a compound of the invention, and either administered separately or in the same pharmaceutical composition and are useful for the treatment of diseases other than cancer, include, but are not limited to the compound classes and specific compounds listed in the following:

30 - Multiple sclerosis (MS): beta interferones, dimethyl fumarate, glatiramer acetate, azathioprine, immunoglobulines, natalizumab, fingolimod, mitoxantrone, cyclophosphamide;

- Rheumatoid arthritis (RA): methotrexate, leflunomide, sulfasalazine, chloroquine, hydroxychloroquine, cyclosporine A, azathioprine, auranofin, adalimumab, certilizumab, etanercept, golimumab, infliximab, anakinra, rituximab, abatacept, tocilizumab, cortisone;
- 5 - Systemic lupus erythematoses (SLE): NSAIDs, chloroquine, cortisone, azathioprine, cyclophosphamide, cyclosporine, mycophenolate-motefil (MMF), methotrexate, thalidomide;
- Inflammatory bowel disease: mesalazine, prednisone, azathioprine, methotrexate, 6-mercaptopurine, immunosuppressants;
- 10 - Osteoarthritis: NSAIDs, COX-2 inhibitors;
- Alzheimer's disease: memantine, galantamine, rivastigmine, donepezil.

A further embodiment of the present invention is a process for the manufacture of the pharmaceutical compositions of the present invention, characterized in that one or more compounds according to the invention and one or more compounds selected from the group consisting of solid, liquid or semiliquid excipients, auxiliaries, adjuvants, diluents, carriers and pharmaceutically active agents other than the compounds according to the invention, are converted in a suitable dosage form.

20

In another aspect of the invention, a set or kit is provided comprising a therapeutically effective amount of at least one compound of the invention and/or at least one pharmaceutical composition as described herein and a therapeutically effective amount of at least one further pharmacologically active substance other than the compounds of the invention. It is preferred that this set or kit comprises separate packs of

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a) an effective amount of a compound of formula (I), or its derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, and

30

b) an effective amount of a further active ingredient that further active ingredient not being a compound of formula (I).

5 The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by oral, parenteral, topical, enteral, intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal, transocular, subcutaneous, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the
10 oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. Parenteral administration is preferred. Oral administration is especially preferred.

15 Suitable dosage forms include, but are not limited to capsules, tablets, pellets, dragees, semi-solids, powders, granules, suppositories, ointments, creams, lotions, inhalants, injections, cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion, which can be produced according to methods known in the art, for example as described below:

20 Tablets: mixing of active ingredient/s and auxiliaries, compression of said mixture into tablets (direct compression), optionally granulation of part of mixture before compression.

25 Capsules: mixing of active ingredient/s and auxiliaries to obtain a flowable powder, optionally granulating powder, filling powders/granulate into opened capsules, capping of capsules.

30 Semi-solids (ointments, gels, creams): dissolving/dispersing active ingredient/s in an aqueous or fatty carrier; subsequent mixing of aqueous/fatty phase with complementary fatty/ aqueous phase, homogenization (creams only).

Suppositories (rectal and vaginal): dissolving/dispersing active ingredient/s in carrier material liquified by heat (rectal: carrier material normally a wax; vaginal: carrier normally a heated solution of a gelling agent), casting said mixture into suppository forms, annealing and withdrawal suppositories from the forms.

Aerosols: dispersing/dissolving active agent/s in a propellant, bottling said mixture into an atomizer.

10

In general, non-chemical routes for the production of pharmaceutical compositions and/or pharmaceutical preparations comprise processing steps on suitable mechanical means known in the art that transfer one or more compounds of the invention into a dosage form suitable for administration to a patient in need of such a treatment. Usually, the transfer of one or more compounds of the invention into such a dosage form comprises the addition of one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds of the invention. Suitable processing steps include, but are not limited to combining, milling, mixing, granulating, dissolving, dispersing, homogenizing, casting and/or compressing the respective active and non-active ingredients. Mechanical means for performing said processing steps are known in the art, for example from Ullmann's Encyclopedia of Industrial Chemistry, 5th Edition. In this respect, active ingredients are preferably at least one compound of the invention and optionally one or more additional compounds other than the compounds of the invention, which show valuable pharmaceutical properties, preferably those pharmaceutical active agents other than the compounds of the invention, which are disclosed herein.

Particularly suitable for oral use are tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops, suitable for rectal use are suppositories, suitable for parenteral use are solutions, preferably oil-based

- or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical use are ointments, creams or powders. The compounds of the invention may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The preparations
- 5 indicated may be sterilised and/or comprise assistants, such as lubricants, preservatives, stabilisers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, dyes, flavours and/or a plurality of further active ingredients, for example one or more vitamins.
- 10 Suitable excipients are organic or inorganic substances, which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the compounds of the invention, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose, sucrose, mannitol, sorbitol or starch
- 15 (maize starch, wheat starch, rice starch, potato starch), cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, magnesium stearate, talc, gelatine, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, polyvinyl pyrrolidone and/or vaseline.
- 20 If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries include, without limitation, flow-regulating agents and lubricants, for example,
- 25 silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings, which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol
- 30 and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices or to provide a dosage form affording the advantage of prolonged action, the

tablet, dragee or pill can comprise an inner dosage and an outer dosage component the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permits the inner component to pass intact
5 into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, acetyl alcohol, solutions of suitable cellulose preparations such as acetyl-cellulose phthalate, cellulose acetate or hydroxypropylmethyl-cellulose
10 phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Suitable carrier substances are organic or inorganic substances which are
15 suitable for enteral (e.g. oral) or parenteral administration or topical application and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. In particular, tablets, coated tablets, capsules, syrups, suspensions, drops or
20 suppositories are used for enteral administration, solutions, preferably oily or aqueous solutions, furthermore suspensions, emulsions or implants, are used for parenteral administration, and ointments, creams or powders are used for topical application. The compounds of the invention can also be lyophilized and the lyophilizates obtained can be used, for example, for the
25 production of injection preparations.

Other pharmaceutical preparations, which can be used orally include push-fit capsules made of gelatine, as well as soft, sealed capsules made of gelatine and a plasticizer such as glycerol or sorbitol. The push-fit capsules can
30 contain the active compounds in the form of granules, which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules,

the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

- 5 The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable
10 dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatine.

- Suitable formulations for parenteral administration include aqueous solutions
15 of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or
20 polyethylene glycol-400 (the compounds are soluble in PEG-400).

- Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, including, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran, optionally, the suspension may also
25 contain stabilizers.

- For administration as an inhalation spray, it is possible to use sprays in which the active ingredient is either dissolved or suspended in a propellant gas or propellant gas mixture (for example CO₂ or chlorofluorocarbons). The active
30 ingredient is advantageously used here in micronized form, in which case one or more additional physiologically acceptable solvents may be present,

for example ethanol. Inhalation solutions can be administered with the aid of conventional inhalers.

5 Possible pharmaceutical preparations, which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatine rectal capsules, which consist of a combination of the active compounds with a base. Possible base materials
10 include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

For use in medicine, the compounds of the present invention may be in the form of pharmaceutically acceptable salts. Other salts may, however, be
15 useful in the preparation of the compounds of the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention are those described hereinbefore and include acid addition salts which may, for example be formed by mixing a solution of the compound according to the invention with a solution of a
20 pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali
25 metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic bases, e.g. quaternary ammonium salts.

The pharmaceutical preparations can be employed as medicaments in
30 human and veterinary medicine. As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is

being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function. Said therapeutic effective amount of one or more of the compounds of the invention is known to the skilled artisan or can be easily determined by standard methods known in the art.

The compounds of the present invention and the optional additional active substances are generally administered analogously to commercial preparations. Usually, suitable doses that are therapeutically effective lie in the range between 0.0005 mg and 1000 mg, preferably between 0.005 mg and 500 mg and especially between 0.5 mg and 100 mg per dose unit. The daily dose is preferably between about 0.001 mg/kg and 10 mg/kg of body weight.

Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Some of the specific compounds are more potent than others. Preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means. A preferred means is to measure the physiological potency of a given compound.

The specific dose for the individual patient, in particular for the individual human patient, depends, however, on the multitude of factors, for example on the efficacy of the specific compounds employed, on the age, body weight, general state of health, the sex, the kind of diet, on the time and route of administration, on the excretion rate, the kind of administration and the dosage form to be administered, the pharmaceutical combination and

severity of the particular disorder to which the therapy relates. The specific therapeutic effective dose for the individual patient can readily be determined by routine experimentation, for example by the doctor or physician, which advises or attends the therapeutic treatment.

5

The compounds of the present invention can be prepared according to the procedures of the following Schemes and Examples, using appropriate materials, and are further exemplified by the following specific examples.

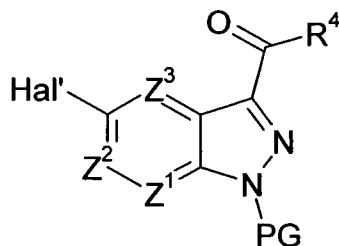
10 Moreover, by utilizing the procedures described herein, in conjunction with ordinary skills in the art, additional compounds of the present invention claimed herein can be readily prepared. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The examples further illustrate details for the
15 preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

20 The starting materials for the preparation of compounds of the present invention can be prepared by methods as described in the examples or by methods known per se, as described in the literature of synthetic organic chemistry and known to the skilled artisan, or can be obtained commercially.

25 The present invention also refers to a process for manufacturing a compound according to formula (I), or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing.

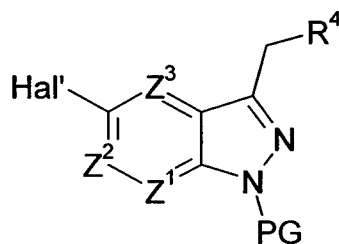
30 In a first variant of that process a compound of formula (I) wherein Z^1 , Z^2 , Z^3 , R^2 , R^3 , R^4 are as defined above or in claim 1 and R^1 denotes Hetar¹ or Hetcyc¹ that are defined as above or in claim 1, wherein that Hetar¹ or

Hetcyc¹ is connected to its pendant group via a ring carbon atom, is manufactured by reacting a compound of formula (II)



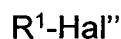
(II)

with Z¹, Z², Z³, R⁴ being as defined above, Hal' being Cl, Br or I and PG being a suitable protecting group, in a step (a) with a suitable reduction means to form a compound of formula (III)



(III)

with Z¹, Z², Z³, R⁴, Hal' and PG being as defined above; this compound of formula (III) is then further transformed in a step (b1) by means of a C-C-coupling reaction utilizing a compound of formula (IV)



(IV)

wherein R¹ denotes Hetar¹ or Hetcyc¹ that are defined as above or in claim 1, wherein that Hetar¹ or Hetcyc¹ is connected to Hal'' via a ring carbon atom, and Hal'' denotes Cl, Br or I, and subsequent removal of PG into a compound of formula (I) with Z¹, Z², Z³, R¹, R², R³, R⁴ being defined as above in this section.

In the context of the process described above a suitable protecting group, PG, is a moiety which suppresses the unwanted reaction of the N-1 atom of

the various indazoles or related heterocycles in the chemical transformation steps in which these compounds are involved and that are described herein; as the skilled person will recognize, in case a particular chemical transformation would not affect the non-protected N-1 atom, PG may also be replaced by a hydrogen atom, H. Suitable protecting groups as well as methods for introducing and removing them are well-known to the person skilled in the art of chemical synthesis and are described, in more detail, in, e.g., P.G.M. Wuts, T.W. Greene, "Greene's Protective Groups in Organic Synthesis", 4th edition (2006) (John Wiley & Sons). They may be selected, for instance, from benzyl or oxan-2-yl (tetrahydropyran-2-yl). (It is to be noted that the terms "protecting group(s)" and "protective group(s)" are used interchangeably throughout this specification and the claims.)

Suitable reduction means for performing process step (a), i.e., means for reducing the carbonyl group to which R^4 is attached to into a CH_2 moiety, are well-known to the person skilled in the art of chemical synthesis. Examples of suitable reduction means are strong bases like potassium tert.-butoxide in an appropriate solvent, e.g., DMSO; metal halides like sodium borohydride ($NaBH_4$)/trifluoroacetic acid or $LiAlH_4$; or alkylsilanes like triethylsilane.

The C-C coupling reaction by which means the transformation according to reaction step (b1) above is performed may be any suitable C-C coupling reaction of an aryl (or heteroaryl) system with a suitably substituted halide. Depending on the specific coupling reaction applied, it may well be that one or both of the reaction partners are subject to chemical transformation into intermediates before the reaction with the appropriate reaction partner occurs; for instance, the suitably substituted halide may be transformed into a respective boronic acid or boronic acid ester derivative before the reaction with the aryl (or heteroaryl) system occurs. Preferably, this coupling reaction is performed in the presence of a transition metal catalyst. Well-known examples of such C-C coupling reactions are, among others, the Heck reaction, the Suzuki coupling, the Stille coupling, the Negishi coupling and

coupling reactions utilizing organo cuprates. Depending on the specific method applied reagents, solvents and reaction conditions are selected accordingly. For instance, in case reaction step (b1) is performed by utilizing the Suzuki coupling, the compound of formula (III) with Hal' being Br may be
5 reacted with boronic acid (B(OH)₃) or a suitable boronic acid ester (B(OR)₃) (like trimethylborate or 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane) in the presence of an organometallic palladium (II) catalyst (like [1,1'-bis(diphenyl)phosphino]ferrocene]-dichloropalladium(II) dichloromethane complex) and optionally potassium acetate in order to form
10 a derivative of the compound of formula (III) in which the Hal' substituent is replaced by -B(OH)₂ or -B(OR)₂; this derivative may then be reacted with a halide R⁶-Hal'' of formula (IV) in the presence of a palladium(0) complex (e.g., tetrakis(triphenylphosphine)palladium(0)) and a base (e.g., sodium, potassium or cesium carbonate) to build a compound of formula (I).

15 The subsequent removal of protecting group PG, if still present, is achieved by means depending on the chemical nature of the protecting group and which are well-known to the person skilled in the art of chemical synthesis and described in P.G.M. Wuts, T.W. Greene, "Greene's Protective Groups in
20 Organic Synthesis", 4th edition (2006) (John Wiley & Sons). For instance, if PG is benzyl, then it may be removed by applying a strong base, e.g. potassium tert.-butoxide under oxidative conditions (e.g. O₂(g) (oxygen gas) atmosphere); if it is oxan-2-yl, it may be removed by means of an organic sulfonate, e.g. pyridinium p-toluenesulfonate or under reductive conditions
25 utilizing a metal catalyst (e.g. Pd/C) under H₂(g) (hydrogen gas) atmosphere.

In a second variant of the process according to the present invention a compound of formula (I) wherein Z¹, Z², Z³, R², R³, R⁴ are as defined above or in claim 1 and R¹ denotes -NHR⁷ or Hetcyc¹ wherein Hetcyc¹ is defined as
30 above or in claim 1 and Hetcyc¹ is connected to its pendant group via a ring nitrogen atom, is manufactured by reacting a compound of formula (III)

defined above in a reaction step (b2) by means of a C-N-coupling reaction utilizing a compound of formula (V)

5



with R^1 being $-\text{NHR}^7$ or Hetcyc^1 that is defined as above and as in claim 1, wherein that Hetcyc^1 is connected to the hydrogen atom H in formula (V) via a ring nitrogen atom, and subsequent removal of PG.

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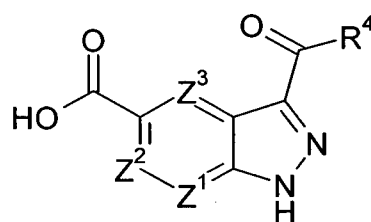
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The C-N coupling reaction by which means the transformation according to reaction step (b2) above is performed may be any suitable C-N coupling reaction of a heterocyclic system or a molecule bearing a reactive amino group with a suitably substituted halide. Depending on the specific coupling reaction applied, it may well be that one or both of the reaction partners are subject to chemical transformation into intermediates before the reaction with the appropriate reaction partner occurs; for instance, the suitably substituted halide may be transformed into a respective boronic acid or boronic acid ester derivative before the reaction with the heterocyclic system or the reactive amine derivative occurs. Preferably, this coupling reaction is performed in the presence of a transition metal catalyst. Well-known examples of such C-N coupling reactions are, among others, the Hartwig-Buchwald reaction, the Ullmann coupling reaction, reactions similar to Suzuki or Heck reaction and coupling reactions utilizing organo cuprates. Depending on the specific method applied reagents, solvents and reaction conditions are selected accordingly. For instance, in case reaction step (b2) is performed by utilizing boronic acids as intermediates and copper(II)acetate, the compound of formula (III) with Hal' being Br may be reacted with boronic acid B(OH)_3 or a suitable boronic acid ester B(OR)_3 (like boronic acid or 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane) in the presence of a organometallic palladium (II) catalyst (like [1,1'-bis(diphenyl)phosphino]ferrocene]-dichloropalladium(II) dichloromethane

complex) and optionally potassium acetate in order to form a derivative of the compound of formula (III) in which the Hal' substituent is replaced by – B(OH)₂ or –B(OR)₂; this derivative may then be reacted with the amine R¹-H of formula (V) in the presence of a copper(II) compound, e.g.,
 5 copper(II)acetate and a base like a tertiary amine, e.g., triethylamine; after removal of the protecting group, PG, with a suitable removal agent (for instance, tetrahydro-pyran-2-yl as PG is removed by applying a hydrogen chloride solution) the compound of formula (I) with R¹ being Hetcyc¹ and Z¹, Z², Z³, R², R³, R⁴ being defined as above or in claim 1 is obtained. In similar
 10 manner, compounds of formula (I) with R¹ being –NHR⁷ can be obtained.

In a third variant of the process according to the present invention a compound of formula (I) wherein Z¹, Z², Z³ and R⁴ are as defined above or in claim 1, R² and R³ are both hydrogen and R¹ denotes –C(=O)R⁶ with R⁶
 15 being as defined above or in claim 1, a compound of formula (II) as defined above is reacted in a reaction step (c) with potassium acetate in the presence of a suitable catalyst under CO(g) (carbon monoxide) atmosphere and subsequently a strong base - depending on the PG this may be under oxidative conditions, e.g., O₂(g) atmosphere (see discussion above) - to form
 20 a compound of formula (VI)



(VI)

with Z¹, Z², Z³ and R⁴ being as defined above; which compound of formula (VI) is then reacted in a subsequent step (d) with a suitable reduction means and subsequently in a reaction step (e) with a compound of formula VII

30



with R⁶ being as defined above or in claim 1, in the presence of a suitable base and a suitable catalyst to form a compound of formula (I) with R¹ being –C(=O)R⁶.

- 5 Suitable catalysts and appropriate reaction conditions as well as strong bases to be applied in reaction step (c) are well-known to the person skilled in the art of chemical synthesis. The suitable catalyst may be a palladium(II) complex, e.g., bis(diphenylphosphino)ferrocene)-palladium(II) chloride dichloromethane complex; the reaction may be performed by applying
- 10 potassium acetate under CO(g) (carbon monoxide) atmosphere in methanol and DMF in the presence of the suitable catalyst. The intermediate carboxylic acid methyl ester may either be reacted after isolation or, preferably, directly, i.e., without isolating, be converted into the compound of formula (VI) by using a strong base, for instance, potassium tert-butyrate under O₂(g)
- 15 atmosphere (depending on the PG), in a suitable solvent, e.g. DMSO. Subsequent reaction step (d) may utilize any reagent suitable for reducing the –C(=O)-R⁴ carbonyl moiety into a CH₂-R⁴ moiety and may be the same as for reaction step (a) hereinabove. Such suitable reduction means are, for instance, NaBH₄ or triethylsilane in trifluoroacetic acid. The choice of a
- 20 suitable base and a suitable catalyst for performing the final reaction step (e) depends on the chemical nature of compound (VII) to be reacted with the product of reaction step (d). Typically, compound (VII) is an amine, the suitable base may be N,N-diisopropylethylamine, preferably in the presence of DMF, and the suitable catalyst may be HATU (1-
- 25 [bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5b]pyridinium-3-oxidhexyfluorophosphate.

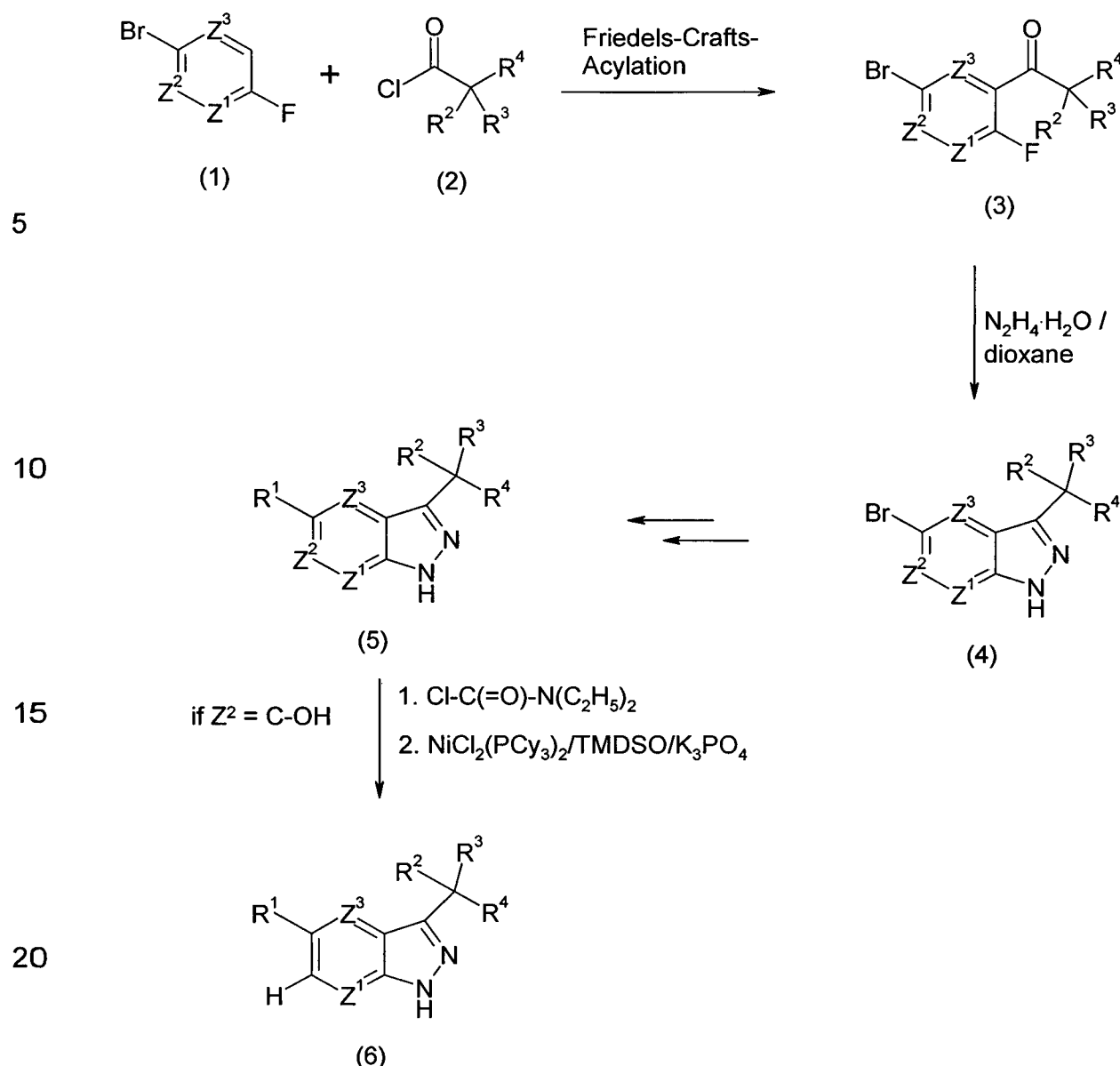
- It is well understood that the process for manufacturing compounds of the present invention, including its various variants, as described herein may be
- 30 further adapted, if necessary or useful. For instance, the process according to the present invention also encompasses synthetic routes in which one or more of the substituents of the compounds of formula (I) may be formed,

introduced or modified in a stepwise manner; this applies in particular to substituents having a rather complex structure. If, e.g., R^4 denotes Ar^4 being substituted with a substituent R^{4a} which in turn denotes $Hetar^{4a}$ (i.e., R^4 being $Ar^4-Hetar^{4a}$), that substituent can be formed by first introducing a suitably functionalized moiety Ar^4-FG (with FG being a functional group suitable for further synthetic transformation) (to build, e.g., a compound of formula (II) or (VI) with $R^4 = Ar^4-FG$) and afterwards – in one the subsequent reaction steps – transforming that Ar^4-FG moiety by means of a suitable C-C or C-N coupling reaction into a substituent $R^4 = Ar^4-Hetar^{4a}$. The skilled person will recognize that the same methodology may be applied for introducing other complex substituents like, for instance, $Hetar^4-Ar^{4b}$, $Hetar^4-Hetar^{4b}$ or $Hetar^4-Hetcyc^{4b}$.

Compounds of formula (I) with R^2 and R^3 having the meaning as given above or in claim 1 but not being H (hydrogen) at the same time, are readily available by adapting synthetic procedures described by H.-P. Buchstaller et al., *Bioorg. Med. Chem. Lett.* 22 (2012) 4396-4403, and subsequent introducing of substituent R^1 by methods already described hereinabove; if the synthetic procedure applied required a hydroxy substituent in 6-position of the heterocyclic compound, i.e. Z^2 being C-OH in formula (I), then the OH group can be replaced by hydrogen by applying the methodology described by T. Mesganaw et al., *Org. Lett.* 14 (2012) 2918-21 (transforming the hydroxyl group into a carbamate and subsequent removal of the carbamate by using bis(tricyclohexylphosphine)-nickel(II) dichloride/TMDSO (i.e., 1,1,3,3-tetramethyldisiloxane)/potassium phosphate). The synthetic route is schematically depicted in Scheme 1 hereinafter:

Scheme 1

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Compounds of formula (1) with Z¹, Z², Z³ being as defined for formula (I) above or in claim 1 wherein Z² may also be C-OH may undergo acylation reaction with compounds of formula (2) wherein R² and R³ are defined as in the previous paragraph and R⁴ is defined as above or in claim 1, e.g., under typical Friedel-Craft conditions, i.e. in the presence of aluminium trichloride or other suitable Lewis acids, followed by the addition of an acid like hydrochloride, to build compounds of formula (3). They are subsequently cyclized to form compounds of formula (4) by means of hydrazine hydrate. These compounds (4) may then readily be transformed into compounds of formula (5) (i.e., of formula (I)) by introducing R¹ utilizing the synthetic

methods described hereinabove and hereinbelow. In case, Z^2 happens to be C-OH, the hydroxyl substituent is then converted into hydrogen by forming the respective carbamate and subsequent reduction using the methodology described in T. Mesganaw et al., Org. Lett. 14 (2012) 2918-21.

5

Any starting material, compounds and reagents utilized in the synthesis of the compounds of the present invention are well-known to the skilled person and readily available either from commercial sources or by applying well-established methods of the art of organic synthesis.

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For instance, compounds of formula (II) are either commercially available or can be readily prepared according to the synthetic route depicted in Scheme 2 hereinafter:

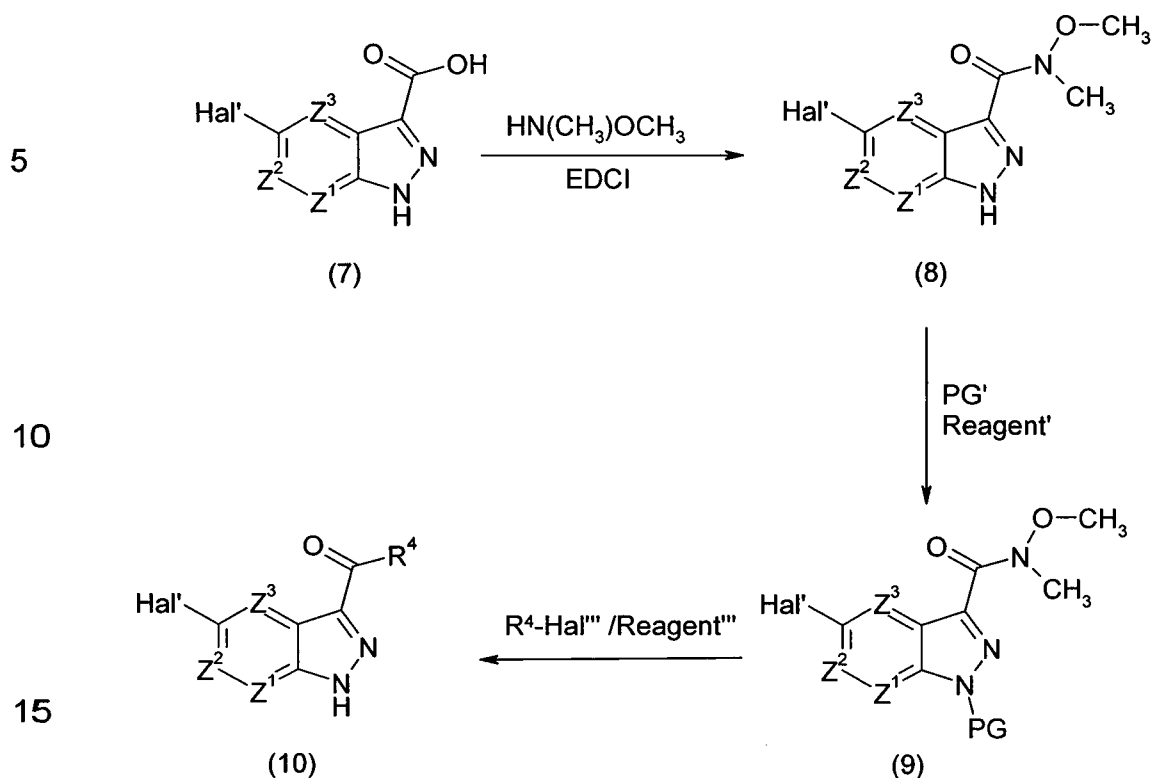
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Scheme 2



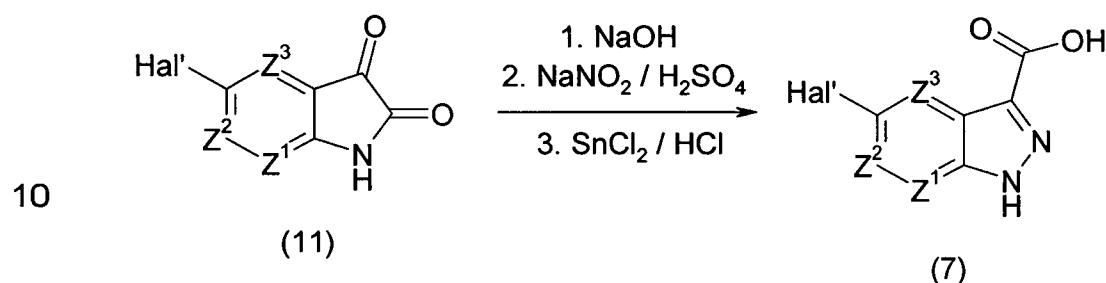
EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

PG' means a suitable precursor of a suitable protecting group PG to be introduced into the compounds of formula (9). Likewise, "Reagent'" means a reagent or reagents suitable for introducing such protecting group. For instance, when PG is a benzyl group, then PG' may stand for benzylbromide or benzylchloride and Reagent' is a base like cesiumcarbonate (Cs_2CO_3). Similarly, "Reagent'" means a reagent or reagents suitable for reacting the halogenide $\text{R}^4\text{-Hal}'''$ - with Hal''' being Cl, Br, I - with the compound of formula (9) to form the compound of formula (10) (which is a compound of formula (II), too). For instance, Hal''' may be Br and I and the Reagent'" may be Mg (magnesium) in an appropriate solvent for performing the Grignard coupling of (9) with $\text{R}^4\text{-Hal}'''$; other suitable reagents may be, for instance, alkyl lithium bases, like n-butyl lithium.

Compounds of formula (7) in Scheme 2 are either commercially available as well or can be readily prepared by well-known synthetic procedures. For

instance, they are available by utilizing and adapting a methodology described by F. Crestey et al., Tetrahedron Lett. 48 (2007) 2457-2460 which is schematically depicted in Scheme 3 hereinafter:

5 Scheme 3



15 The compounds of the present invention obtained by the synthetic methods described hereinabove and hereinafter are generally isolated as such, e.g. as the free base or acid, as the case may be, or in the form of their pharmaceutically acceptable salts, such as those described hereinabove.

20 The compounds of the present invention prepared according to the synthetic method described and exemplified hereinabove and hereinafter can be isolated from the reaction mixture by usual work-up procedures, such as concentrating the crude reaction mixture, taking it up in an organic solvent, washing and/or neutralizing with an appropriate reagent like aqueous sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, ammonium chloride, hydrogen chloride, brine, sodium chloride,

25 drying of the organic phases over a suitable drying agent such as sodium sulfate, and removing of the organic solvent(s) by evaporation. The product so obtained may further be purified by standard methods like liquid column chromatography, vacuum distillation and/or recrystallization from an appropriate solvent or solvent mixture; it may also be converted into one of its pharmaceutically acceptable salts as described herein.

30

Experimental SectionAbbreviations

- 5 Some abbreviations that may appear in this application are defined as follows in Table 1 below:

	Table	Meaning
	1Abbreviation	
	¹ H NMR	Proton Nuclear Magnetic Resonance
10	aq.	aqueous
	b	broad
	BINAP	1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine
	Bu	Butyl
	BuLi	Butyl lithium
15	CDCl ₃	Deuteriochloroforme
	d	Doublet
	dd	Double doublet
	DIEA	<i>N,N</i> -Diisopropylethylamine
	DMSO	Dimethylsulfoxide
20	DMSO-d ₆	Hexadeutero-dimethylsulfoxide
	dt	Double triplet
	h	hour(s)
	HATU	1-[Bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxid hexafluorophosphate
25	HPLC	High Performance Liquid Chromatography
	J	Coupling constant
	LCMS	Liquid Chromatography coupled to Mass Spectrometry
	m	Multiplet
	min	Minute
30	mL	Milliliter
	MS	Mass spectrometry

Table 1Abbreviation	Meaning
n.d.	not determined
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
Pd(dppf)Cl ₂	1,1'-Bis(diphenylphosphino)ferrocene]dichloro- palladium(II)
Pd(PCy ₃) ₂ Cl ₂	<u>Dichlorobis(tricyclohexylphosphine)palladium(II)</u>
Ph	Phenyl
rH	Relative humidity
RT	Room Temperature
Rt.	Retention time
s	Singlet
SFC	Supercritical Fluid Chromatography
t	Triplet
TFA	Trifluoroacetic acid
TLC	Thin Layer Chromatography
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

The compounds of the present invention can be prepared according to the procedures of the following Schemes and Examples, using appropriate materials and are further exemplified by the following specific examples.

The invention will be illustrated, but not limited, by reference to the specific embodiments described in the following examples. Unless otherwise indicated in the schemes, the variables have the same meaning as described above.

Unless otherwise specified, all starting materials are obtained from commercial suppliers and used without further purifications. Unless otherwise specified, all temperatures are expressed in °C and all reactions are conducted at RT. Compounds were purified by either silica chromatography or preparative HPLC.

¹H NMR:

¹H NMR was recorded on a 300, 400 or 500 MHz spectrometer (as indicated), using residual signal of deuterated solvent as internal reference.

5 Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 2.49 ppm for ¹H NMR in DMSO-d₆). ¹H NMR data are reported as follows: chemical shift (multiplicity, coupling constants, and number of hydrogens). Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

10

HPLC/MS:

HPLC/MS-Analysis was performed under the following conditions:

Method A

15 Solvent A: water + 0,05% TFA
Solvent B: acetonitrile + 0,05% TFA
Flow: 1 mL/min, wave length: 220 nm
Gradient: 0,01 min 5% B
3,00 min 50% B
20 5,00 min 50% B
5,20 min 5% B
5,60 min, stop
Column: Shim-pack VP-ODS 50-3 mm
Column temp: 40°C

25

Method B

Solvent A: water + 0,05% TFA
Solvent B: acetonitrile + 0,05% TFA
Flow: 1 mL/min, wave length: 220 nm
30 Gradient: 0,01 min 5% B
2,20 min 100% B
3,20 min 100% B

3,30 min 5% B
3,60 min, stop
Column: Shim-pack VP-ODS 50-3 mm
Column temp: 40°C

5

Method C

Solvent A: water + 0,05% TFA
Solvent B: acetonitrile + 0,05% TFA
Flow: 1,5 mL/min, wave length: 220 nm

10 Gradient: 0,01 min 10% B
2,10 min 100% B
2,70 min 100% B
2,75 min 10% B
3,00 min, stop
15 Column: XBridge BEH C18 2.5 μ M 50-3 mm
Column temp: 45°C

Method D

Solvent A: water + 0,05% TFA
20 Solvent B: acetonitrile + 0,05% TFA
Flow: 1 mL/min, wave length: 220 nm
Gradient: 0,01 min 5% B
2,20 min 100% B
3,20 min 100% B
25 3,30 min 5% B
3,60 min, stop
Column: Shim-pack XR-ODS 2,2 μ M 50-3 mm
Column temp: 40°C

30 Method E

Solvent A: water + 0,1% TFA
Solvent B: acetonitrile + 0,1% TFA

Flow: 1,5 mL/min, wave length: 220 nm
Gradient: 0,01 min 10% B
2,00 min 100% B
2,60 min 100% B
5 2,70 min 10% B
3,00 min, stop
Column: Phenomenex Kinetext 2,6 μ M 50-3 mm
Column temp: 40°C

10 Method F
Solvent A: water + 0,05% TFA
Solvent B: acetonitrile + 0,05% TFA
Flow: 1 mL/min, wave length: 220 nm
Gradient: 0,01 min 5% B
15 4,2 min 70% B
5,20 min 70% B
5,30 min 5% B
5,60 min, stop
Column: Shim-pack VP-ODS 50-3 mm
20 Column temp: 40°C

Method G
Solvent A: water + 0,05% TFA
Solvent B: acetonitrile + 0,05% TFA
25 Flow: 1 mL/min, wave length: 220 nm
Gradient: 0,01 min 5% B
5,00 min 50% B
7,90 min 50% B
8,10 min 5% B
30 8,50 min, stop
Column: Shim-pack VP-ODS 50-3 mm
Column temp: 40°C

Method H

Solvent A: water + 0,05% TFA

Solvent B: acetonitrile + 0,05% TFA

5 Flow: 1 mL/min, wave length: 220 nm

Gradient: 0,01 min 5% B

4,20 min 100% B

5,20 min 100% B

5,30 min 5% B

10 5,60 min, stop

Column: Shim-pack VP-ODS 50-3 mm

Column temp: 40°C

Method I

15 Solvent A: water + 0,05% TFA

Solvent B: acetonitrile + 0,05% TFA

Flow: 1 mL/min, wave length: 220 nm

Gradient: 0,01 min 5% B

1,20 min 100% B

20 2,20 min 100% B

2,30 min 5% B

2,60 min, stop

Column: Shim-pack XR-ODS 2,2 µM 50-3 mm

Column temp: 40°C

25

Method J

Solvent A: water + 0,05% TFA

Solvent B: acetonitrile + 0,05% TFA

Flow: 1 mL/min, wave length: 220 nm

30 Gradient: 0,01 min 5% B

3,5 min 80% B

5,20 min 80% B

5,30 min 5% B

5,60 min, stop

Column: Shim-pack XR-ODS 50-3 mm, 2.2 μ M

Column temp: 40°C

5

Method K

Solvent A: water + 0,05% TFA

Solvent B: acetonitrile + 0,05% TFA

Flow: 1 mL/min, wave length: 220 nm

10 Gradient: 0,01 min 5% B

4,0 min 60% B

5,20 min 60% B

5,30 min 5% B

5,60 min, stop

15 Column: Shim-pack XR-ODS 50-3 mm, 2.2 μ M

Column temp: 40°C

Method L

Solvent A: water + 0,1% TFA

20 Solvent B: acetonitrile + 0,1% TFA

Flow: 2 mL/min, wave length: 220 nm

Gradient: 0,2 min 1% B

3,8 min 100% B

4,20 min stop

25 Column: Chromolith Performance RP18e; 100 mm length inner diameter 3 mm

Method M

Solvent A: methanol + 0.1% formic acid

30 Solvent B: water +0.1% formic acid

Flow: 3 mL/min, wave length 254 nm

Gradient: 0.0 min 90% B

- 1.25 min 10% B
1.75 min 10%B
1.90 min 90% B
2.0 min 90% B
- 5 Column: Merck Purospher STAR column (RP-18e, 30 x 4 mm)
Column temp: 40°C

Method N

- Solvent A: methanol + 0.1% formic acid
- 10 Solvent B: water +0.1% formic acid
Flow: 1.5 mL/min, wave length 254 nm
Gradient: 0.0 min 90% B
2.50 min 10% B
3.50 min 10%B
- 15 3.80 min 90% B
4.00 min 90% B
Column: Merck Purospher STAR column (RP-18e, 30 x 4 mm)
Column temp: 30°C

20 Method O

- Solvent A: methanol + 0.1% formic acid
Solvent B: water +0.1% formic acid
Flow: 0.5 mL/min, wave length 254 nm
Gradient: 0.0 min 90% B
- 25 1.25 min 10% B
1.75 min 10%B
1.90 min 90% B
2.0 min 90% B
Column: Phenomenex Kinetex XB-C18 column (30 x 2.1 mm, 1.7u, 100A)
- 30 Column temp: 30°C

Method P

68

Solvent A: methanol + 0.1% formic acid

Solvent B: water +0.1% formic acid

Flow: 0.3 mL/min, wave length 254 nm

Gradient: 0.0 min 90% B

5 3.00 min 10% B

3.50 min 10%B

3.80 min 90% B

4.00 min 90% B

Column: Merck Purospher STAR column (RP-18e, 30 x 4 mm)

10 Column temp: 30°C

15

20

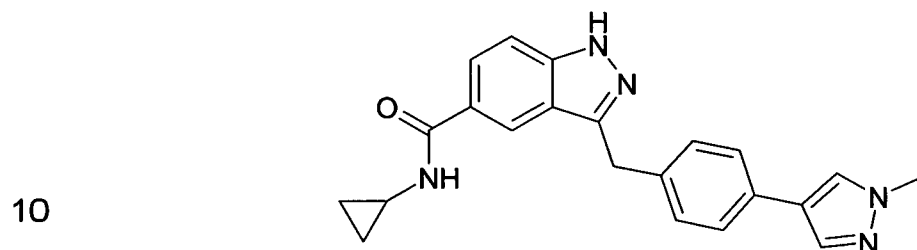
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Synthetic Examples

Synthetic Example 1:

5 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid cyclo-propylamide **17** and other amide derivatives



1.1 4-(4-Bromo-phenyl)-1-methyl-1H-pyrazole



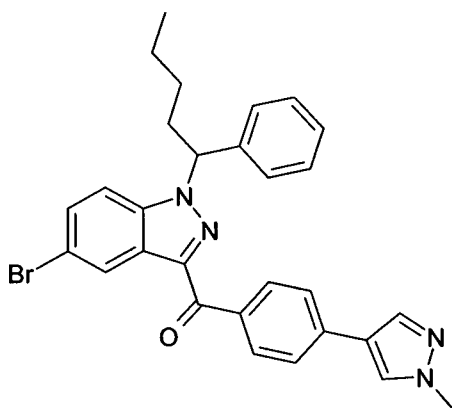
20 Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 1-methyl-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.00 g, 9.61 mmol), 1,4-dibromobenzene (2.30 g, 9.75 mmol), Pd(PPh₃)₄ (550 mg, 0.48 mmol), potassium carbonate (2.60 g, 18.8 mmol), dioxane (40 mL) and water (10 mL). The resulting solution was stirred for 3 h at 80°C. The resulting mixture was evaporated to dryness. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1/10). This resulted in 1.70 g (75%) of 4-(4-bromophenyl)-1-methyl-1H-pyrazole as a yellow solid.

1.2 [5-Bromo-1-(1-phenyl-pentyl)-1H-indazol-3-yl]-[4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-methanone

30

70

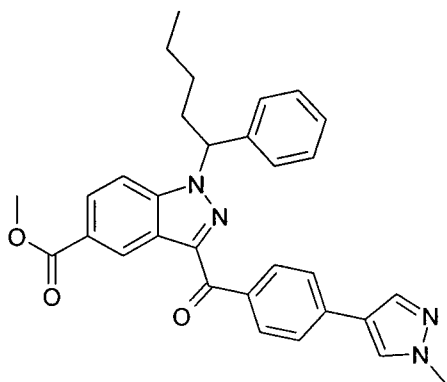
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10 Into a 500-mL 3-necked round-bottom flask, were placed 4-(4-bromophenyl)-
1-methyl-1H-pyrazole (3.80 g, 16.0 mmol) and tetrahydrofuran (50 mL). This
was followed by the addition of n-BuLi (7.00 mL, 74.3 mmol) dropwise with
stirring at -80 °C within 5 min. To this was added 1-benzyl-5-bromo-N-
methoxy-N-methyl-1H-indazole-3-carboxamide (2.00 g, 5.34 mmol, synthesis
15 see below). The resulting solution was stirred for 150 min at -80 °C. The
reaction was then quenched by the addition of 50 mL of ice water. The
resulting solution was extracted twice with 50 mL of ethyl acetate and the
organic layers combined and dried over anhydrous sodium sulfate and
concentrated under vacuo. The residue was applied onto a silica gel column
20 with dichloromethane/methanol (100/1). This resulted in 1.70 g (60%) of 5-
bromo-3-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]carbonyl-1-(1-phenylpentyl)-
1H-indazole as a yellow solid.

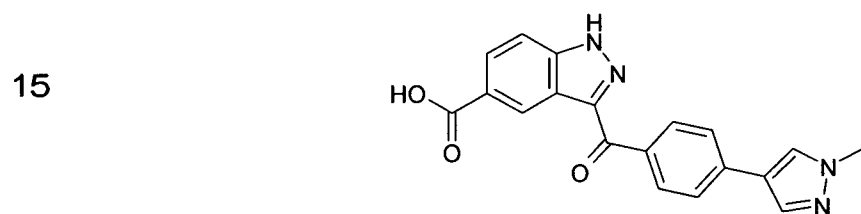
1.3. 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzoyl]-1-(1-phenyl-pentyl)-1H-
25 indazole-5-carboxylic acid methyl ester

30



Into a pressure tank reactor purged and maintained with an atmosphere of CO(g) was placed 5-bromo-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]carbonyl]-1-(1-phenylpentyl)-1H-indazole (1.70 g, 3.22 mmol), (1,1'-bis(diphenylphosphino)ferrocene)-palladium(II) chloride dichloromethane complex (13.1 mg, 0.02 mmol), potassium acetate (940 mg, 9.58 mmol), methanol (15 mL) and N,N-dimethylformamide (15 mL). The resulting mixture was stirred for 24 h at 80°C. The solids were filtered out and the filtrate was evaporated to dryness. This resulted in 1.50 g (92%) of methyl 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]carbonyl]-1-(1-phenylpentyl)-1H-indazole-5-carboxylate as a yellow solid.

1.4. 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzoyl]-1H-indazole-5-carboxylic acid

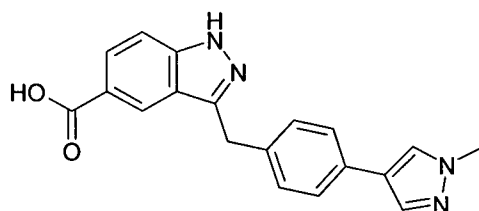


Into a 50-mL round-bottom flask was placed methyl 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]carbonyl]-1-(1-phenylpentyl)-1H-indazole-5-carboxylate (850 mg, 1.68 mmol), dimethyl sulfoxide (25 mL) and potassium tert.-butoxide (3.50 g, 31.2 mmol). The resulting solution was stirred for 24 h at 25°C. The reaction was then quenched by the addition of 50 mL of water. The pH value of the solution was adjusted to 7 with hydrogen chloride solution. The solids were collected by filtration. The solid was dried and resulted in 0.59 g (100%) of 3-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]carbonyl]-1H-indazole-5-carboxylic acid as a yellow solid.

1.5. 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid

30

72

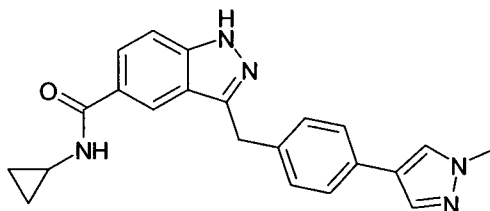


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Into a 50-mL round-bottom flask was placed 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]carbonyl]-1H-indazole-5-carboxylic acid (700 mg, 2.02 mmol), trifluoroacetic acid (10 mL). This was followed by the addition of triethylsilane (4.70 g, 40.4 mmol) dropwise with stirring. The resulting solution was stirred for 3 h at 25°C and evaporated to dryness to result in 0.60 g (89%) of 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-carboxylic acid as a light yellow solid.

15

1.6. 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid cyclopropylamide **17**



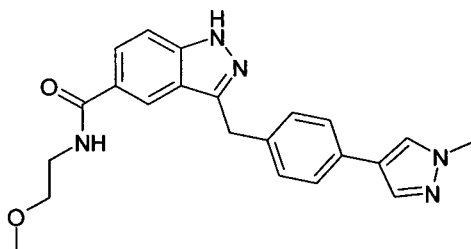
20

Into a 25-mL round-bottom flask was placed amino cyclopropane (45.0 mg, 0.79 mmol), 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-carboxylic acid (130 mg, 0.39 mmol), N,N-dimethylformamide (5 mL) and N,N-diisopropylethylamine (100 mg, 0.77 mmol). This was followed by the addition of a solution of 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 222 mg, 0.58 mmol) in N,N-dimethylformamide (1 mL) dropwise with stirring. The resulting solution was stirred for 3 h at 25°C. The product was precipitated by the addition of water. The solids were collected by filtration and purified by prep-HPLC to result in 17.2 mg (6%) of N-cyclopropyl-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-carboxamide as a brown solid.

30

1.7. 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (2-methoxy-ethyl)-amide **18**

5



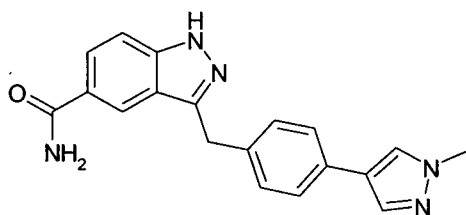
10 Into a 25-mL round-bottom flask was placed 2-methoxyethan-1-amine (68.0 mg, 0.91 mmol), 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-carboxylic acid (150 mg, 0.45 mmol), N,N-dimethylformamide (2 mL) and N,N-diisopropylethylamine (116 mg, 0.90 mmol). This was followed by the addition of a solution of 1-[bis(dimethylamino)methylene]-1H-1,2,3-

15 triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 256 mg, 0.67 mmol) in N,N-dimethylformamide (1 mL) dropwise with stirring. The resulting solution was stirred for 3 h at 25°C. The product was precipitated by the addition of water. The solids were collected by filtration and purified by preparative HPLC to result in 19.4 mg (6%) of N-(2-methoxyethyl)-3-[[4-(1-

20 methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-carboxamide as a white solid.

1.8. 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid amide **20**

25

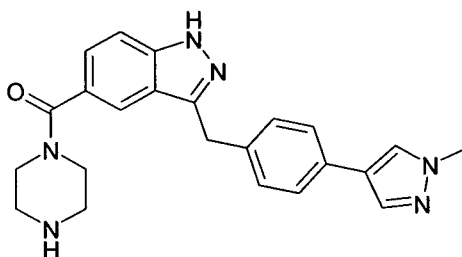


30

Into a 25-mL round-bottom flask was placed 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-carboxylic acid (150 mg, 0.45 mmol), N,N-diisopropylethylamine (116 mg, 0.90 mmol), ammonium chloride (48.0 mg,

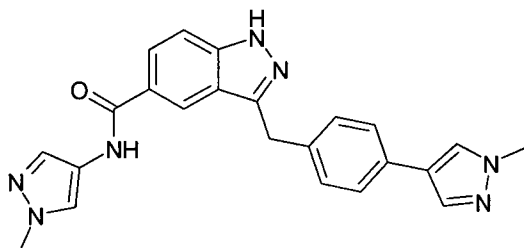
0.90 mmol) and N,N-dimethylformamide (2 mL). This was followed by the addition of 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 256 mg, 0.67 mmol) dropwise with stirring. The resulting solution was stirred for 3 h at 25°C. The product was precipitated by the addition of water. The solids were collected by filtration and purified by preparative HPLC to result in 30.0 mg (20%) of 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-carboxamide as a brown solid.

1.9. {3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-piperazin-1-yl-methanone **21**



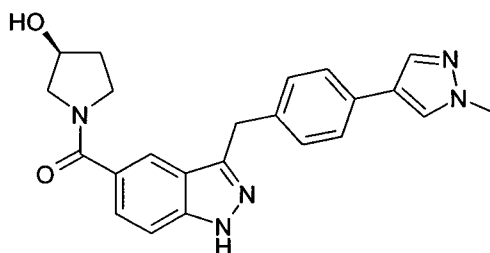
Into a 25-mL round-bottom flask was placed tert-butyl 4-[(3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazol-5-yl)carbonyl]piperazine-1-carboxylate (225 mg, 0.45 mmol), dichloromethane (3 mL) and trifluoroacetic acid (259 mg, 2.27 mmol). The resulting solution was stirred for 3 h at 25°C. The resulting mixture was evaporated to dryness and purified by preparative HPLC to result in 30.0 mg (17%) of 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-5-[(piperazin-1-yl)carbonyl]-1H-indazole as a brown solid.

1.10. 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (1-methyl-1H-pyrazol-4-yl)-amide **22**



Into a 25-mL round-bottom flask was placed 1-methyl-1H-pyrazol-4-amine (150 mg, 1.54 mmol), 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-carboxylic acid (88.0 mg, 0.26 mmol), N,N-diisopropylethylamine (116 mg, 0.90 mmol) and N,N-dimethylformamide (2 mL). This was followed by the addition of 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 256 mg, 0.67 mmol) dropwise with stirring. The resulting solution was stirred for 3 h at 25°C. The product was precipitated by the addition of water. The solids were collected by filtration and purified by preparative HPLC to result in 30.0 mg (5%) of N-(1-methyl-1H-pyrazol-4-yl)-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-carboxamide as a brown solid.

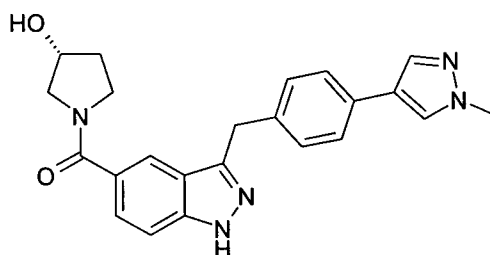
1.11. ((S)-3-Hydroxy-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone **31**



Into a 25-mL round-bottom flask was placed 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-carboxylic acid (180 mg, 0.54 mmol), (S)-pyrrolidin-3-ol hydrochloride (135 mg, 1.09 mmol), N,N-diisopropylethylamine (140 mg, 1.08 mmol) and N,N-dimethylformamide (3 mL). A solution of 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 315 mg, 0.83 mmol) in N,N-dimethylformamide (1 mL) was added at room temperature. The resulting solution was stirred for 3 h at 25°C. The resulting mixture was evaporated to dryness. The residue was applied onto a silica gel column with dichloromethane/methanol (1:1). This resulted in 12.0 mg (79%) of (3S)-1-[(3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazol-5-yl)carbonyl]pyrrolidin-3-ol as a white solid.

1.12. ((R)-3-Hydroxy-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone **34**

5



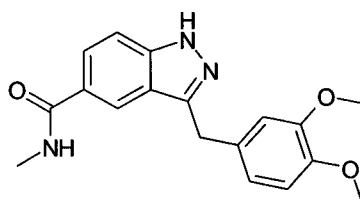
10 Into a 25-mL round-bottom flask was placed 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-carboxylic acid (180 mg, 0.54 mmol), (R)-pyrrolidin-3-ol hydrochloride (135 mg, 1.09 mmol), N,N-diisopropylethylamine (140 mg, 1.08 mmol) and N,N-dimethylformamide (3 mL). A solution of 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid
15 hexafluorophosphate (HATU, 315 mg, 0.83 mmol) in N,N-dimethylformamide (1 mL) was added at room temperature. The resulting solution was stirred for 3 h at 25°C. The resulting mixture was evaporated to dryness and purified by preparative HPLC to result in 12.0 mg (79%) of (3R)-1-[(3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazol-5-yl)carbonyl]pyrrolidin-3-ol as a white
20 solid.

In analogy to this synthetic route also compounds **16**, **52**, **53**, **61**, **62**, **63**, **79-87**, **91**, **92** and **102** were synthesized.

25 To synthesize the sulfonamides **64** and **65** the intermediate obtained from step 1.2. (5-bromo-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]carbonyl]-1-(1-phenylpentyl)-1H-indazole) can be reacted with n-butyl lithium and sulfur dioxide (as, for example, described in M. Tercel et al., *J. Med. Chem.* **2009**, 52, 7258-7272) followed by the reduction in analogy to 1.4. and subsequent
30 sulfonamide formation after activation with oxalyl chloride and treatment with the corresponding amines. In a similar manner, other compounds of formula (I) with R¹ being -SO₂R⁸ as defined above or in claim 1 can be obtained.

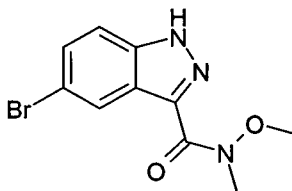
Synthetic Example 2:3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid methylamide 1

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2.1. 5-Bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide

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15 Into a 100-mL round-bottom flask was placed 5-bromo-1H-indazole-3-carboxylic acid (2.56 g, 10.6 mmol) and N,O-dimethylhydroxylamine hydrochloride (1.20 g, 12.3 mmol). This was followed by the addition of pyridine (3.53 g, 44.6 mmol) dropwise with stirring at 0°C. The mixture was stirred for 30 min at 0°C and 1h at 25°C. To this was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI, 4.07 g, 21.2 mmol) at 0°C,

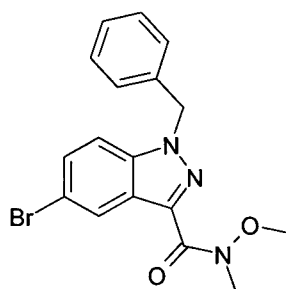
20 dissolved in tetrahydrofuran (40 mL). The resulting solution was stirred for 16 h at 25°C. The resulting solution was diluted with of water. The solids were collected by filtration. The solid was dried and resulted in 3.00 g (89%) of 5-bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide as an off-white

25 solid.

2.2. 1-Benzyl-5-bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide

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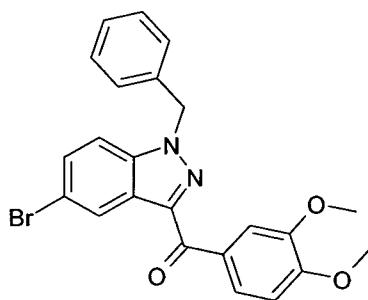
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Into a 250-mL round-bottom flask was placed 5-bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide (5.30 g, 18.7 mmol), cesium carbonate (8.20 g, 25.2 mmol) and N,N-dimethylformamide (50 mL). Then benzyl bromide (3.50 g, 20.5 mmol) was added at 0°C. The resulting solution was stirred for 1.5 h at 25°C. The reaction mixture was poured onto ice. The resulting solution was extracted twice with 50 mL of ethyl acetate. The combined organic phase was washed twice with 40 mL of brine. The mixture was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. This resulted in 6.64 g (81%) of 1-benzyl-5-bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide as an off-white solid.

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2.3. 1-Benzyl-5-bromo-3-[(3,4-dimethoxyphenyl)carbonyl]-1H-indazole



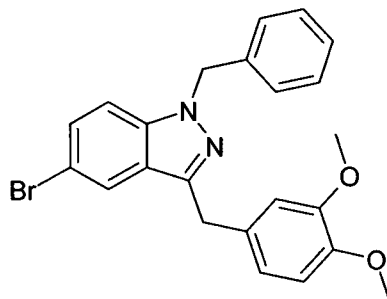
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Into a 100-mL three-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed Mg (1.69 g, 69.3 mmol) and iodine (5.00 mg). Then a portion of the solution of 4-bromo-1,2-dimethoxybenzene (12.9 g, 59.4 mmol) in tetrahydrofuran (60 mL) was added. After the color of the solution was fade under refluxing, the remaining solution of 4-bromo-1,2-dimethoxybenzene in tetrahydrofuran was added

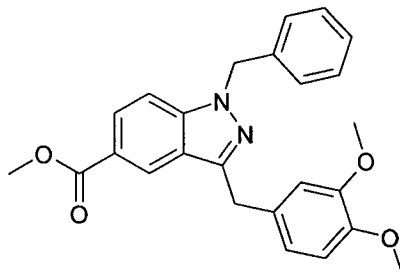
dropwise at 80°C. Then the resulting solution was stirred for 1 h at 80°C, cooled to 25°C, and added to the solution of 1-benzyl-5-bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide (2.22 g, 5.93 mmol) in tetrahydrofuran (10 mL) at room temperature. The resulting solution was stirred for 1 h at 25°C. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated to dryness. The residue was purified by a silica gel column with petroleum ether/ethyl acetate (10:1). This resulted in 2.60 g (87%) of 1-benzyl-5-bromo-3-[(3,4-dimethoxyphenyl)carbonyl]-1H-indazole as a yellow oil.

2.4. 1-benzyl-5-bromo-3-[(3,4-dimethoxyphenyl)methyl]-1H-indazole



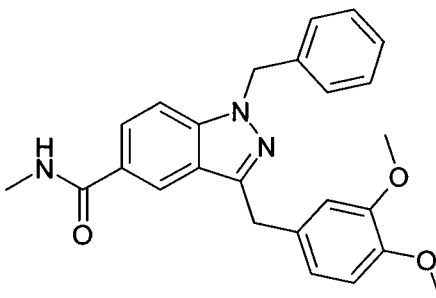
Into a 25-mL round-bottom flask was placed 1-benzyl-5-bromo-3-[(3,4-dimethoxyphenyl)carbonyl]-1H-indazole (1.31 g, 2.90 mmol), triethylsilane (2.45 mL, 15.2 mmol) and trifluoroacetic acid (6 mL). The resulting solution was stirred for 16 h at 25°C. The reaction mixture was poured onto ice. The pH value of the solution was adjusted to 7 with sodium bicarbonate. The resulting solution was extracted twice with 20 mL of ethyl acetate. The combined organic layer was washed twice with 20 mL of brine. The mixture was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. This resulted in 1.40 (83%) of 1-benzyl-5-bromo-3-[(3,4-dimethoxyphenyl)methyl]-1H-indazole as a yellow oil.

2.5. Methyl 1-benzyl-3-[(3,4-dimethoxyphenyl)methyl]-1H-indazole-5-carboxylate



Into a 100-mL pressure tank reactor purged and maintained with an atmosphere of CO(g) was placed 1-benzyl-5-bromo-3-[(3,4-dimethoxyphenyl)methyl]-1H-indazole (1.25 g, 2.86 mmol), (1,1'-bis(diphenylphosphino)ferrocene)-palladium(II) chloride dichloromethane complex (372 mg, 0.46 mmol), potassium acetate (895 mg, 9.12 mmol), methanol (25 mL) and N,N-dimethylformamide (25 mL). The resulting solution was stirred for 20 h at 80°C. The reaction mixture was cooled to 25°C and evaporated to dryness. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:4). This resulted in 756 mg (57%) of methyl 1-benzyl-3-[(3,4-dimethoxyphenyl)methyl]-1H-indazole-5-carboxylate as a yellow oil.

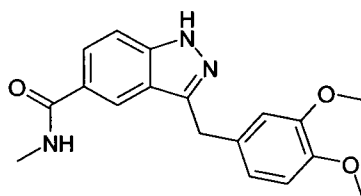
2.6. 1-Benzyl-3-[(3,4-dimethoxyphenyl)methyl]-N-methyl-1H-indazole-5-carboxamide



Into a 10-mL sealed tube was placed methyl 1-benzyl-3-[(3,4-dimethoxyphenyl)methyl]-1H-indazole-5-carboxylate (150 mg, 0.36 mmol), a

solution of methylamine (310 mg, 9.98 mmol) in methanol (5 mL). The resulting solution was stirred for 24 h at 60°C. The reaction mixture was cooled to 25°C and evaporated to dryness. This resulted in 140 mg (80%) of 1-benzyl-3-[(3,4-dimethoxyphenyl)methyl]-N-methyl-1H-indazole-5-carboxamide as a yellow oil.

2.7. 3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid methylamide

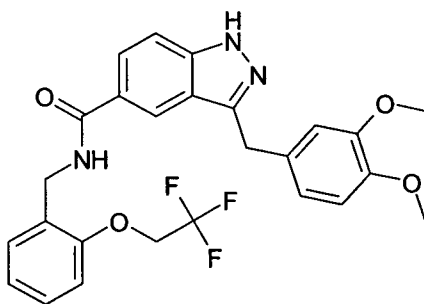


Into a 30-mL pressure tank reactor purged and maintained with an atmosphere of hydrogen was placed 1-benzyl-3-[(3,4-dimethoxyphenyl)methyl]-N-methyl-1H-indazole-5-carboxamide (130 mg, 0.31 mmol), Pd/C (100 mg, 0.94 mmol), methanol (3 mL) and hydrogen chloride solution (33%, 0.05 mL, 1.65 mmol). The resulting mixture was stirred for 8 h at 60°C. The reaction mixture was cooled to 25°C. The solids were filtered off and the filtrate was evaporated to dryness. The crude product was purified by preparative HPLC to result in 15.0 mg (14%) of 3-[(3,4-dimethoxyphenyl)methyl]-N-methyl-1H-indazole-5-carboxamide as a white solid. The compound exhibited a melting point of 196°C.

In analogy to this synthetic route also compounds **2**, **3**, **11**, **12**, **13**, **19**, **40** and **41** were synthesized.

2.8. 3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid 2-(2,2,2-trifluoro-ethoxy)-benzylamide **39**

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Into a 8-mL round-bottom flask was placed a solution of 3-[(3,4-dimethoxyphenyl)methyl]-1H-indazole-5-carboxylic acid (100 mg, 0.32 mmol) in N,N-dimethylformamide (3 mL), [2-(2,2,2-trifluoroethoxy)phenyl]methylamine (78.8 mg, 0.38 mmol) and N,N-diisopropylethylamine (124 mg, 0.96 mmol). This was followed by the addition of a solution of 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 134 mg, 0.35 mmol) in N,N-dimethylformamide (1 mL) dropwise with stirring. The resulting solution was stirred for 2 h at room temperature. The resulting mixture was evaporated to dryness. The residue was applied onto a silica gel column with petroleum ether/ethyl acetate (20:1). The crude product was purified by recrystallization from acetonitrile. This resulted in 79.6 mg (50%) of 3-[(3,4-dimethoxyphenyl)methyl]-N-[[2-(2,2,2-trifluoroethoxy)phenyl]methyl]-1H-indazole-5-carboxamide as a white solid.

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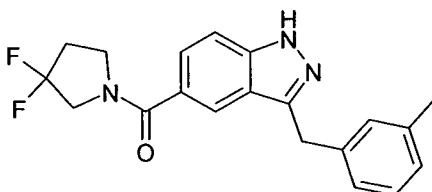
Compounds **43-50** can be prepared by utilizing the the procedures described in Synthetic Examples 1 and 2 hereinbefore in an analogous manner starting either with 5-bromo-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid or with 5-bromo-1H-pyrazolo[4,3-b]pyridine-3-carboxylic acid, as the case may be, as the starting material and applying synthetic steps 2.1., 2.2. 1.2., 1.3., 1.4., 1.5., 1.6..

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Synthetic Example 3:

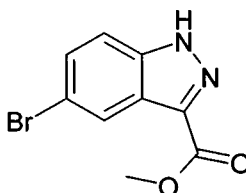
(3,3-Difluoro-pyrrolidin-1-yl)-[3-(3-methyl-benzyl)-1H-indazol-5-yl]-methanone

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3.1. Methyl 5-bromo-1H-indazole-3-carboxylate

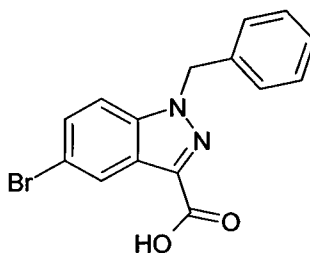


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Into a 100-mL round-bottom flask was placed 5-bromo-1H-indazole-3-carboxylic acid (1.00 g, 4.15 mmol), sulfuric acid (0.50 mL, 9.19 mmol, 98%) and methanol (30 mL). The resulting solution was stirred for 3 h at 80°C. The solids were collected by filtration. This resulted in 650 mg (61%) of methyl 5-bromo-1H-indazole-3-carboxylate as a white solid.

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3.2. 1-Benzyl-5-bromo-1H-indazole-3-carboxylic acid



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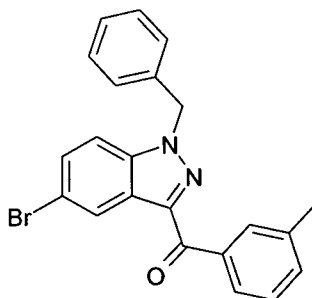
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Into a 100-mL round-bottom flask was placed methyl 1-benzyl-5-bromo-1H-indazole-3-carboxylate (700 mg, 2.03 mmol), LiOH (840 mg, 35.1 mmol) and tetrahydrofuran (6 mL), water (2 mL). The resulting solution was stirred for 1 h at 50°C. The pH value of the solution was adjusted to 2 with aqueous hydrogen chloride solution. The mixture was extracted with of ethyl acetate twice and the combined organic layer were dried over sodium sulfate, filtered

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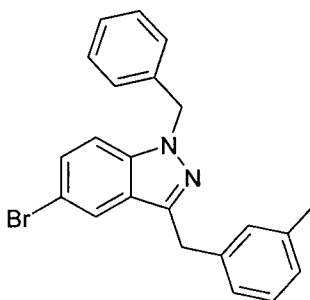
and evaporated to dryness. This resulted in 600 mg (89%) of 1-benzyl-5-bromo-1H-indazole-3-carboxylic acid as a yellow solid.

3.3. 1-Benzyl-5-bromo-3-[(3-methylphenyl)carbonyl]-1H-indazole



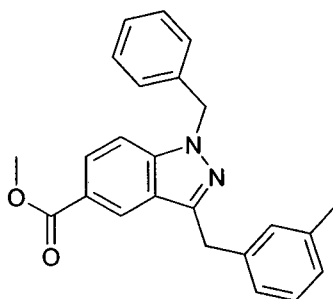
Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 1-benzyl-5-bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide (2.00 g, 5.34 mmol) and tetrahydrofuran (20 mL). This was followed by the addition of m-tolylmagnesium bromide (19% in tetrahydrofuran, 1 mol/L, 53.4 mL, 53.4 mmol) dropwise with stirring at 0°C. The resulting solution was stirred for 1 h at 0°C. The reaction was then quenched by the addition of 100 mL of ammonium chloride solution. The resulting solution was extracted with 200 mL of ethyl acetate and the organic layer was dried over sodium sulfate, filtered and evaporated to dryness. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). This resulted in 2.00 g (92%) of 1-benzyl-5-bromo-3-[(3-methylphenyl)carbonyl]-1H-indazole as a yellow solid.

3.4. 1-Benzyl-5-bromo-3-[(3-methylphenyl)methyl]-1H-indazole



Into a 100-mL round-bottom flask was placed 1-benzyl-5-bromo-3-[(3-methylphenyl)carbonyl]-1H-indazole (1.90 g, 4.69 mmol), trifluoroacetic acid (30 mL) and triethylsilane (2.70 g, 23.2 mmol). The resulting solution was stirred overnight at 25°C. The pH value of the solution was adjusted to 8 with saturated sodium bicarbonate solution. It was extracted with 200 mL of ethyl acetate, the organic layer was dried over sodium sulfate, filtered and evaporated to dryness. The residue was applied onto a silica gel column with petroleum ether/ethyl acetate (20:1). This resulted in 1.70 g (93%) of 1-benzyl-5-bromo-3-[(3-methylphenyl)methyl]-1H-indazole as a yellow oil.

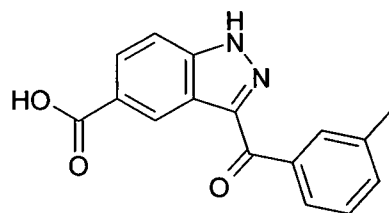
3.5. Methyl 1-benzyl-3-[(3-methylphenyl)methyl]-1H-indazole-5-carboxylate



Into a 250-mL sealed tube was placed 1-benzyl-5-bromo-3-[(3-methylphenyl)methyl]-1H-indazole (1.70 g, 4.34 mmol), a solution of N,N-dimethylformamide/methanol (30 mL, 1:1). This was followed by the addition of (1,1'-bis(diphenylphosphino)ferrocene)-palladium(II) chloride (320 mg, 0.44 mmol). To the mixture CO(g) was introduced and potassium acetate (1.28 g, 13.0 mmol) was added. The resulting solution was stirred for 1 h overnight at 80°C. The resulting mixture was evaporated to dryness. The residue was applied onto a silica gel column with petroleum ether/ethyl acetate (20/1). This resulted in 1.10 g (68%) of methyl 1-benzyl-3-[(3-methylphenyl)methyl]-1H-indazole-5-carboxylate as a white solid.

3.6. 3-(3-Methyl-benzoyl)-1H-indazole-5-carboxylic acid

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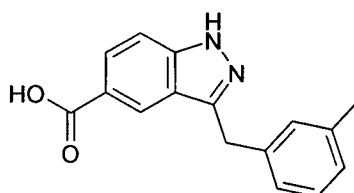
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Into a 100-mL round-bottom flask was placed methyl 1-benzyl-3-[(3-methylphenyl)methyl]-1H-indazole-5-carboxylate (1.00 g, 2.70 mmol), dimethyl sulfoxide (20 mL). This was followed by the addition of t-BuOK (3.00 g, 26.74 mmol). To the above O₂(g) was introduced in. The resulting solution was stirred for 3 h at 25°C. The reaction was then quenched by the addition of 30 mL of water. The pH value of the solution was adjusted to 6 with hydrogen chloride solution (10 %). The solids were collected by filtration. This resulted in 500 mg (66%) of 3-[(3-methylphenyl)carbonyl]-1H-indazole-5-carboxylic acid as a yellow solid.

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3.7. 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid

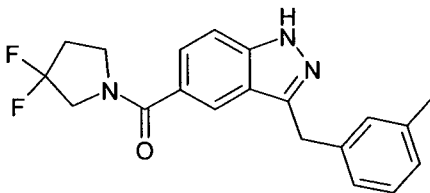


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Into a 25-mL round-bottom flask was placed 3-[(3-methylphenyl)carbonyl]-1H-indazole-5-carboxylic acid (500 mg, 1.78 mmol), trifluoroacetic acid (10 mL) and triethylsilane (1.00 g, 8.60 mmol). The resulting solution was stirred for 1h overnight at 25°C. The resulting mixture was evaporated to dryness. The pH value of the solution was adjusted to 8 with saturated sodium bicarbonate. The resulting solution was extracted with 30 mL of ethyl acetate and the organic layer was dried over sodium sulfate, filtered and evaporated to dryness. This resulted in 480 mg (100%) of 3-[(3-methylphenyl)methyl]-1H-indazole-5-carboxylic acid as a yellow solid.

3.8. (3,3-Difluoro-pyrrolidin-1-yl)-[3-(3-methyl-benzyl)-1H-indazol-5-yl]-methanone **4**



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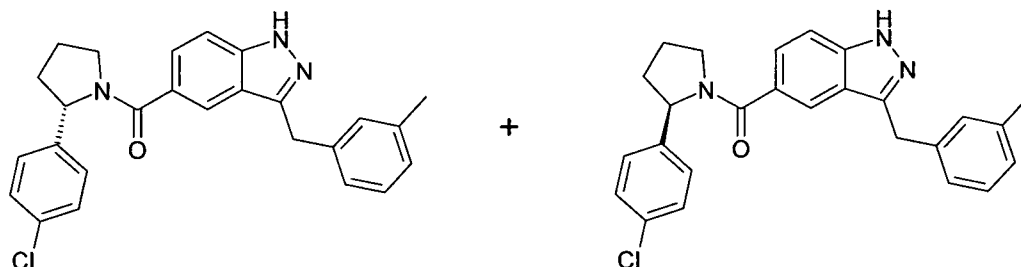
Into a 25-mL round-bottom flask was placed 3-[(3-methylphenyl)methyl]-1H-indazole-5-carboxylic acid (80.0 mg, 0.30 mmol), 3,3-difluoropyrrolidine hydrochloride (64.7 mg, 0.45 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 114 mg, 0.30 mmol), N,N-diisopropylethylamine (58.0 mg, 0.45 mmol) and N,N-dimethylformamide (2 mL). The resulting solution was stirred for 60 min at 25°C. The mixture was evaporated to dryness. The crude product was purified by preparative HPLC to result in 30.0 mg (28%) of 5-[(3,3-difluoropyrrolidin-1-yl)carbonyl]-3-[(3-methylphenyl)methyl]-1H-indazole as an off-white solid.

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In analogy to this synthetic route also compounds **5**, **6**, **7**, **8**, **9**, **27** and **42** were synthesized.

3.9. [(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3-methyl-benzyl)-1H-indazol-5-yl]-methanone **38** and the corresponding (R)-isomer **36**



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Into a 25-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 3-[(3-methylphenyl)methyl]-1H-indazole-5-carboxylic acid (20.0 mg, 0.08 mmol), 2-(4-chlorophenyl)pyrrolidine (20.0 mg, 0.11 mmol), N,N-dimethylformamide (1 mL), dichloromethane (1 mL),

N,N-diisopropylethylamine (48.0 mg, 0.37 mmol) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 37.0 mg, 0.10 mmol). The resulting solution was stirred for 3 h at 25°C. The resulting mixture was evaporated to dryness.

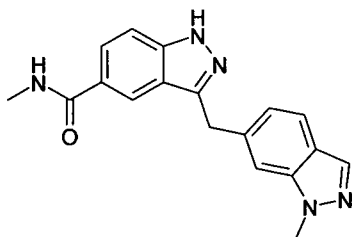
5 The crude product was purified by preparative HPLC to result in 35.0 mg (99%) of the racemic mixture. The racemic mixture was purified by chiral preparative HPLC (column: Repaired IA, 21.2*150 mm, 5 µm; mobile phase: hexane/ethanol) to result in 15.0 mg (43%) of 5-[(2S)-2-(4-chlorophenyl)pyrrolidin-1-yl]carbonyl]-3-[(3-methylphenyl)methyl]-1H-indazole

10 as a white solid and 14.8 mg (42%) of the corresponding (R)-isomer

Synthetic Example 4:

3-(1-Methyl-1H-indazol-6-ylmethyl)-1H-indazole-5-carboxylic acid methylamide 10

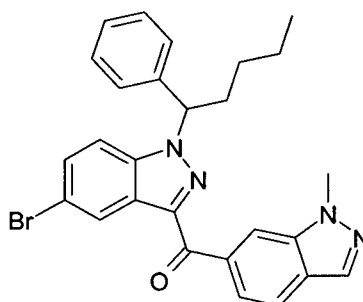
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4.1. 5-Bromo-3-[(1-methyl-1H-indazol-6-yl)carbonyl]-1-(1-phenylpentyl)-1H-indazole

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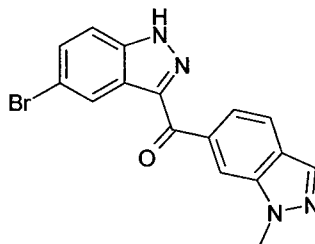


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Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 6-bromo-1-methyl-1H-indazole (2.85 g, 13.5 mmol) and tetrahydrofuran (10 mL). Then n-BuLi (6.00 mL, 15.0

mmol) was added dropwise at -78°C. The resulting solution was stirred for 1.5 h at -60°C. Then the solution of 1-benzyl-5-bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide (1.68 g, 4.50 mmol) in tetrahydrofuran (8 mL) was added dropwise at -78°C. The resulting solution was warmed up to room temperature overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution. The resulting solution was extracted three times with 15 mL of ethyl acetate. The combined organic phase was washed with 20 mL of brine. The mixture was dried over sodium sulfate, filtered and evaporated to dryness. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:3). This resulted in 1.65 g (66%) of 5-bromo-3-[(1-methyl-1H-indazol-6-yl)carbonyl]-1-(1-phenylpentyl)-1H-indazole as a yellow oil.

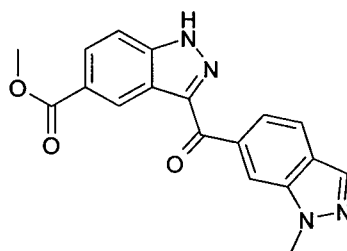
4.2. 5-bromo-3-[(1-methyl-1H-indazol-6-yl)carbonyl]-1H-indazole



Into a 100-mL round-bottom flask purged and maintained with an atmosphere of oxygen was placed 5-bromo-3-[(1-methyl-1H-indazol-6-yl)carbonyl]-1-(1-phenylpentyl)-1H-indazole (1.15 g, 2.29 mmol), potassium tert-butyrate (2.57 g, 22.90 mmol) and dimethyl sulfoxide (11 mL). The resulting solution was stirred for 5 h at 25°C. The mixture was diluted with 30 mL of ethyl acetate. The organic phase was washed with 3 times with 15 mL of brine. The mixture was dried over sodium sulfate, filtered and evaporated to dryness. This resulted in 900 mg (88%) of 5-bromo-3-[(1-methyl-1H-indazol-6-yl)carbonyl]-1H-indazole as a yellow solid.

4.3. Methyl 3-[(1-methyl-1H-indazol-6-yl)carbonyl]-1H-indazole-5-carboxylate

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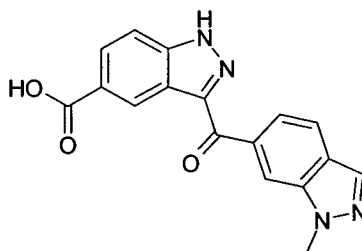


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Into a 50-mL pressure tank reactor purged and maintained with an atmosphere of CO(g) was placed 5-bromo-3-[(1-methyl-1H-indazol-6-yl)carbonyl]-1H-indazole (650 mg, 1.83 mmol), (1,1'-bis(diphenylphosphino)ferrocene)-palladium(II) chloride dichloromethane complex (119 mg, 0.15 mmol), potassium acetate (430 mg, 4.38 mmol), N,N-dimethylformamide (7.5 mL) and methanol (7.5 mL). The resulting solution was stirred for 20 h at 80°C. The reaction mixture was cooled to 25°C and evaporated to dryness. The residue was applied onto a silica gel column with dichloromethane/ethyl acetate (4:1). This resulted in 140 mg (21%) of methyl 3-[(1-methyl-1H-indazol-6-yl)carbonyl]-1H-indazole-5-carboxylate as a light brown solid.

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4.4. 3-[(1-Methyl-1H-indazol-6-yl)carbonyl]-1H-indazole-5-carboxylic acid



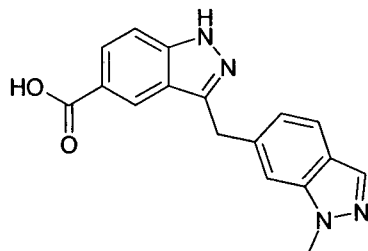
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Into a 25-mL round-bottom flask was placed methyl 3-[(1-methyl-1H-indazol-6-yl)carbonyl]-1H-indazole-5-carboxylate (250 mg, 0.75 mmol), LiOH (614 mg, 14.63 mmol), tetrahydrofuran (10 mL) and water (5 mL). The resulting solution was stirred for 24 h at 45°C. The reaction mixture was cooled to 25°C, conc. hydrogen chloride was added slowly to adjust the pH to 2. The solids formed were filtered off and washed with the mixture of dichloromethane/petroleum ether. This resulted in 145 mg (48%) of 3-[(1-

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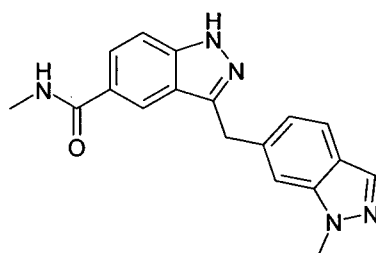
methyl-1H-indazol-6-yl)carbonyl]-1H-indazole-5-carboxylic acid as a light brown solid.

4.5. 3-[(1-Methyl-1H-indazol-6-yl)methyl]-1H-indazole-5-carboxylic acid



Into a 25-mL round-bottom flask was placed 3-[(1-methyl-1H-indazol-6-yl)carbonyl]-1H-indazole-5-carboxylic acid (145 mg, 0.45 mmol), triethylsilane (828 mg, 7.12 mmol) and trifluoroacetic acid (5 mL). The resulting solution was stirred for 5 days at 25°C. The mixture was diluted with 20 mL of water and the trifluoroacetic acid was neutralized with sodium bicarbonate. Then conc. hydrogen chloride solution was slowly added to adjust the pH to 2. The solids were collected by filtration, and washed with diethyl ether. This resulted in 100 mg (47%) of 3-[(1-methyl-1H-indazol-6-yl)methyl]-1H-indazole-5-carboxylic acid as a brown solid.

4.6. 3-(1-Methyl-1H-indazol-6-ylmethyl)-1H-indazole-5-carboxylic acid methylamide **10**



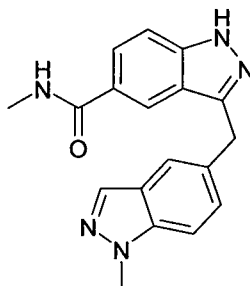
Into a 25-mL round-bottom flask was placed 3-[(1-methyl-1H-indazol-6-yl)methyl]-1H-indazole-5-carboxylic acid (100 mg, 0.33 mmol), methylamine hydrochloride (33 mg, 0.49 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 149 mg,

0.39 mmol), N,N-diisopropylethylamine (84 mg, 0.65 mmol) and N,N-dimethylformamide (2 mL). The resulting solution was stirred for 2 h at 25°C. The mixture was diluted with 20 mL of ethyl acetate. The organic phase was washed with three time with 15 mL of brine. The mixture was dried over sodium sulfate, filtered and evaporated to dryness. The crude product (100 mg) was purified by preparative HPLC to yield in 24.0 mg (22%) of the title compound as a light brown solid.

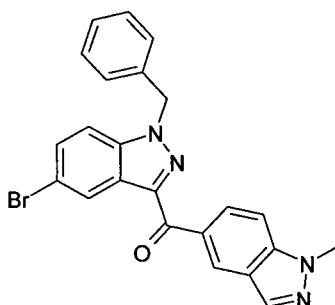
In analogy to this synthetic route also compounds **28**, **29**, **32**, **33**, **35**, **37** and **88** were synthesized.

Synthetic Example 5:

3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid methylamide **14**



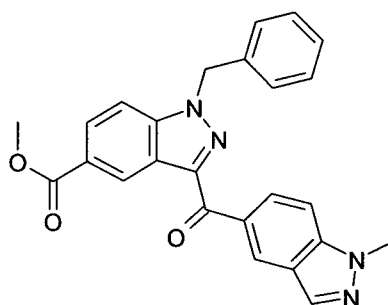
5.1. (1-Benzyl-5-bromo-1H-indazol-3-yl)-(1-methyl-1H-indazol-5-yl)-methanone



Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 5-bromo-1-methyl-1H-indazole (2.70

g, 12.8 mmol) and tetrahydrofuran (50 mL). This was followed by the addition of n-BuLi (5.70 mL, 60.5 mmol) dropwise with stirring at -78°C. The mixture was stirred for 60 min at -78°C and warmed to -40°C. After recooling to -78°C a solution of 1-benzyl-5-bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide (1.60 g, 4.28 mmol) in tetrahydrofuran (50 mL) was added dropwise with stirring. The resulting solution was stirred for 1 h at 0°C. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted twice with 200 mL of ethyl acetate and the combined organic layer was washed 3 times with 100 mL of brine. The organic phase was dried over sodium sulfate, filtered and evaporated to dryness. The residue was applied onto a silica gel column with petroleum ether/ethyl acetate (10:1). This resulted in 1.50 g (79%) of 1-benzyl-5-bromo-3-[(1-methyl-1H-indazol-5-yl)carbonyl]-1H-indazole as a yellow solid.

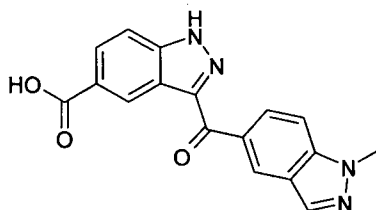
5.2. 1-Benzyl-3-(1-methyl-1H-indazole-5-carbonyl)-1H-indazole-5-carboxylic acid methyl ester



Into a 100-mL sealed tube was placed 1-benzyl-5-bromo-3-[(1-methyl-1H-indazol-5-yl)carbonyl]-1H-indazole (2.80 g, 6.29 mmol), potassium carbonate (1.85 g, 18.9 mmol), (1,1'-bis(diphenylphosphino)ferrocene)-palladium(II) chloride (460 mg, 0.63 mmol), methanol (30 mL) and N,N-dimethylformamide (30 mL). To the above CO(g) was introduced. The resulting solution was stirred for 1 h overnight at 80°C. The resulting mixture was evaporated to dryness. The resulting solution was diluted with 200 mL of ethyl acetate. The mixture was washed 3 times with 100 mL of brine. The mixture was dried over sodium sulfate, filtered and evaporated to dryness. The residue was

applied onto a silica gel column with petroleum ether/ethyl acetate (10:1). This resulted in 2.20 g (82%) of methyl 1-benzyl-3-[(1-methyl-1H-indazol-5-yl)carbonyl]-1H-indazole-5-carboxylate as a yellow oil.

5.3. 3-(1-Methyl-1H-indazole-5-carbonyl)-1H-indazole-5-carboxylic acid

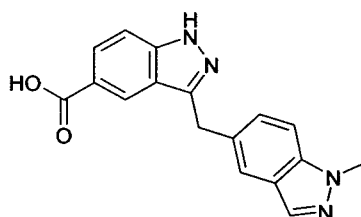


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Into a 50-mL round-bottom flask was placed methyl 1-benzyl-3-[(1-methyl-1H-indazol-5-yl)carbonyl]-1H-indazole-5-carboxylate (1.10 g, 2.59 mmol) and dimethyl sulfoxide (15 mL), followed by the addition of potassium tert.-butylate (2.90 g, 25.8 mmol). To the mixture O₂(g) was introduced. The resulting solution was stirred for 1 h overnight at 25°C. The reaction was then quenched by the addition of 10 ml of water. The pH value of the solution was adjusted to 6 with hydrogen chloride solution. The solids were collected by filtration. This resulted in 0.45 g (54%) of 3-[(1-methyl-1H-indazol-5-yl)carbonyl]-1H-indazole-5-carboxylic acid as a yellow solid.

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5.4. 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid



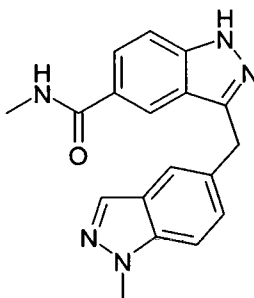
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Into a 50-mL round-bottom flask was placed 3-[(1-methyl-1H-indazol-5-yl)carbonyl]-1H-indazole-5-carboxylic acid (300 mg, 0.94 mmol), trifluoroacetic acid (10 mL) and sodium borohydride (1.00 g, 26.4 mmol). The resulting mixture was stirred for 2 h overnight at 25°C. The resulting solution was diluted with 200 mL of water. The solids were collected by filtration. The

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crude product was purified by re-crystallization from ethyl acetate. This resulted in 150 mg (52%) of 3-[(1-methyl-1H-indazol-5-yl)methyl]-1H-indazole-5-carboxylic acid as a yellow solid.

5.5. 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid methylamide **14**



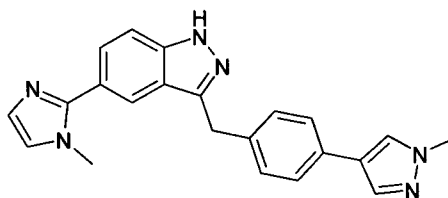
Into a 25-mL round-bottom flask was placed 3-[(1-methyl-1H-indazol-5-yl)methyl]-1H-indazole-5-carboxylic acid (90.0 mg, 0.29 mmol), methylamine hydrochloride (30.0 mg, 0.44 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 112 mg, 0.29 mmol), N,N-diisopropylethylamine (113 mg, 0.88 mmol) and N,N-dimethylformamide (2 mL). The resulting solution was stirred for 2 h at 25°C. The resulting mixture was evaporated to dryness. The crude product (150 mg) was purified by preparative HPLC to result in 20.0 mg (21%) of N-methyl-3-[(1-methyl-1H-indazol-5-yl)methyl]-1H-indazole-5-carboxamide as a white solid.

In analogy to this synthetic route also compounds **15, 23, 24, 25, 26, 30, 66, 68, 70-73, 93, 100 and 101** were synthesized. Compounds **67** and **69** can be prepared in an analogous manner.

Synthetic Example 6:

5-(1-Methyl-1H-imidazol-2-yl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole **94**

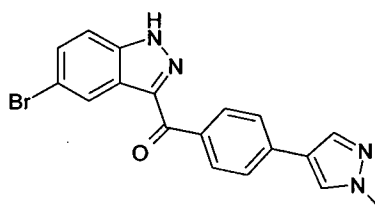
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6.1. [5-Bromo-1-(1-phenyl-pentyl)-1H-indazol-3-yl]-[4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-methanone

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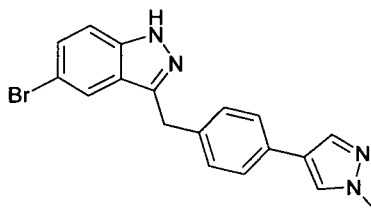
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Into a 500 mL round-bottom flask was placed 5-bromo-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]carbonyl]-1-(1-phenylpentyl)-1H-indazole (6.00 g, 11.4 mmol), potassium tert.-butoxide (28.0 g, 250 mmol) and DMSO (300 mL). The mixture was purged and maintained within an atmosphere of oxygen. The solution was stirred for 3 days at RT. The reaction mixture was diluted with 500 mL of water and extracted five times with 200 mL of ethyl acetate and the organic layers were combined. The organic phase was washed 3 times with 400 mL of sodium chloride solution. The mixture was dried over anhydrous sodium sulfate and concentrated to dryness under vacuum. This resulted in 3.50 g (81%) of 5-bromo-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]carbonyl]-1H-indazole as a yellow solid.

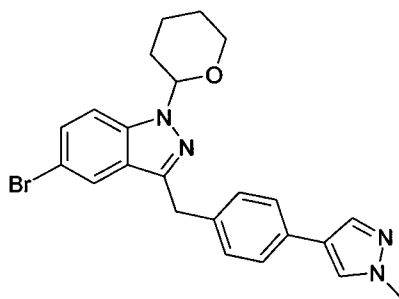
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6.2. 5-Bromo-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole



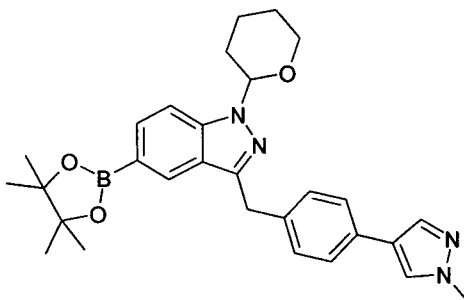
Into a 500 mL round-bottom flask was placed 5-bromo-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]carbonyl]-1H-indazole (3.50 g, 9.18 mmol), Et₃SiH (21.4 g, 184 mmol) and trifluoroacetic acid (150 mL). The solution was stirred for 20 h at RT. The reaction mixture was concentrated under vacuum. The remainder was diluted with 100 mL of dichloromethane. The mixture was washed three times with 50 mL of sodium chloride solution. The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (9/1). This resulted in 2.5 g (74%) of 5-bromo-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole as a yellow solid.

6.3. 5-bromo-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazole



Into a 500 mL round-bottom flask was placed 5-bromo-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole (2.10 g, 5.72 mmol), 3,4-dihydro-2H-pyran (1.06 g, 12.6 mmol), Pyridinium *p*-toluenesulfonate (144 mg, 0.57 mmol), dichloromethane (200 mL). The resulting solution was stirred for 14 h at 40°C. The reaction was then quenched by the addition of 10 mL of sodium bicarbonate solution. The mixture was diluted with 100 mL of dichloromethane and the organic phase was washed three times with 80 mL of sodium chloride solution. The mixture was dried over anhydrous sodium sulfate and concentrated to dryness under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1/5-2/3). This resulted in 1.90 g (74%) of 5-bromo-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazole as a yellow solid.

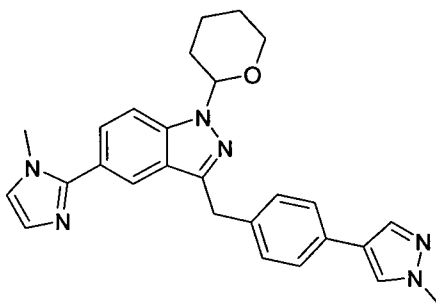
6.4. 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole



Into a 250 mL round-bottom flask was placed 5-bromo-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazole (1.90 g, 4.21 mmol), 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.20 g, 12.6 mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) dichloromethane complex (344 mg, 0.42 mmol), potassium acetate (1.25 g, 12.7 mmol) and dioxane (100 mL). The mixture was stirred for 3 h at 90°C. The reaction mixture was diluted with 150 mL of water and extracted three times with 80 mL of ethyl acetate. The organic layers were combined and washed twice with 100 mL of sodium chloride solution. The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1/1). This resulted in 1.50 g (71%) of 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole as a yellow solid.

6.5. 5-(1-methyl-1H-imidazol-2-yl)-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazole

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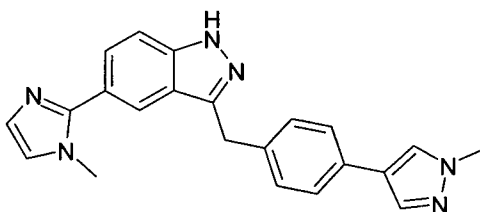
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Into a 50 mL round-bottom flask was placed 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (300 mg, 0.60 mmol), 2-bromo-1-methyl-1H-imidazole (193 mg, 1.20 mmol), tetrakis(triphenylphosphine)palladium(0) (70.0 mg, 0.06 mmol, 0.10 equiv), dioxane (16 mL), potassium carbonate (166 mg, 1.20 mmol) and water (4 mL). The resulting mixture was stirred for 3 h at 80°C. The reaction mixture was diluted with 40 mL of water and was extracted three times with 30 mL of ethyl acetate. The organic layers were combined and washed with 40 mL of sodium chloride solution. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/PE (1/1-99/1). This resulted in 110 mg (40%) of 5-(1-methyl-1H-imidazol-2-yl)-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazole as a yellow solid.

6.6. 5-(1-Methyl-1H-imidazol-2-yl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole **94**

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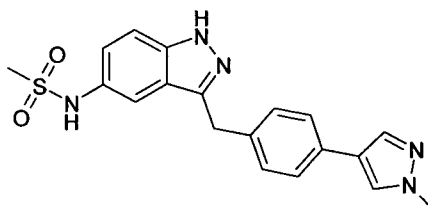
Into a 50 mL round-bottom flask, was placed 5-(1-methyl-1H-imidazol-2-yl)-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazole (110 mg, 0.24 mmol), hydrogen chloride solution (1 mL, 12 mol/L) and acetonitrile (20 mL). The resulting solution was stirred for 1 h at room temperature. The

mixture was concentrated under vacuum and diluted with 15 mL of water. The pH value of the solution was adjusted to 8 with sodium bicarbonate solution. The mixture was concentrated to dryness under vacuum. The crude product was purified by preparative HPLC (acetonitrile/water). This resulted in 17.0 mg (19%) of 5-(1-methyl-1H-imidazol-2-yl)-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole as an off-white solid.

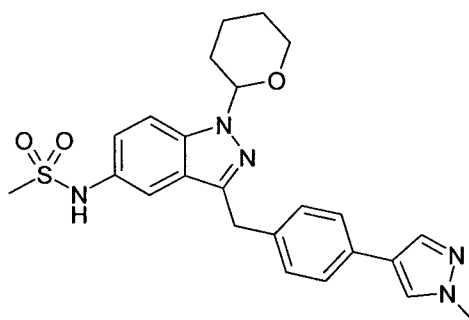
In analogy to this synthetic route also compound **89**, **90**, **95-97**, **99**, **105-107** and **114** were synthesized.

Synthetic Example 7:

N-[3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl]-methanesulfonamide **55**



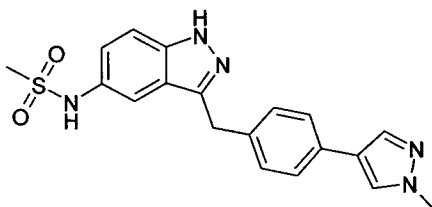
7.1. N-[3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-5-yl]-methanesulfonamide



Into a 50 mL round-bottom flask was placed (3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazol-5-yl)boronic acid (110 mg, 0.26 mmol), methanesulfonamide (50.0 mg, 0.53 mmol), Cu(II)acetate (53.0 mg, 0.29 mmol), triethylamine (32.0 mg, 0.32 mmol) and dichloromethane (20

mL). The solution was stirred for 16 h at room temperature was then diluted with 30 mL of dichloromethane. The mixture was washed with 3 times with 25 mL of sodium chloride solution. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column with ethyl acetate/petroleum ether. This resulted in 55.0 mg (45%) of N-(3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazol-5-yl)methanesulfonamide as a yellow solid.

7.2 N-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanesulfonamide **55**



Into a 50 mL round-bottom flask was placed N-(3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazol-5-yl)methanesulfonamide (50.0 mg, 0.11 mmol), acetonitrile (20 mL) and hydrogen chloride solution (12M, 1.00 mL). The solution was stirred for 1 h at room temperature and then concentrated under vacuum. The mixture diluted with 10 mL of water. The pH value of the solution was adjusted to 8 with sodium bicarbonate. The resulting mixture was concentrated under vacuum. The crude product was purified by preparative HPLC (acetonitrile/water) to resulted in 12.0 mg (29%) of N-(3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazol-5-yl)methanesulfonamide as a white solid.

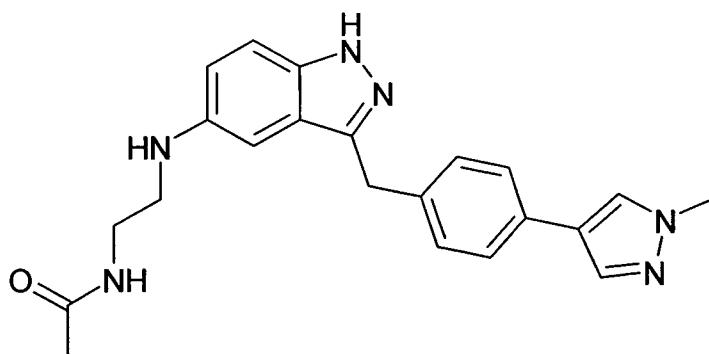
In analogy to this synthetic route also compound **59-60 and 98** were synthesized. Compounds **54, 56-58 and 74-78** can be synthesized in an analogous manner.

Synthetic Example 8

8. N-(2-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-ylamino}-ethyl)-acetamide **113**

102

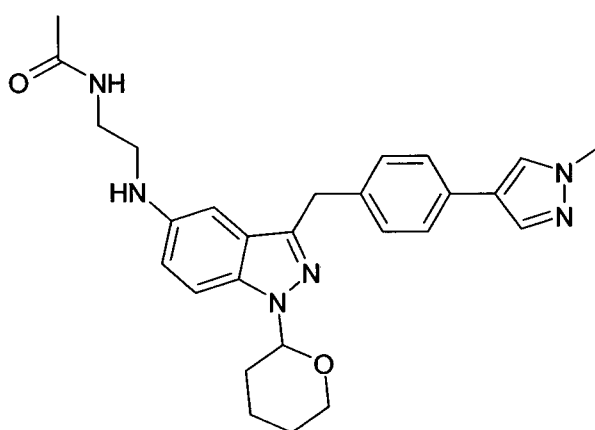
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8.1. N-{2-[(3-{[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-1-(oxan-2-yl)-1H-indazol-5-yl)amino]ethyl}acetamide

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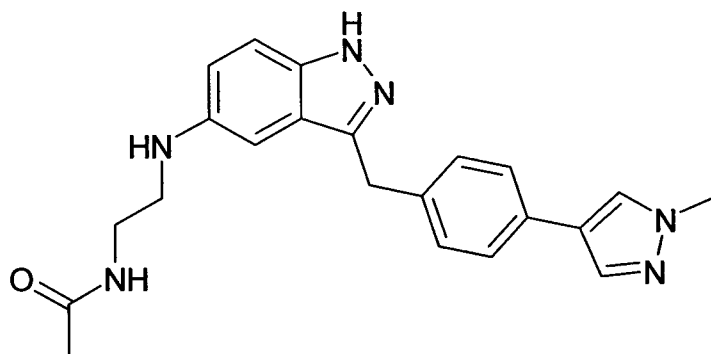
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Into a 100-mL round-bottom flask was placed (3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazol-5-yl)boronic acid (90.0 mg, 0.22 mmol), N-(2-aminoethyl)acetamide (44.1 mg, 0.43 mmol), $\text{Cu}(\text{OAc})_2$ (43.0 mg, 0.24 mmol), triethylamine (26.2 mg, 0.26 mmol) and dichloromethane (50 mL). The reaction mixture was stirred for 1 h overnight at 25°C. The solution was extracted with 100 mL of dichloromethane and the organic layers combined. The mixture was washed three times with 40 mL of sodium chloride, dried over sodium sulfate and concentrated under vacuum. The residue was purified over a silica gel column with methanol/dichloromethane (1:4). This resulted in 40.2 mg (39%) of N-[2-[(3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazol-5-yl)amino]ethyl]acetamide as a yellow solid. $[\text{M}+\text{H}]^+$ 473.

8.2. N-(2-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-ylamino}-ethyl)-acetamide **113**

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Into a 25-mL round-bottom flask was placed N-[2-[(3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazol-5-yl)amino]ethyl]acetamide (40.0 mg, 0.08 mmol) in acetonitrile (5 mL) and conc. hydrogen chloride (0.3 mL, 9.87 mmol) was added at RT. The solution was stirred for 2 h at RT. The mixture was concentrated under vacuum. The crude product was purified by prep-HPLC (acetonitrile/water) to yield in 3.01 mg (9%) of N-[2-[(3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazol-5-yl)amino]ethyl]acetamide as an off-white solid.

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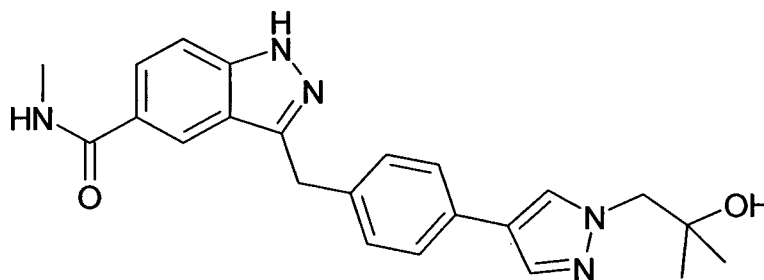
In analogy to these procedures compound **103** was prepared.

Synthetic Example 9:

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3-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazole-5-carboxylic acid methylamide **112**

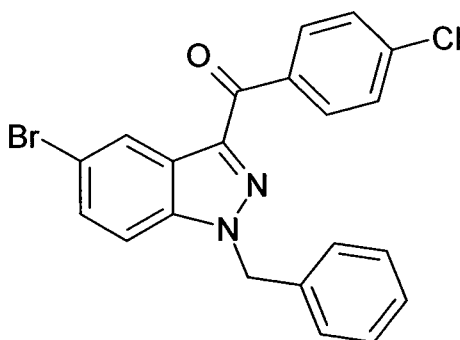
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9.1. 1-benzyl-5-bromo-3-[(4-chlorophenyl)carbonyl]-1H-indazole

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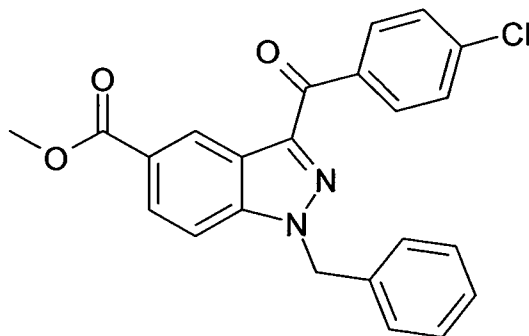
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Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 1-bromo-4-chlorobenzene (6.60 g, 34.5 mmol) and tetrahydrofuran (50 mL). This was followed by the addition of n-BuLi (13.6 mL, 3.61 mmol, 2.5 M) at -78°C. The mixture was stirred for 60 min at -78°C and a solution of 1-benzyl-5-bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide (6.50 g, 17.4 mmol) in tetrahydrofuran (40 mL) was added at -78°C. The solution was stirred for 2 h at -78°C. The reaction was then quenched by the addition of 100 mL of water. The solution was extracted with 200 mL of ethyl acetate and the organic layer was concentrated to dryness. The residue was purified over a silica gel column with petrol ether/ethyl acetate (20:1). This resulted in 2.31 g (31%) of 1-benzyl-5-bromo-3-[(4-chlorophenyl)carbonyl]-1H-indazole as a yellow solid.

9.2. Methyl 1-benzyl-3-[(4-chlorophenyl)carbonyl]-1H-indazole-5-carboxylate



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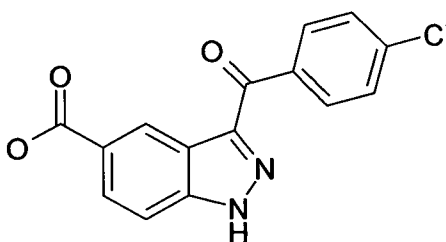
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Into a 250-mL sealed tube was placed 1-benzyl-5-bromo-3-[(4-chlorophenyl)carbonyl]-1H-indazole (4.21 g, 9.87 mmol), Pd(dppf)Cl₂ (720 mg, 0.98 mmol), KOAc (2.90 g, 29.6 mmol) and N,N-dimethylformamide (40 mL). Methanol (40 mL) was added at RT and the solution was stirred for 12 h

at 80°C under a CO atmosphere. The mixture was concentrated under vacuum. The residue was purified over a silica gel column with petrol ether/ethyl acetate (10:1). This resulted in 3.05 g (75%) of methyl 1-benzyl-3-[(4-chlorophenyl)carbonyl]-1H-indazole-5-carboxylate as a yellow solid.

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9.3. 3-[(4-Chlorophenyl)carbonyl]-1H-indazole-5-carboxylic acid

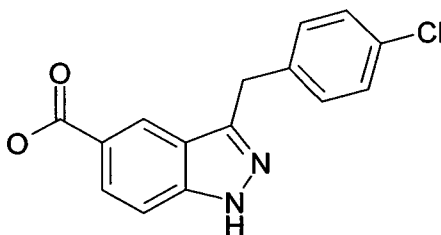


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Into a 500-mL round-bottom flask was placed methyl 1-benzyl-3-[(4-chlorophenyl)carbonyl]-1H-indazole-5-carboxylate (3.00 g, 7.41 mmol) and DMSO (100 mL). This was followed by the addition of t-BuOK (8.30 g, 74.0 mmol). To the mixture oxygen was introduced and the reaction mixture stirred overnight at RT. The solution was diluted with 200 mL of water. The pH of the solution was adjusted to 6 with hydrogen chloride (1 M). The solids were collected by filtration. This resulted in 0.91 g (40%) of 3-[(4-chlorophenyl)carbonyl]-1H-indazole-5-carboxylic acid as a yellow solid.

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9.4. 3-[(4-Chlorophenyl)methyl]-1H-indazole-5-carboxylic acid



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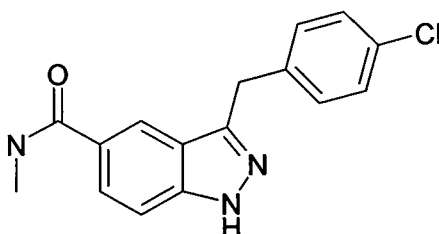
Into a 500-mL round-bottom flask was placed 3-[(4-chlorophenyl)carbonyl]-1H-indazole-5-carboxylic acid (900 mg, 2.99 mmol), trifluoroacetic acid (200 mL) and SiH(Et)₃ (6.96 g, 59.9 mmol). The solution was stirred overnight at RT. The mixture was concentrated under vacuum. The residue was diluted with 200 ml of petrol ether. The solids were collected by filtration. This

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resulted in 600 mg (70%) of 3-[(4-chlorophenyl)methyl]-1H-indazole-5-carboxylic acid as a brown solid.

9.5. 3-[(4-chlorophenyl)methyl]-N-methyl-1H-indazole-5-carboxamide

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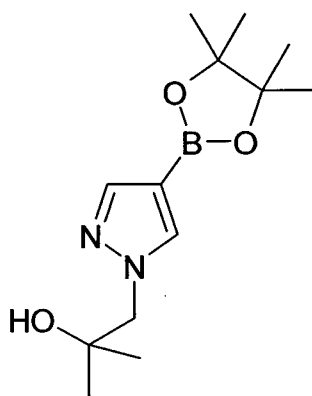
Into a 25-mL round-bottom flask was placed 3-[(4-chlorophenyl)methyl]-1H-indazole-5-carboxylic acid (150 mg, 0.52 mmol), methylamine hydrochloride (46.0 mg, 0.68 mmol), HATU (199 mg, 0.52 mmol), DIEA (203 mg, 1.57 mmol) and N,N-dimethylformamide (3 mL). The solution was stirred for 3 h at RT. The mixture was concentrated under vacuum. The residue was purified over a silica gel column with dichloromethane/methanol (50:1). This resulted in 140 mg (89%) of 3-[(4-chlorophenyl)methyl]-N-methyl-1H-indazole-5-carboxamide as a yellow solid.

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9.6. 2-methyl-1-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]propan-2-ol

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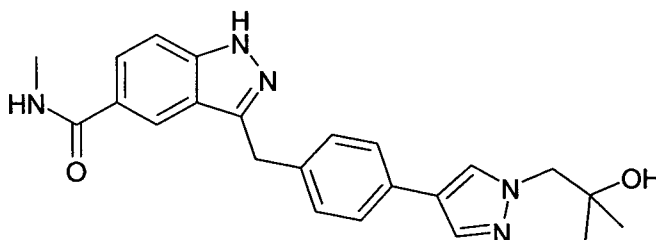
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Into a 30-mL sealed tube was placed 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.00 g, 5.15 mmol), 2,2-dimethyloxirane (8 mL), cesium carbonate (260 mg, 0.8 mmol). The reaction mixture was irradiated with microwave radiation for 30 min at 100°C. The solids were filtered off. The

filtrate was concentrated under vacuum and resulted in 1.00 g (73%) of 2-methyl-1-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]propan-2-ol as a white solid.

5 9.7. 3-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazole-5-carboxylic acid methylamide

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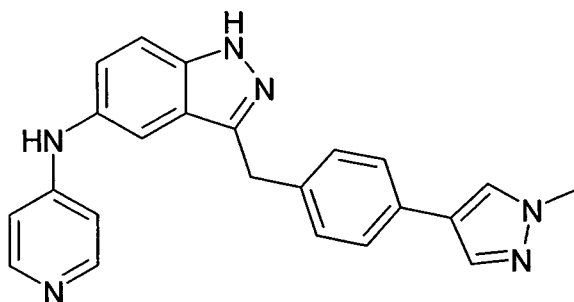
Into a 10-mL sealed tube purged and maintained with an inert atmosphere of nitrogen was placed 3-[(4-chlorophenyl)methyl]-N-methyl-1H-indazole-5-carboxamide (140 mg, 0.47 mmol), 2-methyl-1-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]propan-2-ol (149 mg, 0.56 mmol), Pd(PCy₃)₂Cl₂ (34.5 mg, 0.05 mmol), KOAc (92.0 mg, 0.94 mmol), N,N-dimethylformamide (5 mL) and water (0.5 mL). The mixture was irradiated with microwave radiation for 2 h at 110°C and concentrated to dryness under vacuum. The residue was purified over a silica gel column with dichloromethane/methanol (50:1) and by prep-HPLC (acetonitrile/water) to yield in 20.3 mg (11%) of 3-[(4-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]phenyl)methyl]-N-methyl-1H-indazole-5-carboxamide as a white solid. In analogy to these procedures compounds **109-111** were prepared.

Synthetic Example 10:

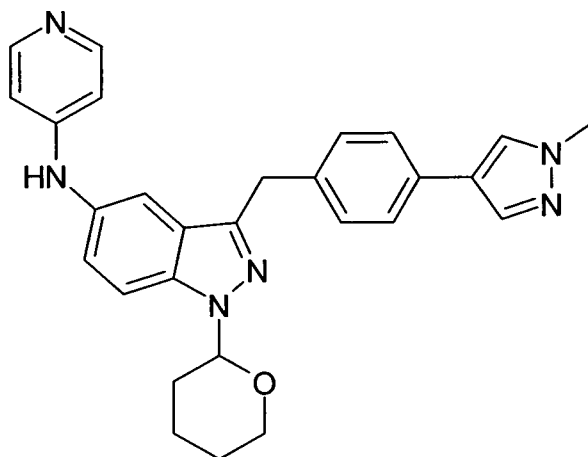
{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyridin-4-yl-amine (108)

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108



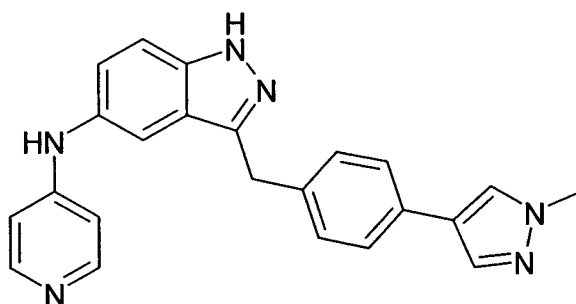
10.1. 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-N-(pyridin-4-yl)-1H-indazol-5-amine



Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 5-bromo-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazole (100 mg, 0.22 mmol), pyridin-4-amine (31.7 mg, 0.34 mmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (23.3 mg, 0.02 mmol), XantPhos (27.0 mg, 0.05 mmol), K_3PO_4 (134 mg, 0.63 mmol) and toluene (20 mL). The reaction mixture was stirred overnight at 110°C and concentrated under vacuum. The residue was purified over a silica gel column with dichloromethane/methanol (5:1). This resulted in 42.0 mg (41%) of 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-N-(pyridin-4-yl)-1H-indazol-5-amine as a yellow solid.

10.2. {3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyridin-4-yl-amine

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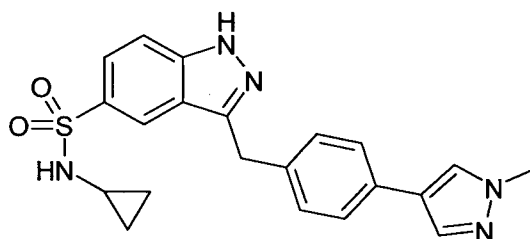
Into a 25-mL round-bottom flask was placed 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-N-(pyridin-4-yl)-1H-indazol-5-amine (50.0 mg, 0.11 mmol) in acetonitrile (5 mL) and conc. hydrogen chloride (0.3 mL) was added at RT. The solution was stirred for 2 h at RT and concentrated under vacuum. The crude product was purified by prep-HPLC (acetonitrile/water) to yield in 17.9 mg (44%) of 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-N-(pyridin-4-yl)-1H-indazol-5-amine as a grey solid.

In analogy to these procedures compound 104 was synthesized.

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Synthetic Example 11

3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-sulfonic acid cyclopropylamide **64**



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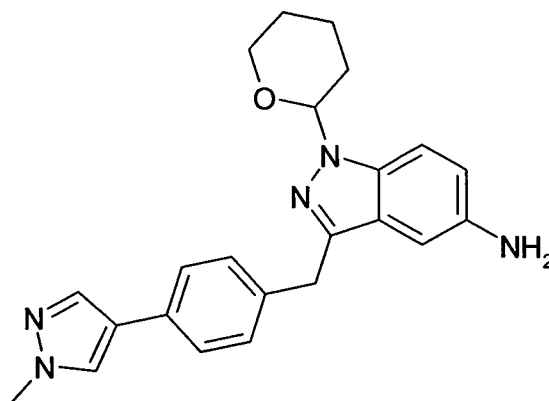
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11.1. 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazol-5-amine

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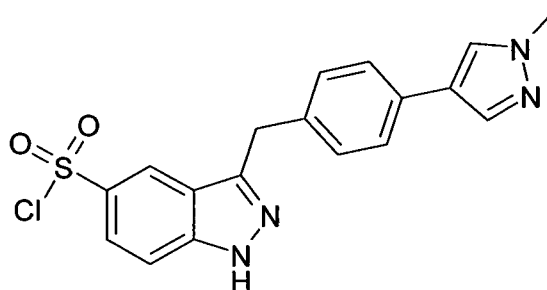
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Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed toluene (15 mL), 5-bromo-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazole (300 mg, 0.50 mmol, 75%), diphenylmethanimine (108 mg, 0.60 mmol), t-BuONa (67.1 mg, 0.70 mmol), Pd₂(dba)₃*CHCl₃ (51.6 mg, 0.05 mmol) and BINAP (9.31 mg, 0.01 mmol). The solution was stirred for 3 h at 100°C. The pH of the solution was adjusted to 8 with sodium hydroxide solution (12 mol/L). The mixture was extracted three times with 15 mL of dichloromethane and the combined organic layers were evaporated to dryness. The residue was purified over a silica gel column with ethyl acetate/petroleum ether (2:1). This resulted in 130 mg (47%) of 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazole-5-amine as a light yellow solid.

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11.2 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-sulfonyl chloride

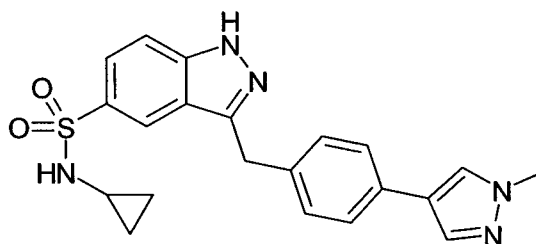


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Into a 50-mL 3-necked round-bottom flask was placed conc. hydrogen chloride (1 mL) and 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1-(oxan-2-yl)-1H-indazole-5-amine (130 mg, 0.23 mmol, 70%). This was followed by the

addition of NaNO_2 (32.4 mg, 0.47 mmol) at 0°C . The mixture was stirred for 1 h at 0°C . To this was added SO_2 (50 mL) at 0°C . The mixture solution was stirred for additional 30 min. To the mixture was added CuCl_2 (158 mg, 1.17 mmol) and stirring was continued for 1 h at 25°C . The solution was extracted three times with 10 mL of dichloromethane and the combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness. This resulted in 50.0 mg (22%) of 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-sulfonyl chloride as yellow oil.

11.3. 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-sulfonic acid cyclopropylamide



Into a 25-mL round-bottom flask was placed dioxane (10 mL), 3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-sulfonyl chloride (50.0 mg, 0.05 mmol, 40%), cyclopropylamine (4.43 mg, 0.08 mmol) and DIEA (10.0 mg, 0.08 mmol). The solution was stirred for 2 h at 25°C and was concentrated under vacuum. The residue was purified over a silica gel column with ethyl acetate/petroleum ether (2:1). The crude product was then purified by prep-HPLC (acetonitrile/water) to give 3.05 mg (15%) of the title compound as a white solid.

In analogy to the procedures described in example 6 the compounds 105-107 and 114 were synthesized.

Relevant analytical data as well as HPLC conditions of exemplary compounds of the present invention are given in Tables 2A and 2B below.

Table 2A

Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
1	3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid methylamide		326
2	3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid cyclopropylamide		352
3	3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid (2-methoxy-ethyl)-amide		370
4	(3,3-Difluoro-pyrrolidin-1-yl)-[3-(3-methyl-benzyl)-1H-indazol-5-yl]-methanone		356
5	3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid amide		266
6	3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid cyclopropylamide		306
7	3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid methylamide		280

Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
8	3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid (2-methoxy-ethyl)-amide		324
9	[3-(3-Methyl-benzyl)-1H-indazol-5-yl]-piperazin-1-yl-methanone		335
10	3-(1-Methyl-1H-indazol-6-ylmethyl)-1H-indazole-5-carboxylic acid methylamide		320
11	(3,3-Difluoro-pyrrolidin-1-yl)-[3-(3,4-dimethoxy-benzyl)-1H-indazol-5-yl]-methanone		402
12	3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid amide		312
13	[3-(3,4-Dimethoxy-benzyl)-1H-indazol-5-yl]-((R)-3-hydroxy-pyrrolidin-1-yl)-methanone		382

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
14	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid methylamide		320
15	(3,3-Difluoro-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone		396
16	(3,3-Difluoro-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone		422
17	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid cyclopropylamide		372
18	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (2-methoxy-ethyl)-amide		390
19	[3-(3,4-Dimethoxy-benzyl)-1H-indazol-5-yl]-((S)-3-hydroxy-pyrrolidin-1-yl)-methanone		382
20	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid amide		331

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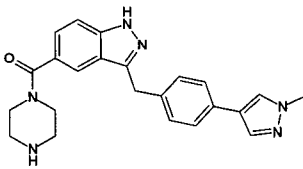
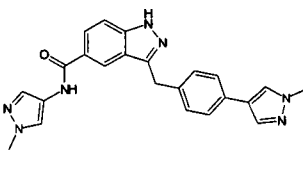
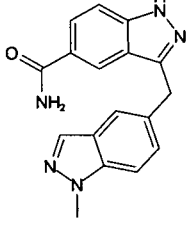
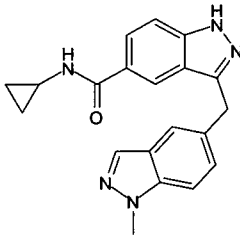
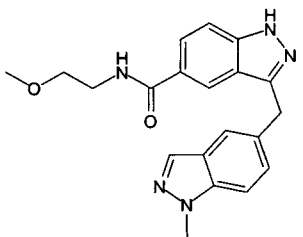
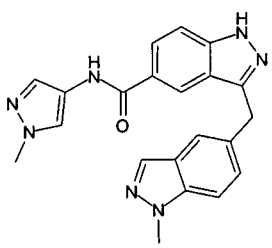
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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
21	{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-piperazin-1-yl-methanone		401
22	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (1-methyl-1H-pyrazol-4-yl)-amide		411
23	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid amide		306
24	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid cyclopropylamide		346
25	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (2-methoxy-ethyl)-amide		364
26	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (1-methyl-1H-pyrazol-4-yl)-amide		386

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
27	3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid (4-hydroxy-cyclohexyl)-amide		364
28	(3,3-Difluoro-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone		396
29	3-(1-Methyl-1H-indazol-6-ylmethyl)-1H-indazole-5-carboxylic acid cyclopropylamide		346
30	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (4-hydroxy-cyclohexyl)-amide		404
31	((S)-3-Hydroxy-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone		402
32	((R)-3-Hydroxy-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone		376
33	((S)-3-Hydroxy-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone		376

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
34	((R)-3-Hydroxy-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone		402
35	[(R)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone		470
36	[(R)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3-methyl-benzyl)-1H-indazol-5-yl]-methanone		430
37	[(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone		470
38	[(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3-methyl-benzyl)-1H-indazol-5-yl]-methanone		430
39	3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid 2-(2,2,2-trifluoroethoxy)-benzylamide		500
40	[(R)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3,4-dimethoxy-benzyl)-1H-indazol-5-yl]-methanone		476

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
41	[(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3,4-dimethoxy-benzyl)-1H-indazol-5-yl]-methanone		476
42	3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid 2-(2,2,2-trifluoro-ethoxy)-benzylamide		454
43	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-pyrazolo[4,3-b]pyridine-5-carboxylic acid methylamide		321*
44	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid methylamide		321*
45	(3,3-Difluoro-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-ethanone		397*
46	(3,3-Difluoro-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-pyrazolo[4,3-b]pyridin-5-yl]-ethanone		397*

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
47	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-pyrazolo[4,3-b]pyridine-5-carboxylic acid methylamide		347*
48	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid methylamide		347*
49	(3,3-Difluoro-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}-methanone		423*
50	(3,3-Difluoro-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-pyrazolo[4,3-b]pyridin-5-yl}-methanone		423*
51	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (2-amino-ethyl)-amide		375*
52	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (2-dimethylamino-ethyl)-amide		403*

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
53	N-(4-hydroxybutyl)-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole-5-carboxamide		404
54	N-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-acetamide		346*
55	N-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanesulfonamide		382*
56	1-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyrrolidin-2-one		372*
57	(S)-3-Methyl-1-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyrrolidin-2-one		386*
58	(R)-3-Methyl-1-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyrrolidin-2-one		386*
59	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-5-morpholin-4-yl-1H-indazole		374*
60	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-5-piperazin-1-yl-1H-indazole		373*

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
61	5-[(4,4-difluoropiperidin-1-yl)carbonyl]-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole		436
62	5-[(3,3-difluoropiperidin-1-yl)carbonyl]-3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-1H-indazole		436
63	3-[[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl]-5-[(morpholin-4-yl)carbonyl]-1H-indazole		402
64	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-sulfonic acid cyclopropylamide		408*
65	5-(3-Methoxy-azetidine-1-sulfonyl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole		438*
66	(3-Methoxy-azetidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone		376
67	(3-Hydroxy-azetidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone		362

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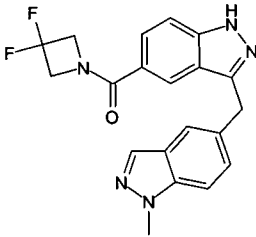
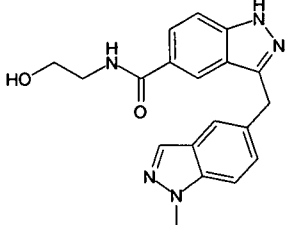
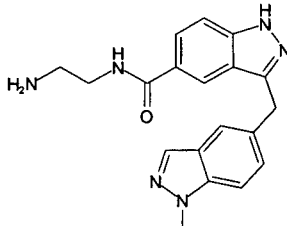
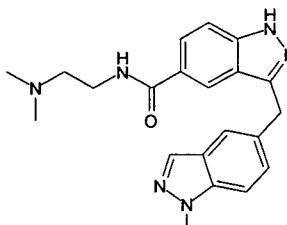
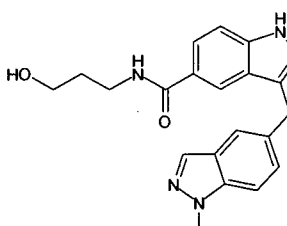
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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
68	(3,3-Difluoro-azetidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone		382
69	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (2-hydroxy-ethyl)-amide		350*
70	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (2-amino-ethyl)-amide		349
71	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (2-dimethylamino-ethyl)-amide		377
72	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (3-hydroxy-propyl)-amide		364*

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
73	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (4-hydroxy-butyl)-amide		378
74	N-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-acetamide		320*
75	N-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanesulfonamide		356*
76	1-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-pyrrolidin-2-one		346*
77	(S)-3-Methyl-1-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-pyrrolidin-2-one		360*

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
78	(R)-3-Methyl-1-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-pyrrolidin-2-one		360*
79	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid methylamide		346
80	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (4-hydroxy-cyclohexyl)-amide		430
81	(3-Methoxy-azetidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone		402
82	(3-Hydroxy-azetidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone		388
83	(3,3-Difluoro-azetidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone		408
84	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (2-hydroxy-ethyl)-amide		376

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
85	3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (3-hydroxy-propyl)-amide		390
86	{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyrrolidin-1-yl-methanone		386
87	{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-piperidin-1-yl-methanone		400
88	3-(1-Methyl-1H-indazol-6-ylmethyl)-1H-indazole-5-carboxylic acid 2-(2,2,2-trifluoro-ethoxy)-benzylamide		494
89	5-(1-Methyl-1H-pyrazol-3-yl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole		369
90	4-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyridin-2-ylamine		381
91	[(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone		497
92	3-{[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-N-[(2-(2,2,2-trifluoroethoxy)phenyl)methyl]-1H-indazole-5-carboxamide		520

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
93	[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-piperazin-1-yl-methanone		375
94	5-(1-Methyl-1H-imidazol-2-yl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole		369
95	2-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyridin-4-ylamine		381
96	5-(1-Methyl-1H-imidazol-4-yl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole		369
97	2-(2-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-imidazol-1-yl)-ethanol		399
98	4-[3-[(1-methylindazol-5-yl)methyl]-1H-indazol-5-yl]morpholine		348
99	1-methyl-5-[[5-(1-methylpyrazol-3-yl)-1H-indazol-3-yl]methyl]indazole		343

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
100	((S)-3-Hydroxy-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone		376
101	((R)-3-Hydroxy-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone		376
102	[(R)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl]-methanone		497
103	N-[2-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-ylamino]-ethyl]-acetamide		363
104	3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-pyridin-4-yl-amine		355
105	1-methyl-5-[[5-(1-methylimidazol-4-yl)-1H-indazol-3-yl]methyl]indazole		343

Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
106	1-methyl-5-[[5-(1-methylimidazol-2-yl)-1H-indazol-3-yl]methyl]indazole		343
107	2-{2-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-imidazol-1-yl}-ethanol		373
108	{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyridin-4-yl-amine		381
109	(3,3-Difluoro-pyrrolidin-1-yl)-(3-{4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazol-5-yl)-methanone		480
110	(3-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazol-5-yl)-pyrrolidin-1-yl-methanone		444
111	(3,3-Difluoro-azetidin-1-yl)-(3-{4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazol-5-yl)-methanone		466
112	3-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazole-5-carboxylic acid methylamide		404
113	N-(2-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-ylamino}-ethyl)-acetamide		389

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Compound Number	Compound Name	Structural Formula	[M+1] ⁺ (m/z)
114	2-{4-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-imidazol-1-yl}-ethanol		373

* calculated values

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Table 2B:

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Compound Number	Rt [min]	HPLC method	NMR data
1	2,33	A	¹ H NMR (300 MHz, DMSO-d ₆) ppm = 12.93 (s, 1H), 8.37 (br.s, 1H), 8.24 (s, 1H), 7.80 (d, 1H), 7.47 (d, 1H), 6.95 (s, 1H), 6.85-6.78 (m, 2H), 4.22 (s, 2H), 3.70 (s, 3H), 3.68 (s, 3H), 2.79-2.78 (m, 3H).
2	3,59	A	¹ H NMR (300 MHz, DMSO-d ₆) ppm = 12.93 (s, 1H), 8.37 (d, 1H), 8.24 (s, 1H), 7.80 (dd, 1H), 7.47 (d, 1H), 6.97 (s, 1H), 6.90 (dd, 1H), 6.76 (dd, 1H), 4.22 (s, 2H), 3.76 (s, 3H), 3.71 (s, 3H), 2.88-2.80 (m, 1H), 0.83-0.81 (m, 2H), 0.77-0.73 (m, 2H).
3	3,36	A	¹ H NMR (300 MHz, DMSO-d ₆) ppm = 12.94 (s, 1H), 8.47 (m, 1H), 8.29 (s, 1H), 7.83 (dd, 1H), 7.48 (d, 1H), 6.97 (s, 1H), 6.85-6.75 (m, 2H), 4.23 (s, 2H), 3.71 (s, 3H), 3.68 (s, 3H), 3.50-3.41 (m, 4H), 3.27 (s, 3H).
4	3,63	A	¹ H-NMR (400MHz, CD ₃ OD) ppm = 7.71 (s, 1H), 7.58-7.54 (m, 2H), 7.19-7.10 (m, 3H), 7.04 (d, J=8Hz, 1H), 4.33 (s, 1H), 3.97-3.69 (m, 4H), 2.46-2.40 (m, 2H), 2.29 (s, 3H).
5	0,94	C	¹ H-NMR (300MHz, DMSO-d ₆) ppm = 12.96 (s, 1H), 8.29 (s, 1H), 7.93 (s, 1H), 7.86 (d, J=9Hz, 1H), 7.48 (d, J=6Hz, 1H), 7.23 (s, 1H), 7.18-7.09 (m, 3H), 6.99 (d, J=6Hz, 1H), 4.24 (s, 2H), 2.24 (s, 3H).
6	3,22	C	¹ H-NMR (300MHz, DMSO-d ₆): ppm = 12.95 (s, 1H), 8.38 (s, 1H), 8.21 (s, 1H), 7.81 (d, J=9Hz, 1H), 7.48 (d, J=9Hz, 1H), 7.18-7.06 (m, 3H), 7.00 (d, J=9Hz, 1H), 4.25 (s, 2H), 2.87-2.80 (m, 1H), 2.27 (s, 3H), 0.72-0.67 (m, 2H), 0.66-0.61 (m, 2H).

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Compound Number	Rt [min]	HPLC method	NMR data
7	1,02	B	¹ H NMR (300MHz,DMSO-d ₆): ppm = 12.97 (s,1H), 8.38 (d,J=6Hz,1H), 8.22 (s,1H), 7.82 (d,J=9Hz,1H), 7.50 (d,J=9Hz,1H), 7.18-7.08 (m,3H), 7.00 (d,J=9Hz,1H), 4.24 (s,2H), 2.79 (d,J=3Hz,3H), 2.24 (s,3H).
8	3,03	A	¹ H NMR(400MHz,CD ₃ OD-d ₆) ppm = 8.19(s,1H),7.86(d,J=12Hz,1H),7.54(d,J=8 Hz,1H),7.18-7.09(m,3H),7.02(d,J=8Hz,1H), 4.33(s,2H),3.58(s,4H), 3.40(s,3H),2.29(s,3H).
9	1,28	B	¹ H NMR(400MHz,DMSO-d ₆): ppm = 12.93(s,1H),7.62(s,1H),7.50(d,J=8Hz,1H) ,7.32(d,J=8Hz,1H),7.17-7.10(m,3H),7.00(d,J=8Hz,1H), 4.24 (s,2H),3.50(m,4H),3.32(m,4H),2.23(s,3H)
10	1,89	B	¹ H NMR(300MHz,DMSO-d ₆): ppm = 12.99 (s, 1H), 8.39-8.35 (m, 1H), 8.28 (s, 1H), 7.95 (s, 1H), 7.81 (dd, J = 8.8, 1.4 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.59 (s, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.16-7.03 (m, 1H), 6.94 (s, 1H), 4.44 (s, 2H), 4.00 (s, 3H), 2.78 (d, J = 4.5 Hz, 3H).
11	1,73	D	¹ H NMR (300 MHz, DMSO-d ₆) ppm = 12.96 (s, 1H), 7.86 (s, 1H), 7.50 (s, 2H), 6.96 (s, 1H), 6.83 (s, 2H), 4.23 (s, 2H), 3.88 (t, J = 13.1 Hz, 2H), 3.70-3.68 (m, 8H), 2.44-2.41 (m, 2H).
12	1,41	D	¹ H NMR (300 MHz, DMSO-d ₆) ppm = 12.93 (s, 1H), 8.32 (s, 1H), 7.93 (br.s, 1H), 7.85 (dd, J = 8.7, 1.4 Hz, 1H), 7.47 (d, J = 8.9 Hz, 1H), 7.23 (br.s, 1H), 7.03 (br.s, 1H), 6.96 (d, J = 1.8 Hz, 1H), 6.85-6.77 (m, 2H), 4.22 (s, 2H), 3.71 (s, 3H), 3.68 (s, 3H).
13	1,42	D	¹ H NMR(300MHz,DMSO-d ₆): ppm = 12.90 (s,1H),7.80 (s,1H),7.47 (s,2H),6.95 (s,1H),6.83 (s,2H),4.99-4.89 (d,1H),4.31-4.22 (m,3H), 3.68 (s,6H), 3.56-3.53 (m,3H), 3.68-3.14 (m,1H), 1.92-1.76 (m,2H).
14	2,29	A	¹ H NMR(300MHz,DMSO-d ₆): ppm = 8.36(m,1H),8.24(s,1H),7.94(s,1H),7.81(d, J=9Hz,1H), 7.62(s,1H),7.54-7.47(m,2H),7.37(d,J=6Hz,1H),4.39 (s,2H), 3.98(s,3H),2.78(d,J=6Hz, 3H).
15	2,95	A	¹ H NMR(400MHz,DMSO-d ₆): ppm =13.01(s,1H),7.95(s,1H),7.83(s,1H),7.70(s,1H),7.54-7.47(m,3H), 7.37(d,J=8Hz,1H), 4.42(s,2H),3.99(s,3H), 3.82(m,2H), 3.68-3.54(m,2H),2.38(m, 2H).

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Compound Number	Rt [min]	HPLC method	NMR data
16	1,29	D	¹ H NMR(300Hz, DMSO-d ₆) ppm = 12.99 (s, 1H), 8.04 (s, 1H), 7.87 (s, 1H), 7.77 (s, 1H), 7.50 (s, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 4.29 (s, 2H), 3.92 - 3.88 (m, 5H), 3.67 (br s, 2H), 2.50 - 2.27 (m, 2H).
17	1, 01	E	¹ H NMR(300Hz, DMSO-d ₆) ppm = 12.96 (s, 1H), 8.39 - 8.38 (m, 1H), 8.23 (s, 1H), 8.04 (s, 1H), 7.85-7.78 (m, 2H), 7.49-7.44 (m, 3H), 7.27 (d, J = 8.1 Hz, 2H), 4.28 (s, 2H), 3.83 (s, 3H), 2.84-2.81 (m, 1H), 0.72-0.68 (m, 2H), 0.58-0.56 (m, 2H).
18	0,97	E	¹ H NMR(300Hz, DMSO-d ₆) ppm = 12.98 (s, 1H), 8.47 (s, 1H), 8.28 (s, 1H), 8.05 (s, 1H), 7.85-7.82 (m, 1H), 7.78 (s, 1H), 7.51-7.44 (m, 3H), 7.28 (d, J = 8.1 Hz, 2H), 4.28 (s, 1H), 3.83 (s, 3H), 3.45-3.40 (m, 4H), 3.26 (s, 3H).
19	1,42	D	¹ H NMR(300MHz, DMSO-d ₆): ppm = 12.91 (s, 1H), 7.79 (s, 1H), 7.46 (s, 2H), 6.95-6.83 (m, 3H), 4.22 (m, 3H), 3.68 (s, 6H), 3.54 (m, 4H), 1.82 (m, 2H).
20	0,79	C	¹ H NMR(300MHz, DMSO-d ₆): ppm = 13.08-13.06(m, 1H), 8.55(s, 1H), 8.30-8.23(m, 1H), 8.04 (s, 1H), 7.93 (s, 1H), 7.85-7.83 (m, 1H), 7.77 (s, 1H), 7.46-7.44 (m, 2H), 7.30-7.28(m, 2H), 7.23 (s, 1H), 4.27 (s, 2H), 3.83 (s, 3H).
21	0,66	E	¹ H NMR(300MHz, DMSO-d ₆): ppm = 12.94(s, 1H), 8.05(s, 1H), 7.77(s, 1H), 7.65(s, 1H), 7.51-7.43(m, 3H), 7.32-7.27(m, 3H), 4.27(s, 2H), 3.83(s, 3H), 2.72-2.50(m, 4H), 2.38-2.27(m, 2H).
22	0,96	E	¹ H NMR(300MHz, DMSO-d ₆): ppm = 13.08-13.04(m, 1H), 10.34-10.30(m, 1H), 8.35(s, 1H), 8.04-8.01(m, 2H), 7.93-7.91(m, 1H), 7.78(s, 1H), 7.57-7.54(m, 2H), 7.48-7.45(m, 2H), 7.31-7.28(m, 2H), 4.31(s, 2H), 3.83-3.82 (m, 6H).
23	2,08	F	¹ H NMR(400MHz, DMSO-d ₆): ppm = 12.97 (s, 1H), 8.30 (s, 1H), 7.95 (m, 2H), 7.85 (d, J=8Hz, 1H), 7.65 (s, 1H), 7.55 (d, J=12Hz, 1H), 7.49 (d, J=12Hz, 1H), 7.39 (m, 1H), 7.24 (m, 1H), 4.40 (s, 2H), 3.99 (s, 3H).
24	1,52	B	¹ H NMR(300MHz, DMSO-d ₆): ppm = 12.97(s, 1H), 8.37(d, J=6Hz, 1H), 8.20(s, 1H), 7.94(s, 1H), 7.80(d, J=9Hz, 1H), 7.61(s, 1H), 7.55-7.45(m, 2H), 7.37(d, J=9Hz, 1H), 4.40(s, 2H), 3.98(s, 3H), 2.84-2.78(m, 1H), 0.71-0.62(m, 2H), 0.60-0.52(m, 2H).

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Compound Number	Rt [min]	HPLC method	NMR data
25	2,44	A	1H NMR(400MHz,CD3OD): ppm = 8.20(s,1H),7.92(s,1H),7.85(d,J=8Hz,1H), 7.69(s,1H),7.55(m,1H), 7.48-7.46(m,1H), 7.43-7.40(m,1H),4.49(s,2H),4.03(s,3H), 3.56(m,4H), 3.37(s,3H).
26	2,48	A	1H NMR(300MHz, DMSO-d6) ppm = 13.04(s,1H),10.33(s,1H),8.33(s,1H),8.00(s,1H),7.95-7.89(m,2H),7.64(s,1H), 7.56-7.53(m,3H), 7.39(d,J=9Hz,1H),4.43(s,2H), 3.98(s,3H),3.81(s,3H).
27	2,83	A	1H NMR(400MHz,DMSO-d6): ppm = 12.95(s,1H),8.23(s,1H),8.10(d,J=8Hz,1H) ,7.82(d,J=8Hz,1H),7.48(d,J=8Hz,1H),7.17-7.11(m,3H),7.08(d,J=8Hz,1H),4.56(d,J=4 Hz,1H),4.25(s,2H),3.74-3.70(m,1H),3.40-3.36(m,1H),2.24(s,3H).1.86-1.80(m,4H),1.42-1.22(m,4H).
28	4,11	G	1H NMR (300 MHz, DMSO-d6) ppm = 13.02 (s, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.50 (s, 2H), 7.09 (d, J = 8.2 Hz, 1H), 4.46 (s, 2H), 3.99 (s, 3H), 3.90-3.80 (m, 2H), 3.76-3.45 (m, 2H), 2.43-2.30 (m, 2H).
29	2,08	H	1H NMR (300 MHz, DMSO-d6) ppm = 12.99 (s, 1H), 8.39 (s, 1H), 8.26 (s, 1H), 7.95 (s, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 13.2 Hz, 2H), 7.48 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 4.44 (s, 2H), 4.00 (s, 3H), 2.83 (tt, J = 7.8, 4.1 Hz, 1H), 0.69 (d, J = 6.2 Hz, 2H), 0.56 (s, 2H).
30	2,36	A	1H NMR(400MH, DMSO-d6) ppm = 8.17(s,1H),7.93(s,1H), 7.84(d,J=8Hz,1H),7.70(d,J=4Hz,1H), 7.54-7.41(m,3H), ,4.50(s,2H),4.03(s,3H),3.94-3.87(m,2H),1.85-1.76(m,4H),1.73-1.63(m,4H).
31	1,46	D	1H NMR(300Hz,DMSO-d6): ppm = 12.96(s,1H),8.48(s,1H),8.04(s,1H),7.78(s,2H),7.47-7.44(m,4H),7.31-7.28(m,2H),4.90(s,1H),4.28-4.14(m,3H),3.83(s,3H),3.56-3.51(m,3H),1.88-1.81(m,2H)
32	2,16	A	1H NMR (300 MHz, DMSO-d6) ppm = 12.96 (s, 1H), 7.95 (s, 1H), 7.85 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.47 (s, 2H), 7.09 (d, J = 5.6 Hz, 1H), 4.92 (d, J = 36.2 Hz, 1H), 4.45 (s, 2H), 4.21 (d, 1H), 4.00 (s, 3H), 3.66-3.44 (m, 3H), 1.99-1.66 (m, 2H).

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Compound Number	Rt [min]	HPLC method	NMR data
33	1,33	B	¹ H NMR (300 MHz, DMSO-d ₆) ppm = 12.97 (s, 1H), 7.95 (s, 1H), 7.84 (s, 1H), 7.62 (d, J = 9.5 Hz, 2H), 7.47 (s, 2H), 7.08 (s, 1H), 4.92 (d, 1H), 4.44 (s, 2H), 4.21 (d, 1H), 3.99 (s, 3H), 3.46 (s, 3H), 1.85-1.70 (m, 2H).
34	1,27	I	¹ H NMR(300MHz,DMSO-d ₆): ppm = 12.94(s,1H),8.36(s,1H),8.04(s,1H),7.77(s,2H),7.47-7.44(m,4H),7.31-7.28(m,2H),4.99-4.87(m,1H).
35	2,04	D	¹ H NMR (300 MHz, DMSO-d ₆) ppm = 12.69 (s, 1H), 7.92 (s, 1H), 7.71-7.58 (m, 2H), 7.58-7.48 (m, 1H), 7.43-7.34 (m, 2H), 7.31-7.20 (m, 2H), 7.20-7.08 (m, 2H), 7.08-6.95 (m, 1H), 5.18-4.86 (m, 1H), 4.56-4.24 (m, 2H), 3.97 (s, 3H), 3.74-3.33 (m, 2H), 2.36-2.15 (m, 1H), 1.95-1.51 (m, 3H).
36	1,57	E	¹ H NMR(300MHz,DMSO-d ₆): ppm = 12.66-12.62 (s,1H), 7.63-7.58 (s,1H), 7.40 (s,2H), 7.31-7.28 (s,2H), 7.20-7.11 (t,4H), 7.06-6.99 (dd,2H), 5.06 (s,1H), 4.20 (s,2H),3.72-3.68 (s,1H), 3.58 (s,1H), 2.49-2.48 (s,1H), 2.25 (s,3H), 1.85-1.72 (s,3H).
37	2,04	B	¹ H NMR (300 MHz, DMSO-d ₆) ppm = 12.69 (s, 1H), 7.92 (s, 1H), 7.71-7.58 (m, 2H), 7.58-7.48 (m, 1H), 7.43-7.34 (m, 2H), 7.31-7.20 (m, 2H), 7.20-7.08 (m, 2H), 7.08-6.95 (m, 1H), 5.18-4.86 (m, 1H), 4.56-4.24 (m, 2H), 3.97 (s, 3H), 3.74-3.33 (m, 2H), 2.36-2.15 (m, 1H), 1.95-1.51 (m, 3H).
38	1,58	E	¹ H NMR(300MHz,DMSO-d ₆): ppm = 12.65 (s,1H), 7.63 (s,1H), 7.94 (s,2H),7.31-7.28 (s,2H), 7.20-7.11 (t,4H), 7.06-6.99 (dd,2H), 5.07 (s,1H), 4.20-4.14 (s,2H), 3.69-3.66 (s,1H), 3.59 (s,1H), 2.49-2.48 (s,1H), 2.36-2.25 (s,3H), 1.85-1.73 (m,3H).
39	3,66	F	¹ H NMR(400MHz,DMSO-d ₆): ppm = 12.97 (s, 1H), 8.85-8.82 (m, 1H), 8.35 (s, 1H), 7.90-7.88 (m, 1H), 7.52-7.50 (m, 1H), 7.28-7.24 (m, 2H), 7.22-7.20 (m, 1H), 7.13-7.00 (m, 2H), 6.98-6.96 (m, 2H), 4.85-4.78 (m, 2H), 4.50-4.48 (m, 2H), 4.23 (s, 2H), 3.69 (s, 3H), 3.68 (s, 3H).

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Compound Number	Rt [min]	HPLC method	NMR data
40	3,89	A	¹ H NMR(300MHz,DMSO-d ₆): ppm = 12.63 (s, 1H), 7.63 (s, 1H), 7.39-7.30 (m, 2H), 7.27-7.20 (m, 2H), 7.17-7.10 (m, 2H), 6.93 (s, 1H), 6.87-6.84 (m, 1H), 6.79-6.76 (m, 1H), 5.05 (s, 1H), 4.18-4.11 (m, 2H), 3.70 (s, 6H), 3.68 (s, 1H), 3.65-3.57 (m, 1H), 2.39-2.33 (m, 1H), 1.88-1.79 (m, 3H).
41	3,89	A	¹ H NMR(300MHz,DMSO-d ₆): ppm = 12.62 (s, 1H), 7.63 (s, 1H), 7.42-7.39 (m, 2H), 7.27-7.20 (m, 2H), 7.17-7.10 (m, 2H), 6.92 (s, 1H), 6.87-6.84 (m, 1H), 6.78-6.76 (m, 1H), 5.07 (s, 1H), 4.18-4.11 (m, 2H), 3.70 (s, 6H), 3.68 (s, 1H), 3.65-3.57 (m, 1H), 2.37-2.31 (m, 1H), 1.89-1.79 (m, 3H).
42	3,22	H	¹ H NMR(300MHz,DMSO-d ₆): ppm = 12.99 (s,1H), 8.86-8.84 (t,1H), 8.33 (s,1H),7.91-7.88 (d,1H), 7.53-7.51 (d,1H), 7.29-7.21 (m,2H), 7.19-7.12 (m,4H), 7.03-6.98 (m,2H), 4.86-4.78 (dd,2H), 4.51-4.49 (dd,2H), 4.26 (s,2H), 2.24 (s,3H).
51	2,05	F	¹ H NMR (300Hz, DMSO-d ₆) ppm = 13.06 (s,1H), 8.41-8.37 (m,1H), 8.27 (s,1H), 8.04 (s,1H), 7.85-7.82 (m,1H), 7.78 (s,1H), 7.51-7.44 (m,3H), 7.29-7.26 (m,2H), 4.28 (s,2H), 3.83 (s,3H), 3.41-3.28 (m,2H), 2.75-2.71 (m, 2H).
52	0,63	E	¹ H NMR (300Hz, DMSO-d ₆) ppm = 12.97 (s, 1H), 8.34-8.30 (m, 1H), 8.24 (s, 1H), 8.04 (s,1H), 7.83-7.80 (m, 2H),7.51-7.44 (m, 3H), 7.29-7.26 (m, 2H), 4.28 (s, 2H), 3.83 (s,3H), 3.32-3.30 (m, 2H), 2.45-2.32 (m, 2H), 2.17 (s,6H).
53	1,48	D	¹ H NMR(300Hz,DMSO-d ₆): ppm = 12.96(s,1H),8.41-8.38(m,1H),8.25(s,1H),8.04(s,1H),7.84-7.78(m,2H),7.50-7.44(m,3H),7.30-7.27(m,2H),4.42-4.38(m,1H),4.28(s,2H),3.83(s,3H),3.44-3.39(m,2H),3.27-3.23(m,2H),1.58-1.43(m,4H).
54	0,83	E	¹ H NMR (400MHz, DMSO-d ₆) ppm = 9.85(s,1H), 8.05(s,1H), 7.90(s,1H), 7.78(s,1H), 7.45-7.43(d,J=8Hz,2H), 7.40(s,2H), 7.23-7.21(d,J=8Hz,2H), 4.19(s,2H), 3.83(s,3H), 2.01(s,3H)
55	1,53	D	¹ H NMR (400MHz, DMSO-d ₆) ppm = 12.77 (s, 1H), 7.78 (s, 1H), 7.89(s, 1H) , 7.46-7.41 (m, 4H), 7.25-7.18 (m, 3H), 4.22 (s, 2H), 3.83 (s, 3H) , 2.83 (s, 3H).

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Compound Number	Rt [min]	HPLC method	NMR data
56	1,14	C	¹ H NMR (300MHz, DMSO-d ₆) ppm = 12.74(s,1H), 8.04(s,1H), 7.78(s,1H), 7.70-7.68(d,J=6Hz,2H), 7.47-7.43(m,3H), 7.28-7.25(d,J=9Hz,2H), 4.23(s,2H), 3.85-3.80(m,5H), 2.44(s,2H), 2.08-2.03(m,2H)
57	1,03	E	¹ H NMR (400MHz,DMSO-d ₆) ppm = 12.75(s,1H), 8.04(s,1H), 7.78-7.69(m,3H), 7.47-7.43(m,3H), 7.27-7.25(d,J=8Hz,2H), 4.23(s,2H), 3.83(s,3H), 3.79-3.73(m,2H), 2.64-2.58(m,1H), 2.32-2.29(m,1H), 1.71-1.66(m,1H), 1.17-1.15(d,J=8Hz,3H)
58	1,04	E	¹ H NMR (400MHz, DMSO-d ₆) ppm = 12.75(s,1H), 8.04(s,1H), 7.78-7.69(m,3H), 7.47-7.43(m,3H), 7.27-7.25(d,J=8Hz,2H), 4.23(s,2H), 3.83(s,3H), 3.79-3.73(m,2H), 2.64-2.58(m,1H), 2.32-2.29(m,1H), 1.71-1.66(m,1H), 1.17-1.15(d,J=8Hz,3H)
59	1,38	D	¹ H-NMR (400MHz, DMSO): ppm = 12.51 (s, 1H), 8.05 (s, 1H), 7.78(s, 1H) , 7.46 (d, J=8.4Hz, 2H), 7.36 (d, J=9.2Hz, 1H), 7.29 (d, J=8.0Hz, 2H), 7.15 (m, 1H), 6.97 (s, 1H), 4.20 (s, 2H), 3.84 (s, 3H), 3.74 (t, J=4.8Hz, 4H), 3.00 (t, J=4.8Hz, 4H).
60	2,01	A	¹ H NMR (400MHz, DMSO-d ₆) ppm = 12.49 (s, 1H), 8.04 (s, 1H), 7.78 (s, 1H), 7.46 (d, J=8.4Hz, 2H), 7.32 (d, J=8.8Hz, 1H), 7.29 (d, J=8.4Hz, 2H), 7.12 (m, 1H), 6.92 (d, J=1.6Hz, 1H), 4.19 (s, 2H), 3.83 (s, 3H), 2.92(d, J=4.8Hz, 4H), 2.84 (d, J=4.0Hz, 4H).
61	1,78	D	¹ H NMR (300Hz,DMSO: ppm = 12.97(s,1H),8.04(s,1H),7.80-7.55(m,2H),7.53-7.37(m,4H),7.30-7.28(m,2H),4.28(s,2H),3.83(s,3H),3.65-3.39(m,4H),2.09-1.89(m,4H).
62	1,74	D	¹ H NMR(300Hz,DMSO-d ₆): ppm = 13.00(s,1H),8.05(s,1H),7.78(s,1H),7.72(s,1H),7.55-7.52(m,1H),7.46-7.44(m,2H),7.34-7.27(m,3H),4.28(s,2H),3.83-3.68 (m,5H),3.56-3.37(m,2H),2.11-2.02(m,2H),1.64(s,2H).
63	1,56	D	¹ H NMR(300Hz,DMSO,ppm): ppm = 12.96(s,1H),8.05(s,1H),7.78(s,1H),7.68(s,1H),7.52-7.44(m,3H),7.37-7.27(m,3H),4.28(s,2H),3.83(s,3H),3.56-3.35(m,8H).

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Compound Number	Rt [min]	HPLC method	NMR data
64	1,72	D	1 H NMR (400MHz, MeOD) ppm = 8.108-8.106(s, 1H), 8.23(s, 1H), 7.89(s, 1H), 7.79-7.75(m, 2H), 7.64-7.62(m, 1H), 7.46-7.44(m, 2H), 7.29-7.27(m, 2H), 4.37(s, 2H), 3.89(s, 3H), 1.97-1.92(m, 1H), 1.37(m, 2H), 0.35-0.34(s, 4H)
66	1,49	B	1H NMR(300MHz, CD3OD): ppm = 7.94(s, 1H), 7.74(d, J=9Hz, 2H), 7.65-7.61(m, 1H), 7.54-7.47(m, 2H), 7.40-7.37(m, 1H), 4.48(s, 2H), 4.27(m, 1H), 4.18-4.13(m, 2H), 4.03(s, 3H), 3.92-3.83(m, 2H), 3.23(s, 3H).
68	1,61	D	1H NMR (300MHz, DMSO-d6): ppm = 13.08 (1H, s), 7.95-7.94 (2H, d, J=0.9Hz), 7.72 (1H, s), 7.64-7.62 (1H, d, J=6.0Hz), 7.56-7.50 (2H, m), 7.38-7.35 (1H, d, J=6.0Hz), 4.52-4.43 (6H, m), 3.99 (3H, s)
70	1,19	D	1H NMR (400MHz, DMSO-d6): ppm = 8.23(s, 1H), 7.94(s, 1H), 7.81(d, J=8Hz, 1H), 7.65(d, J=8Hz, 1H), 7.52-7.49(m, 2H), 7.36(d, J=8Hz, 1H), 4.39(s, 2H), 3.96(s, 3H), 3.30-3.25(m, 2H), 3.11(m, 1H), 2.70(m, 1H).
71	0,58	E	1H NMR (400MHz, DMSO-d6): ppm = 12.99(s, 1H), 8.35(m, 1H), 8.23(m, 1H), 7.95(s, 1H), 7.81(m, 1H), 7.63(m, 1H), 7.55-7.48(m, 2H), 7.37(d, J=8Hz, 1H), 4.41(s, 2H), 3.99(s, 3H), 3.35(m, 2H), 2.42-2.39(m, 2H), 2.18(s, 6H).
72	1,38	B	1H NMR (300MHz, DMSO): ppm = 12.97 (1H, s), 8.39-8.37 (1H, m), 8.23 (1H, s), 7.94 (1H, s), 7.82-7.79 (1H, d, J=8.7Hz), 7.63 (1H, s), 7.55-7.47 (2H, m), 7.38-7.35 (1H, m), 4.49-4.45 (1H, m), 4.40 (2H, s), 3.99 (3H, s), 3.46-3.44 (2H, m), 3.30-3.28 (2H, m), 1.69-1.64 (2H, m)
73	0,77	E	1H NMR (400MHz, DMSO): ppm = 12.99(s, 1H), 8.38(m, 1H), 8.23(s, 1H), 7.95(s, 1H), 7.82(d, J=8Hz, 1H), 7.63(s, 1H), 7.55(d, J=8Hz, 1H), 7.50(d, J=8Hz, 1H), 7.37(d, J=8Hz, 1H), 4.41(s, 3H), 3.99(s, 3H), 3.42(m, 2H), 2.28-2.23(m, 2H), 1.56-1.53(m, 2H), 1.47-1.43(m, 2H).
74	0,78	E	1H NMR (400MHz, DMSO-d6) ppm = 12.67(s, 1H), 9.83(s, 1H), 7.94(s, 1H), 7.85(s, 1H), 7.56-7.51(m, 2H), 7.40(s, 2H), 7.31(d, J=8Hz, 1H), 4.32(s, 2H), 3.99(s, 3H), 1.99(s, 3H).
75	0,83	E	1H NMR (400MHz, DMSO-d6) ppm = 2.79(s, 1H), 9.14(s, 1H), 7.94(s, 1H), 7.61(s, 1H), 7.53(d, J=8Hz, 1H), 7.46(d, J=12Hz, 1H), 7.39(s, 1H), 7.32(m, 1H), 7.20(m, 1H), 4.35(s, 2H), 3.99(s, 3H), 2.81(s, 3H).

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Compound Number	Rt [min]	HPLC method	NMR data
76	0,9	E	¹ H NMR (400MHz, DMSO-d ₆) ppm = 7.93(s, 1H), 7.68(m, 2H), 7.61(s, 1H), 7.53(d, J=12Hz, 1H), 7.46(d, J=8Hz, 1H), 7.35(d, J=8Hz, 1H), 4.35(s, 2H), 3.98(s, 3H), 3.81(m, 2H), 2.45(d, J=8Hz, 2H), 2.04(m, 2H).
77	1,03	E	¹ H NMR (400MHz, DMSO-d ₆) ppm = 12.76(s, 1H), 7.94(s, 1H), 7.72-7.68(m, 2H), 7.61(s, 1H), 7.53(d, J=8Hz, 1H), 7.47(d, J=8Hz, 1H), 7.36(d, J=8Hz, 1H), 4.35(s, 2H), 3.99(s, 3H), 3.73(m, 2H), 2.60-2.56(m, 1H), 2.30-2.21(m, 1H), 1.68(m, 1H), 1.16(d, J=8Hz, 3H).
79	2,70	F	¹ H NMR(400MHz, CD ₃ OD): ppm = 8.19(s, 1H), 7.90(s, 1H), 7.85-7.83(m, 1H), 7.77(s, 1H), 7.55-7.53(m, 1H), 7.48-7.46(m, 2H), 7.32-7.30(m, 2H), 4.37(s, 2H), 3.91(s, 3H), 2.93(s, 3H).
80	2,42	F	¹ H NMR(300Hz, CD ₃ OD): ppm = 8.16(s, 1H), 7.89-7.76(m, 3H), 7.53-7.45(m, 3H), 7.32-7.29(m, 2H), 4.37(s, 2H), 3.93-3.90(m, 5H), 1.84-1.61(m, 8H), 3.92-3.87(m, 2H).
81	1,59	D	¹ H NMR(300Hz, DMSO-d ₆): ppm = 12.98(s, 1H), 8.04(s, 1H), 7.85(s, 1H), 7.77(s, 1H), 7.59-7.56(m, 1H), 7.50-7.45(m, 3H), 7.32-7.29(m, 2H), 4.30-4.13(m, 5H), 4.10-3.91(m, 1H), 3.83(s, 4H), 3.16(s, 3H).
82	1,44	D	¹ H NMR(300MHz, DMSO-d ₆): ppm = 8.03(s, 1H), 7.88(s, 1H), 7.79(s, 1H), 7.58-7.55(m, 2H), 7.49-7.46(m, 2H), 7.33-7.30(m, 2H), 4.55-4.38(m, 2H), 4.34-4.20(m, 3H), 4.10-3.92(m, 2H), 3.84(s, 3H).
83	1,71	D	¹ H NMR(300Hz, DMSO-d ₆): ppm = 13.00(s, 1H), 8.05(s, 1H), 7.99(s, 1H), 7.77(s, 1H), 7.65-7.62(m, 1H), 7.53-7.45(m, 3H), 7.33-7.30(m, 2H), 4.59(s, 4H), 4.31(s, 2H), 3.83(s, 3H).
84	1,41	D	¹ H NMR(300Hz, DMSO-d ₆): ppm = 12.97(s, 1H), 8.41-8.37(m, 1H), 8.29(s, 1H), 8.04(s, 1H), 7.85-7.82(m, 1H), 7.77(s, 1H), 7.50-7.44(m, 3H), 7.29-7.26(m, 2H), 4.73-4.70(m, 1H), 4.28(s, 2H), 3.83(s, 3H), 3.54-3.48(m, 2H), 3.36-3.29(m, 2H).

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Compound Number	Rt [min]	HPLC method	NMR data
85	0,87	E	1H NMR(300Hz,DMSO-d6): ppm = 12.95(s,1H),8.38(s,1H),8.25(s,1H),8.04(s,1H),7.83-7.77(m,2H),7.50-7.44(m,3H),7.29-7.26(m,2H),4.48-4.44(m,1H),4.28(s,2H),3.83(s,3H),3.49-3.43(m,2H),3.35-3.33(m,2H),1.70-1.66(m,2H).
86	1,61	D	1H NMR(300Hz,DMSO-d6): ppm = 12.93(s,1H),8.05(s,1H),7.78-7.76(m,2H),7.47-7.44(m,4H),7.31-7.28(m,2H),4.28(s,2H),3.83(s,3H),3.44(s,2H),3.30(s,2H),1.83-1.81(m,2H),1.75-1.72(m,2H).
87	1,75	D	1H NMR(300Hz,DMSO-d6): ppm = 12.93(s,1H),8.05(s,1H),7.78(s,1H),7.61(s,1H),7.51-7.44(m,3H),7.31-7.27(m,3H),4.27(s,2H),3.83(s,3H),3.32(s,2H),1.65-1.38 (m,6H).
88	2,54	F	1H NMR (300 MHz, DMSO-d6): ppm = 13.02 (s, 1H), 8.84 (t, J = 5.5 Hz, 1H), 8.39 (s, 1H), 7.96 (s, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.60 (s, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.35 - 7.16 (m, 2H), 7.16 - 7.05 (m, 2H), 6.99 (t, J = 7.4 Hz, 1H), 4.81 (q, J = 8.9 Hz, 2H), 4.49 (d, J = 5.6 Hz, 2H), 4.46 (s, 2H), 3.98 (s, 3H).
89	1,64	D	1H-NMR (400MHz, DMSO-d6): ppm = 12.79 (s, 1H), 8.04 (s, 1H), 7.99 (s, 1H), 7.77 (d, J=2.4Hz, 2H), 7.70 (d, J=2.4Hz, 1H), 7.47(m, 3H), 7.31 (d, J=8.0Hz, 2H), 6.63 (d, J=2.0Hz, 1H), 4.29 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H).
90	1,42	D	1H-NMR (400MHz, DMSO-d6): ppm = 12.90 (s, 1H), 8.04 (s, 1H), 7.94 (d, J=25.2Hz, 2H), 7.78 (s, 1H), 7.58 (m, 2H), 7.47(d, J=8.4Hz, 2H), 7.32 (d, J=8.0Hz, 2H), 6.78 (m, 1H), 6.71 (s, 1H), 5.91 (s, 2H), 4.32 (s, 2H), 3.83(s,3 H).
91	3,24	F	1H NMR(300Hz,DMSO-d6): ppm = 12.66(s,1H),7.95(s,1H),7.71(s,1H),7.60(s,1H),7.45-7.40(m,4H),7.25-7.18(m,6H),5.04(s,1H),4.23-4.22(m,2H),3.83(s,3H),3.77-3.62(m,1H),3.62-3.45(m,1H),3.29-3.25(m,1H),1.88-1.62(m,3H).
92	1,93	D	1H NMR (300Hz,DMSO,ppm): ppm = 13.00(s,1H),8.85-8.84(m,1H),8.35(s,1H),8.04(s,1H),7.91-7.88(m,1H),7.77(s,1H),7.54-7.51(m,1H),7.47-7.44(m,2H),7.30-7.20(m,4H),7.13-7.10(m,1H),7.02-6.97(m,1H),4.86-4.77(m,2H),4.50-4.49(m,2H),4.29(s,2H),3.83(s,3H).

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Compound Number	Rt [min]	HPLC method	NMR data
93	0,65	C	¹ H NMR(300MHz,DMSO): ppm = 12.95(s,1H),7.94(s,1H),7.67(s,1H),7.63(m,1H),7.51(t,J=9Hz,2H),7.33(t,J=9Hz,2H), 4.39(s,2H), 3.98(s,3H),3.50(m,4H),2.68(m,4H).
94	1,19	B	¹ H-NMR (400MHz, DMSO): ppm = 12.90 (s, 1H), 8.04 (s, 1H), 7.83 (s, 1H), 7.77 (s, 1H), 7.61 (dd, J=8.8Hz, 2H), 7.55 (d, J=8.8Hz, 1H), 7.47 (d, J=8.4Hz, 2H), 7.33 (d, J=8.0Hz, 2H), 6.94 (s, 1H), 6.52 (s, 1H), 4.30 (s, 2H), 3.83 (s, 3H), 3.65 (s, 3H).
95	1,21	B	¹ H-NMR (400MHz, DMSO): ppm = 12.82 (s, 1H), 8.17 (s, 1H), 8.04 (m, 2H), 7.92(m, 1H), 7.77 (s, 1H), 7.51 (d, J=8.8Hz, 1H), 7.46 (d, J=8.4Hz, 2H), 7.28 (d, J=8.4Hz, 2H), 6.98 (d, J=2.0Hz, 1H), 6.41 (m, 1H), 5.99 (s, 2H), 4.30 (s, 2H), 3.82(s, 3H).
96	2,11	A	¹ H-NMR (400MHz, DMSO): ppm = 12.69 (s, 1H), 8.04 (s, 1H), 7.96 (s, 1H), 7.78(s, 1H), 7.69 (m, 1H), 7.58 (s, 1H), 7.50 (s, 1H), 7.46 (m, 3H), 7.29 (d, J=8.4Hz, 2H), 4.26 (s, 2H), 3.83 (s, 3H), 3.67 (s, 3H).
97	0,68	E	¹ H-NMR (400MHz, DMSO-d ₆): ppm = 12.89 (s, 1H), 8.04 (s, 1H), 7.89(s, 1H), 7.77 (s, 1H), 7.58 (m, 2H), 7.46 (d, J=8.4Hz, 2H), 7.32 (d, J=8.0Hz, 3H), 6.96 (d, J=1.2Hz, 1H), 5.03 (t, J=5.2Hz, 1H), 4.28 (s, 2H), 3.99 (t, J=5.2Hz, 2H), 3.83 (s, 3H), 3.67 (t, J=5.2Hz, 2H).
98	0,84	E	¹ H NMR (300MHz,DMSO-d ₆) ppm = 12.50(s,1H),7.94(s,1H),7.62(s,1H),7.50(m,1H),7.37-7.33(m,2H),7.13(m,1H),6.96(s,1H),4.31(s,2H),3.98(s,3H),3.72(m,4H),2.96(m,4H).
99	1,00	E	¹ H NMR (300MHz,DMSO-d ₆) ppm = 7.96(d,J=6Hz,2H),7.78-7.74(m,1H),7.68-7.64(m,2H),7.54-7.35(m,3H),6.60(d,J=3Hz,1H), 4.40(s,2H),3.98(s,3H),3.84(s,3H).
100	0,73	E	¹ H NMR (300MHz,DMSO): ppm = 7.94(s,1H),7.76(s,1H),7.69(s,1H),7.54-7.43(m,3H),7.36(d,J=9Hz,1H),4.40(s,2H), 4.28(s,1H),4.12(s,1H),3.98(s,3H),3.45-3.05(m,4H),1.92-1.68(m,2H).
101	0,73	E	¹ H NMR (300MHz,DMSO): ppm = 7.94(s,1H),7.76(s,1H),7.69(s,1H),7.53-7.43(m,3H),7.36(d,J=9Hz,1H),4.40(s,2H), 4.28(s,1H),4.12(s,1H),3.98(s,3H),3.45-3.05(m,4H),1.92-1.68(m,2H).

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Compound Number	Rt [min]	HPLC method	NMR data
102	3,24	F	¹ H NMR (300MHz, DMSO-d ₆) ppm = 12.67(s, 1H), 7.95(s, 1H), 7.71(s, 1H), 7.60(s, 1H), 7.52-7.32(m, 4H), 7.32-7.08(m, 6H), 5.04(s, 1H), 4.23(s, 2H), 3.83(s, 3H), 3.67-3.54(m, 2H), 2.32-2.26(m, 1H), 1.81-7.72(m, 3H).
103	0,6	E	¹ H NMR (400MHz, DMSO-d ₆) ppm = 7.92 (m, 2H), 7.62 (s, 1H), 7.51 (d, J=8Hz, 1H), 7.34 (d, J=8Hz, 1H), 7.21 (d, J=8Hz, 1H), 6.75 (d, J=8Hz, 1H), 6.55 (s, 1H), 5.27(m, 1H), 4.25(s, 2H), 3.98(s, 3H), 3.20(m, 2H), 2.99(m, 2H), 1.81(s, 3H).
104	0,61	E	¹ H NMR (400MHz, DMSO-d ₆) ppm = 12.74(s, 1H), 8.58(s, 1H), 8.00-7.95(m, 3H), 7.66(s, 1H), 7.55(d, J=8Hz, 1H), 7.47(d, J=8Hz, 1H), 7.34(d, J=8Hz, 1H), 7.26(s, 1H), 7.13(d, J=12Hz, 1H), 6.60(d, J=4Hz, 2H), 4.36(s, 2H), 4.00(s, 3H)
105	0,63	E	¹ H NMR (400MHz, DMSO-d ₆) ppm = 8.90(s, 1H), 7.99(s, 1H), 7.91(s, 1H), 7.82(s, 1H), 7.69-7.64(m, 3H), 7.49-7.41(m, 2H), 4.54(s, 2H), 4.03(s, 3H), 3.97(s, 3H).
106	0,58	E	¹ H NMR (400MHz, DMSO-d ₆) ppm = 7.94(s, 1H), 7.85(s, 1H), 7.71(s, 1H), 7.62-7.51(m, 3H), 7.38(d, J=8Hz, 1H), 7.28(s, 1H), 7.04(s, 1H), 4.42(s, 2H), 3.98(s, 3H), 3.61(s, 3H).
107	0,53	E	¹ H NMR (400MHz, DMSO-d ₆) ppm = 12.88(s, 1H), 7.93(s, 1H), 7.85(s, 1H), 7.69(s, 1H), 7.58-7.50(m, 3H), 7.37(d, J=8Hz, 1H), 7.28(s, 1H), 6.93(s, 1H), 5.01(m, 1H), 4.39(s, 2H), 3.97(s, 3H), 3.95-3.92(m, 2H), 3.64-3.60(m, 2H).
108			¹ H NMR (300MHz, DMSO-d ₆) ppm = 12.43(s, 1H), 8.61(s, 1H), 8.06-8.04(d, J=6,3H), 7.79(s, 1H), 7.48-7.46(d, J=6,3H), 7.32-7.26(m, 3H), 7.15-7.12(d, J=9,1H), 6.67-6.65(d, J=6,2H), 4.23(s, 2H), 3.84(s, 3H)
109	1,01	E	¹ H NMR (300MHz, DMSO-d ₆) ppm = 12.98(s, 1H), 8.00(s, 1H), 7.84(s, 1H), 7.79(s, 1H), 7.50-7.45(m, 4H), 7.31(d, J=6Hz, 2H), 4.69(s, 1H), 4.29(s, 2H), 4.00(s, 2H), 3.91-3.82(m, 2H), 3.65(m, 2H), 2.38(m, 2H), 1.06(s, 6H).

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Compound Number	Rt [min]	HPLC method	NMR data
110	0,95	E	1H NMR (300MHz, DMSO-d6) ppm = 12.92(s, 1H), 8.00(s, 1H), 7.79(s, 1H), 7.72(s, 1H), 7.48-7.46(m, 4H), 7.30(d, J=9Hz, 2H), 4.69(s, 1H), 4.27(s, 2H), 3.99(s, 2H), 3.42(m, 2H), 3.31(m, 2H), 1.81-1.70(m, 4H), 1.05(s, 6H).
111	1,01	E	1H NMR (300MHz, DMSO-d6) ppm = 13.03(s, 1H), 8.00-7.97(d, J=9Hz, 2H), 7.78(s, 1H), 7.64-7.60(m, 1H), 7.52-7.46(m, 3H), 7.32-7.29(d, J=9Hz, 2H), 4.68(s, 1H), 4.57(m, 4H), 4.31(s, 2H), 3.99(s, 2H), 1.05(s, 6H).
112	0,84	E	1H NMR (300MHz, DMSO-d6) ppm = 12.95(s, 1H), 8.36(m, 1H), 8.23(s, 1H), 7.99(s, 1H), 7.81(m, 2H), 7.49-7.45(m, 3H), 7.29-7.26(d, J=9Hz, 2H), 4.68(s, 1H), 4.27(s, 2H), 3.99(s, 2H), 2.78(d, J=3Hz, 3Hz), 1.05(s, 6H)
113	1,61	H	1H NMR (400MHz, MeOH-d4) ppm = 7.92(s, 1H), 7.79(s, 1H), 7.47-7.44(d, J=12Hz, 2H), 7.31-7.28(d, J=12Hz, 3H), 6.92-6.88(m, 1H), 6.64(s, 1H), 4.25(s, 2H), 3.91(s, 3H), 3.40(s, 2H), 3.20-3.13(m, 2H), 1.92(s, 3H)
114			1H NMR (400MHz, DMSO-d6) ppm = 12.69(s, 1H), 7.95(d, J=4Hz, 2H), 7.71-7.68(m, 1H), 7.62(d, J=8Hz, 2H), 7.53(d, J=8Hz, 2H), 7.43(d, J=8Hz, 1H), 7.35(m, 1H), 4.96(s, 1H), 4.38(s, 2H), 4.01-3.98(m, 5H), 3.68(d, J=8Hz, 2H)

Biological Activity

5 FRET based Lanthascreen binding competition assay: A dye-labeled ATP competitive probe served as a FRET acceptor upon binding to CDK8 labeled with a strepavidin -Eu-chelate (via abiotinylated anti His antibody). The result was a fluorescence signal at 647 nm. In case this probe was competed by an inhibitor as such a signal cannot be generated any more. The CDK8 used for this assay was a protein co-expressed with CycC.

10 The assay procedure for an assay in a 1536 well plate was performed according to the following: 2 μ L CDK8 / biotin-anti-His Ab / SA-Eu mix in Assay buffer were pipetted into the wells of a micro plate.

1 μ L compound in 20 mM Hepes buffer / 5 % DMSO was added. The plate was shaken for 30 sec and incubated for 20 min at RT.

15 2 μ L Alexa647-probe in assay buffer were added. The plate was shaken for 30 sec again and incubated for 60 min at RT in the dark.

Then the plate was read out on a Perkin Elmer Envision (mode LANCE/TRF, excitation 340 nm emission 650 nm).

20 The assay buffer was 50 mM Hepes pH 7.5 (Merck # 1.10110), 10 mM $MgCl_2$ (Merck #1.05833), 1 mM EGTA (Merck #1.08435), 0.01% Brij-35 (Pierce #28316).

The final concentrations of the reaction components in 5 μ L total assay volume were: 1% DMSO (Merck # 1.02950), 5 nM CDK8 (CDK8/CycC Invitrogen #PV4402), 2 nM biotin-a-His Ab (Invitrogen #PV6089), 2 nM SA-Europium (Invitrogen #PV5899), 10 nM Alexa647-Tracer (Invitrogen #PV5592).

25 The data is interpreted according to the following:

D	1001-5000 nM;
C	101-1000 nM;
B	10-100 nM;
30 A	< 10 nM (in particular, > 100 pM and < 10 nM).

Table 3

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Compound Number	IC50 CDK8 Binding
1	D
2	C
3	C
4	B
5	C
6	B
7	C
8	C
9	B
10	C
11	C
12	C
13	C
14	B
15	A
16	A
17	A
18	B
19	C
20	C
21	A
22	C
23	B
24	B
25	B
26	C
27	B
28	B
29	C
30	B
31	B
32	B
33	B
34	A
35	C

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36	C
37	C
38	C
39	D
40	D
41	C
42	D
51	C
52	C
53	B
54	B
55	B
56	B
57	B
58	C
59	D
60	D
61	A
62	B
63	A
64	C
66	A
67	A
68	A
69	B
70	C
71	C
72	B
73	B
74	B
75	B
76	B
77	B
79	B
80	C
81	A
82	A

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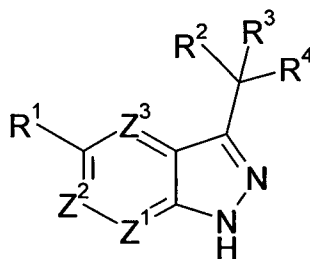
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83	A
84	B
85	B
86	A
87	A
88	C
89	C
90	D
91	C
92	C
93	B
94	B
95	C
96	B
97	B
98	D
99	C
100	A
101	A
102	D
103	C
104	C
105	B
106	B
107	B
108	C
109	B
110	A
111	B
112	B
113	C
114	B

Claims

1. Compound of formula (I)



(I)

or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios,

wherein

Z¹ denotes CH, CF or N;

Z² denotes CR⁵ or N;

Z³ denotes CH, CF or N;

R¹ denotes -C(=O)-R⁶, -NHR⁷, -SO₂R⁸, Hetar¹ or Hetcyc¹;

R² and R³ denote independently from each other H, Hal, straight-chain or branched C₁₋₃-alkyl, or form, together with the carbon atom to which they are attached to, a saturated C₃₋₅-cycloalkyl that may be unsubstituted or mono-substituted with C₁₋₃-alkyl;

R⁴ denotes Ar⁴ or Hetar⁴;

R⁵ denotes H, F or -LA⁵;

R⁶ denotes -NHR^{6a} or Hetcyc⁶;

R⁷ denotes H, -C(=O)-LA^{7a}, -SO₂-LA^{7b}, LA^{7c} or Hetar⁷;

R⁸ denotes -NHR^{8a} or Hetcyc⁸;

Hetar¹ denotes a mono-, bi- or tricyclic aromatic ring system with 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 ring atoms wherein 1, 2, 3, 4 or 5 of said ring atoms is/are a hetero atom(s) selected from N, O and/or S and the remaining ring atoms are carbon atoms wherein

that aromatic ring system may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from $-NR^{1a}R^{1b}$, LA^{1c} , $-O-LA^{1d}$;

5 $Hetcyc^1$ denotes a saturated or partially unsaturated heterocycle with 3, 4, 5, 6, 7 ring atoms wherein 1, 2 or 3 of said ring atoms is/are a hetero atom(s) selected from N, O and/or S and the remaining ring atoms are carbon atoms, wherein that heterocycle may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from straight-chain or branched C_{1-6} -alkyl, straight-chain or branched $-O-C_{1-6}$ -alkyl, Hal or oxo ($=O$);

10 Ar^4 denotes a mono- or bicyclic aromatic ring system with 6, 7, 8, 9, 10 ring carbon atoms wherein that aromatic ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from R^{4a} , R^{4b} , R^{4c} ;

15 $Hetar^4$ denotes a mono-, bi- or tricyclic aromatic ring system with 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 ring atoms wherein 1, 2, 3, 4 or 5 of said ring atoms is/are a hetero atom(s) selected from N, O and/or S and the remaining ring atoms are carbon atoms wherein that aromatic ring system may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from R^{4d} , R^{4e} , R^{4f} ;

20 R^{1a} , R^{1b} denote independently from each other H, straight-chain or branched C_{1-8} -alkyl, or

25 R^{1a} and R^{1b} may form together with the nitrogen atom to which they are attached to a 3-, 4-, 5-, 6- or 7-membered heterocycle that may contain another hetero atom selected from N and O;

30 R^{4a} , R^{4b} , R^{4c} denote independently from each other H, Hal, $Hetar^{4a}$, $Hetcyc^{4a}$, Ar^{4a} , CA^{4a} , straight-chain or branched C_{1-6} -alkyl or $-O-C_{1-6}$ -alkyl which C_{1-6} -alkyl or $-O-C_{1-6}$ -alkyl may be

unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, OH, or two of R^{4a}, R^{4b}, R^{4c} form together a divalent alkylene chain with 2, 3, 4, 5 chain carbon atoms that alkylene chain may be unsubstituted or substituted with straight-chain or branched C₁₋₄-alkyl wherein 1 or 2 non-adjacent methylene groups of that alkylene chain may be replaced by NH, O and/or S;

R^{4d}, R^{4e}, R^{4f} denote independently from each other H, Hal, Hetar^{4b}, Hetcyc^{4b}, Ar^{4b}, CA^{4b}, straight-chain or branched C₁₋₆-alkyl or -O-C₁₋₆-alkyl which C₁₋₆-alkyl or -O-C₁₋₆-alkyl may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, OH;

LA^{1c} denotes a straight-chain or branched C₁₋₈-alkyl which may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, OH, -NR^{1c1}R^{1c2}, and in which C₁₋₈-alkyl 1 or 2 non-terminal and non-adjacent -CH₂- groups may be replaced by -O-, -S-, and/or 1 or 2 non-terminal and non-adjacent -CH₂-, -CH- groups may be replaced by -NH-, -N-;

LA^{1d} denotes a straight-chain or branched C₁₋₈-alkyl which may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, OH, -NR^{1d1}R^{1d2}, and in which C₁₋₈-alkyl 1 or 2 non-terminal and non-adjacent -CH₂- groups may be replaced by -O-, -S-, and/or 1 or 2 non-terminal and non-adjacent -CH₂-, -CH- groups may be replaced by -NH-, -N-;

LA⁵, LA^{7a}, LA^{7b} denote independently from each other a straight-chain or branched C₁₋₈-alkyl which may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal;

LA^{7c} denotes a straight-chain or branched C₁₋₈-alkyl which may be unsubstituted or substituted with 1, 2 or 3 substituents selected

independently from each other from Hal, -NH₂, -NH-C(=O)-C₁₋₆-alkyl, wherein such C₁₋₆-alkyl group may be straight-chain or branched;

R^{6a} denotes H, LA^{6a}, CA^{6a}, Hetar^{6a}, -Ar^{6a}, -C₁₋₄-alkyl-Ar^{6a};

5 Hetcyc⁶ denotes saturated or partially unsaturated heterocycle with 3, 4, 5, 6, 7 ring atoms wherein 1, 2 or 3 of said ring atoms is/are a hetero atom(s) selected from N, O and/or S and the remaining ring atoms are carbon atoms wherein that heterocycle may be unsubstituted or mono- or di-substituted with substituents that
10 are independently from each other selected from straight-chain or branched C₁₋₆-alkyl, straight-chain or branched -O-C₁₋₆-alkyl, Hal, OH, Ar^{6b};

R^{8a} denotes CA^{8a} or LA^{8a};

15 Hetcyc⁸, Hetcyc^{4a}, Hetcyc^{4b} each denote independently from each other saturated or partially unsaturated heterocycle with 3, 4, 5, 6, 7 ring atoms wherein 1, 2 or 3 of said ring atoms is/are a hetero atom(s) selected from N, O and/or S and the remaining ring atoms are carbon atoms wherein that heterocycle may be unsubstituted or mono- or di-substituted with substituents that
20 are independently from each other selected from straight-chain or branched C₁₋₆-alkyl, straight-chain or branched -O-C₁₋₆-alkyl, Hal or OH;

25 Ar^{4a} denotes a mono- or bicyclic aromatic ring system with 6, 7, 8, 9, 10 ring carbon atoms wherein that aromatic ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from R^{4a1}, R^{4a2}, R^{4a3};

30 CA^{4a}, CA^{4b}, CA^{6a}, CA^{8a} each denote independently from each other saturated or partially unsaturated cycloalkyl with 3, 4, 5, 6, 7 ring carbon atoms which cycloalkyl may be unsubstituted or substituted with a substituent selected from straight-chain or

branched C₁₋₄-alkyl, straight-chain or branched -O-C₁₋₄-alkyl or OH;

5 Hetar⁷, Hetar^{4a}, Hetar^{4b}, Hetar^{6a} each denote independently from each other a mono-, bi- or tricyclic aromatic ring system with 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 ring atoms wherein 1, 2, 3, 4 or 5 of said ring atoms is/are a hetero atom(s) selected from N, O and/or S and the remaining ring atoms are carbon atoms wherein that aromatic ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from straight-chain or branched C₁₋₄-alkyl, straight-chain or branched -O-C₁₋₄-alkyl, Hal, wherein that straight-chain or branched C₁₋₄-alkyl group may be unsubstituted or mono-substituted with -OH or -O-C₁₋₄-alkyl;

15 Ar^{4b} denotes a mono- or bicyclic aromatic ring system with 6, 7, 8, 9, 10 ring carbon atoms wherein that aromatic ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from R^{4d1}, R^{4d2}, R^{4d3};

20 LA^{6a} denotes straight-chain or branched C₁₋₈-alkyl which may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, OH, -NR^{6a1}R^{6a2}, and in which C₁₋₈-alkyl 1 or 2 non-terminal and non-adjacent -CH₂- groups may be replaced by -O-, -S-, and/or 1 or 2 non-terminal and non-adjacent -CH₂-, -CH- groups may be replaced by -NH-, -N-;

25 Ar^{6a} denotes a mono-, bi- or tricyclic aromatic ring system with 6, 7, 8, 9, 10, 11, 12, 13, 14 ring carbon atoms wherein that aromatic ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from R^{6a3}, R^{6a4}, R^{6a5};

30 Ar^{6b} denotes a mono-, bi- or tricyclic aromatic ring system with 6, 7, 8, 9, 10, 11, 12, 13, 14 ring carbon atoms wherein that aromatic

ring system may be unsubstituted or mono-, di- or tri-substituted with substituents that are independently from each other selected from R^{6b1} , R^{6b2} , R^{6b3} ;

5 LA^{8a} denotes straight-chain or branched C_{1-8} -alkyl which may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal;

R^{1c1} , R^{1c2} , R^{1d1} , R^{1d2} , R^{6a1} , R^{6a2} denote independently from each other H, straight-chain or branched C_{1-8} -alkyl, or

10 each R^{1c1} and R^{1c2} ; R^{1d1} and R^{1d2} ; R^{6a1} and R^{6a2} independently from the other pairs of substituents form together with the nitrogen atom to which they are attached to a 3-, 4-, 5-, 6- or 7-membered heterocycle that may contain another hetero atom selected from N and O;

15 R^{4a1} , R^{4a2} , R^{4a3} , R^{4d1} , R^{4d2} , R^{4d3} , R^{6a3} , R^{6a4} , R^{6a5} , R^{6b1} , R^{6b2} , R^{6b3} each denote independently from each other H, Hal, straight-chain or branched C_{1-6} -alkyl, straight-chain or branched $-O-C_{1-6}$ -alkyl which C_{1-6} -alkyl or $-O-C_{1-6}$ -alkyl may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from Hal, OH;

20 Hal denotes F, Cl, Br or I.

2. Compound according to the preceding claim, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including
25 mixtures thereof in all ratios, wherein

Z^1 denotes CH or N;

Z^2 denotes CR^5 ;

Z^3 denotes CH or N;

30 wherein, if Z^1 denotes N, then Z^3 denotes CH, and if Z^3 denotes N, then Z^1 denotes CH;

R^2 and R^3 denote independently from each other H, F, or form, together with the carbon atom to which they are attached to, a cyclopropyl ring;

5 $Hetar^1$ denotes a mono-cyclic aromatic ring system with 5 or 6 ring atoms wherein 1 or 2 of said ring atoms is/are nitrogen atom(s) and the remaining ring atoms are carbon atoms wherein that aromatic ring system may be unsubstituted or mono-substituted with a substituent selected from $-NR^{1a}R^{1b}$, LA^{1c} ;

10 $Hetcyc^1$ denotes a saturated heterocycle with 4, 5, 6 ring atoms wherein 1 of said ring atoms is a nitrogen atom or 2 of said ring atoms are either one nitrogen and one oxygen atom or two nitrogen atoms and the remaining ring atoms are carbon atoms, wherein that heterocycle may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from straight-chain or branched C_{1-6} -alkyl or oxo ($=O$);

15 Ar^4 denotes phenyl that may be unsubstituted or mono-, di-substituted with substituents that are independently from each other selected from R^{4a} , R^{4b} ;

20 $Hetar^4$ denotes a mono- or bi-cyclic aromatic ring system with 5, 6, 9, 10 ring atoms wherein 1 of said ring atoms is a nitrogen atom or 2 of said ring atoms are two nitrogen atoms and the remaining ring atoms are carbon atoms wherein that aromatic ring system may be unsubstituted or mono-substituted with a substituent R^{4d} ;

25 R^5 , R^{1a} , R^{1b} each denote H;

LA^{1c} denotes a straight-chain or branched C_{1-4} -alkyl which may be unsubstituted or substituted with 1 substituent being OH;

30 R^{4a} , R^{4b} denote independently from each other H, $Hetar^{4a}$, straight-chain or branched C_{1-4} -alkyl or $-O-C_{1-4}$ -alkyl which C_{1-4} -alkyl or $-O-C_{1-4}$ -alkyl may be unsubstituted or substituted with 1,

2, or 3 substituents independently from each other selected from Hal;

R^{4d} denotes straight-chain or branched C₁₋₄-alkyl;

LA^{7a}, LA^{7b} denote independently from each other a straight-chain or branched C₁₋₄-alkyl;

R^{6a} denotes H, LA^{6a}, CA^{6a}, Hetar^{6a}, -CH₂-Ar^{6a};

Hetcyc⁶ denotes saturated heterocycle with 4, 5, 6 ring atoms wherein 1 of said ring atoms is a nitrogen atom or 2 of said ring atoms are either one nitrogen and one oxygen atom or two nitrogen atoms and the remaining ring atoms are carbon atoms wherein that heterocycle may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from straight-chain or branched C₁₋₄-alkyl, straight-chain or branched -O-C₁₋₄-alkyl, F, Cl, OH, Ar^{6b};

Hetcyc⁸ denotes saturated heterocycle with 4, 5, 6 ring atoms wherein 1 of said ring atoms is a nitrogen atom or 2 of said ring atoms are either one nitrogen and one oxygen atom or two nitrogen atoms and the remaining ring atoms are carbon atoms wherein that heterocycle may be unsubstituted or mono-substituted with -O-C₁₋₄-alkyl;

CA^{6a} denotes saturated cycloalkyl with 3, 5, 6 ring carbon atoms which cycloalkyl may be unsubstituted or substituted with a substituent being OH;

Hetar⁷, Hetar^{4a} and Hetar^{6a} denote independently from each other a mono-cyclic aromatic ring system with 5 or 6 ring atoms wherein 1 of said ring atoms is a nitrogen atom or 2 of said ring atoms are nitrogen atoms and the remaining ring atoms are carbon atoms wherein that aromatic ring system may be unsubstituted or mono-substituted with a substituent being straight-chain or branched C₁₋₄-alkyl, which C₁₋₄-alkyl substituent may be unsubstituted or mono-substituted with -OH;

- Ar^{6a} denotes phenyl that may be unsubstituted or mono-substituted with R^{6a3};
- Ar^{6b} denotes phenyl that may be unsubstituted or mono-substituted with R^{6b1};
- 5 LA^{6a} denotes straight-chain or branched C₁₋₄-alkyl;
- R^{6a3} denotes straight-chain or branched –O-C₁₋₄-alkyl which –O-C₁₋₄-alkyl may be unsubstituted or substituted with 1, 2 or 3 substituents selected independently from each other from F, Cl;
- R^{6b1} denotes H, F, Cl;
- 10 R¹, R⁴, R⁶, R⁷, R⁸, R^{8a}, LA^{7c}, CA^{8a}, LA^{8a} are as defined in claim 1.
3. Compound according to any of the preceding claims, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including
- 15 mixtures thereof in all ratios,
- wherein
- Z¹, Z² and Z³ denote CH;
- R² and R³ denote H;
- Hetar¹ denotes a mono-cyclic aromatic ring system with 5 ring
- 20 atoms wherein 2 of said ring atoms are nitrogen atoms and the remaining ring atoms are carbon atoms wherein that aromatic ring system may be mono-substituted with LA^{1c}, or
- denotes a mono-cyclic aromatic ring system with 6 ring atoms wherein 1 of said ring atoms is a nitrogen atom and the
- 25 remaining ring atoms are carbon atoms wherein that aromatic ring system may be mono-substituted with NH₂;
- Hetcyc¹ denotes –N-morpholinyl, N-piperdiny, N-pyrrolidin-2-one, 3-methyl-pyrrolidin-2-one;
- Ar⁴ denotes phenyl that may be unsubstituted or mono-substituted
- 30 with a substituent selected from methyl, methoxy, Hetar^{4a} or di-substituted with methoxy;
- Hetar⁴ denotes N-methyl-benzimidazole or N-methylindazole;

- R^5 denotes H;
 LA^{1c} denotes methyl, ethyl, 2-hydroxyethyl;
 R^{6a} denotes H, LA^{6a} , CA^{6a} , Hetar^{6a}, $-Ar^{6a}$, $-CH_2-Ar^{6a}$;
 Hetcyc⁶ denotes N-azetidiny which may be unsubstituted or mono-
 5 substituted with a substituent selected from OH, methoxy, F, Cl
 or di-substituted with substituents selected from F, Cl; N-
 pyrrolidiny which may be unsubstituted or mono-substituted with
 a substituent selected from OH, phenyl, p-chlorophenyl or di-
 substituted with substituents selected from F, Cl; N-morpholiny,
 10 N-piperaziny, N-piperidiny which may be unsubstituted or mono-
 substituted with a substituent selected from OH, F, Cl or di-
 substituted with substituents selected from F, Cl;
 LA^{6a} , LA^{7a} and LA^{7b} each denote methyl;
 LA^{7c} denotes $-CH_2-CH_2-NH-C(=O)-CH_3$;
 15 R^{8a} denotes cyclopropyl;
 Hetcyc⁸ denotes N-azetidiny which may be unsubstituted or mono-
 substituted with a substituent selected from OH, methoxy;
 CA^{6a} denotes cyclopropyl or cyclohexyl which may be unsubstituted or
 mono-substituted with OH;
 20 Hetar⁷ denotes pyridyl, pyrid-4-yl;
 Hetar^{4a} is defined as in any of claim 1 or 2;
 Hetar^{6a} denotes N-methyl-pyrazin-3-yl or 1-methyl-1H-pyrazol-4-
 yl;
 Ar^{6a} denotes o-(2,2,2-trifluoroethoxy)-phenyl;
 25 R^1 , R^4 , R^6 , R^7 , R^8 are as defined in claim 1.
4. Compound according to any of the preceding claims, or derivatives,
 prodrugs, solvates, tautomers or stereoisomers thereof as well as the
 physiologically acceptable salts of each of the foregoing, including
 30 mixtures thereof in all ratios,
 wherein
 R^1 denotes $-C(=O)-R^6$ or Hetar¹.

5. Compound according to claim 4, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios,
5 wherein
Hetar¹ denotes a mono-cyclic aromatic ring system with 5 or 6 ring atoms wherein 1 or 2 of said ring atoms is/are nitrogen atom(s) and the remaining ring atoms are carbon atoms wherein that aromatic ring system may be unsubstituted or mono-substituted with a substituent selected from methyl, ethyl, 2-hydroxyethyl;
10
R⁶ denotes –NHR^{6a} or Hetcyc⁶;
R^{6a} denotes H, LA^{6a} or CA^{6a};
15 LA^{6a} denotes straight-chain or branched C₁₋₄-alkyl which may be unsubstituted or substituted with 1 substituent being OH, and in which C₁₋₄-alkyl 1 non-terminal –CH₂– group may be replaced by –O–;
CA^{6a} denotes saturated cycloalkyl with 3 or 6 ring carbon atoms which cycloalkyl may be unsubstituted or substituted with a substituent being OH;
20
Hetcyc⁶ denotes saturated heterocycle with 4, 5, 6 ring atoms wherein 1 of said ring atoms is a nitrogen atom or 2 of said ring atoms are either one nitrogen and one oxygen atom or two nitrogen atoms wherein that heterocycle may be unsubstituted or mono- or di-substituted with substituents that are independently from each other selected from straight-chain or branched straight-chain C₁₋₄-alkyl, or branched –O-C₁₋₄-alkyl, F, OH, and wherein that heterocycle is attached to the carbonyl C-atom of the –C(=O)–R⁶ moiety via a ring nitrogen atom.
25
30

6. Compound according to any of the preceding claims, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios,
5 wherein
R⁴ denotes N-methyl-benzimidazole, N-methylindazole or phenyl that may be unsubstituted or mono-substituted with a substituent selected from methyl, N-methylpyrazole, N-(2-hydroxy-2-methylpropyl)pyrazole, N-methylindazole.
- 10 7. Compound according to any one of claims 1 to 3, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios,
15 wherein
R¹ denotes -C(=O)-R⁶, -NHR⁷, -SO₂R⁸, Hetar¹ or Hetcyc¹;
R⁶ denotes -NH₂, -NH-methyl, -NH-cyclopropyl, -NH-(CH₂)₂-OH, -NH-(CH₂)₃-OH, -NH-(CH₂)₄-OH, -NH-(CH₂)₅-OH, -NH-(CH₂)₂-OCH₃, -NH-(CH₂)₂-NH₂, -NH-(CH₂)₂-N(CH₃)₂, -NH-(1-methyl-1H-pyrazol-4-yl), -NH-(4-hydroxycyclohexyl), -NH-(*trans*-4-hydroxycyclohexyl), -NH-(*cis*-4-hydroxycyclohexyl), -NH-(2-(2,2,2-trifluoroethoxy)-benzyl), 3,3-difluoro-pyrrolidin-1-yl, 3,3-difluoro-piperidin-1-yl, 4,4-difluoro-piperidin-1-yl, piperazin-1-yl, pyrrolidin-1-yl, 3-hydroxy-pyrrolidin-1-yl, (*R*)-3-hydroxy-pyrrolidin-1-yl, (*S*)-3-hydroxy-pyrrolidin-1-yl, 2-(4-chlorophenyl)-pyrrolidin-1-yl, (*R*)-2-(4-chlorophenyl)-pyrrolidin-1-yl, (*S*)-2-(4-chlorophenyl)-pyrrolidin-1-yl, 4,4-difluoro-piperidin-1-yl, N-morpholin-4-yl, 3-hydroxy-azetidiny, 3-methoxy-azetidiny, 3,3-difluoro-azetidiny;
20
25
30 R⁷ denotes -C(=O)-CH₃, SO₂CH₃;
R⁸ denotes NH-cyclopropyl, 3-methoxy-azetidiny;

- Hetar¹ denotes 1-methyl-1H-pyrazol-3-yl, 1-methyl-1H-pyrazol-4-yl, 1-methyl-1H-imidazol-2-yl, 1-methyl-1H-imidazol-4-yl, 1-(2-hydroxyethyl)-1H-imidazol-2-yl, 1-(2-hydroxyethyl)-1H-imidazol-4-yl, 2-amino-pyridin-4-yl, 4-amino-pyridin-2-yl;
- 5 Hetcyc¹ denotes pyrrolidin-2-one, 3-methyl-pyrrolidin-2-one, (*R*)-3-methyl-pyrrolidin-2-one, (*S*)-3-methyl-pyrrolidin-2-one, morpholin-4-yl, piperazin-1-yl;
- and/or
- 10 R⁴ denotes 3,4-dimethoxyphenyl, 3-methylphenyl, 4-(1-methyl-1H-pyrazol-4-yl)-phenyl, 4-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]-phenyl, 1-methyl-1H-indazol-5-yl, 1-methyl-1H-indazol-6-yl.
8. Compound according to any of the preceding claims, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the
- 15 physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios,
- wherein the compound is selected from
- (1) 3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid methylamide
- (2) 3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid
- 20 cyclopropylamide
- (3) 3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid (2-methoxy-ethyl)-amide
- (4) (3,3-Difluoro-pyrrolidin-1-yl)-[3-(3-methyl-benzyl)-1H-indazol-5-yl]-methanone
- 25 (5) 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid amide
- (6) 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid cyclopropylamide
- (7) 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid methylamide
- (8) 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid (2-methoxy-ethyl)-amide
- 30 (9) [3-(3-Methyl-benzyl)-1H-indazol-5-yl]-piperazin-1-yl-methanone
- (10) 3-(1-Methyl-1H-indazol-6-ylmethyl)-1H-indazole-5-carboxylic acid methylamide

- (11) (3,3-Difluoro-pyrrolidin-1-yl)-[3-(3,4-dimethoxy-benzyl)-1H-indazol-5-yl]-methanone
- (12) 3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid amide
- 5 (13) [3-(3,4-Dimethoxy-benzyl)-1H-indazol-5-yl]-((R)-3-hydroxy-pyrrolidin-1-yl)-methanone
- (14) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid methylamide
- (15) (3,3-Difluoro-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone
- 10 (16) (3,3-Difluoro-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- (17) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid cyclopropylamide
- (18) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (2-methoxy-ethyl)-amide
- 15 (19) [3-(3,4-Dimethoxy-benzyl)-1H-indazol-5-yl]-((S)-3-hydroxy-pyrrolidin-1-yl)-methanone
- (20) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid amide
- 20 (21) {3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-piperazin-1-yl-methanone
- (22) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (1-methyl-1H-pyrazol-4-yl)-amide
- (23) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid amide
- 25 (24) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid cyclopropylamide
- (25) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (2-methoxy-ethyl)-amide
- 30 (26) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (1-methyl-1H-pyrazol-4-yl)-amide

- (27) 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid (4-hydroxy-cyclohexyl)-amide
- (28) (3,3-Difluoro-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone
- 5 (29) 3-(1-Methyl-1H-indazol-6-ylmethyl)-1H-indazole-5-carboxylic acid cyclopropylamide
- (30) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (4-hydroxy-cyclohexyl)-amide
- (31) ((S)-3-Hydroxy-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- 10 (32) ((R)-3-Hydroxy-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone
- (33) ((S)-3-Hydroxy-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone
- 15 (34) ((R)-3-Hydroxy-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- (35) [(R)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone
- (36) [(R)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3-methyl-benzyl)-1H-indazol-5-yl]-methanone
- 20 (37) [(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(1-methyl-1H-indazol-6-ylmethyl)-1H-indazol-5-yl]-methanone
- (38) [(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3-methyl-benzyl)-1H-indazol-5-yl]-methanone
- 25 (39) 3-(3,4-Dimethoxy-benzyl)-1H-indazole-5-carboxylic acid 2-(2,2,2-trifluoro-ethoxy)-benzylamide
- (40) [(R)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3,4-dimethoxy-benzyl)-1H-indazol-5-yl]-methanone
- (41) [(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-[3-(3,4-dimethoxy-benzyl)-1H-indazol-5-yl]-methanone
- 30 (42) 3-(3-Methyl-benzyl)-1H-indazole-5-carboxylic acid 2-(2,2,2-trifluoro-ethoxy)-benzylamide

- (43) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-pyrazolo[4,3-b]pyridine-5-carboxylic acid methylamide
- (44) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid methylamide
- 5 (45) (3,3-Difluoro-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-pyrazolo[3,4-b]pyridin-5-yl]-ethanone
- (46) (3,3-Difluoro-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-pyrazolo[4,3-b]pyridin-5-yl]-ethanone
- (47) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-pyrazolo[4,3-b]pyridine-5-carboxylic acid methylamide
- 10 (48) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid methylamide
- (49) (3,3-Difluoro-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-pyrazolo[3,4-b]pyridin-5-yl}-methanone
- 15 (50) (3,3-Difluoro-pyrrolidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-pyrazolo[4,3-b]pyridin-5-yl}-methanone
- (51) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (2-amino-ethyl)-amide
- (52) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (2-dimethylamino-ethyl)-amide
- 20 (53) N-(4-hydroxybutyl)-3-{[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-1H-indazole-5-carboxamide
- (54) N-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-acetamide
- 25 (55) N-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanesulfonamide
- (56) 1-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyrrolidin-2-one
- (57) (S)-3-Methyl-1-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyrrolidin-2-one
- 30 (58) (R)-3-Methyl-1-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyrrolidin-2-one

- (59) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-5-morpholin-4-yl-1H-indazole
- (60) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-5-piperazin-1-yl-1H-indazole
- 5 (61) 5-[(4,4-difluoropiperidin-1-yl)carbonyl]-3-{[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-1H-indazole
- (62) 5-[(3,3-difluoropiperidin-1-yl)carbonyl]-3-{[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-1H-indazole
- (63) 3-{[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-5-[(morpholin-4-yl)carbonyl]-1H-indazole
- 10 (64) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-sulfonic acid cyclopropylamide
- (65) 5-(3-Methoxy-azetidine-1-sulfonyl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole
- 15 (66) (3-Methoxy-azetidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone
- (67) (3-Hydroxy-azetidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone
- (68) (3,3-Difluoro-azetidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone
- 20 (69) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (2-hydroxy-ethyl)-amide
- (70) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (2-amino-ethyl)-amide
- 25 (71) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (2-dimethylamino-ethyl)-amide
- (72) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (3-hydroxy-propyl)-amide
- (73) 3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazole-5-carboxylic acid (4-hydroxy-butyl)-amide
- 30 (74) N-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-acetamide

- (75) N-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanesulfonamide
- (76) 1-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-pyrrolidin-2-one
- 5 (77) (S)-3-Methyl-1-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-pyrrolidin-2-one
- (78) (R)-3-Methyl-1-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-pyrrolidin-2-one
- (79) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid methylamide
- 10 (80) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (4-hydroxy-cyclohexyl)-amide
- (81) (3-Methoxy-azetidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- 15 (82) (3-Hydroxy-azetidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- (83) (3,3-Difluoro-azetidin-1-yl)-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- (84) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (2-hydroxy-ethyl)-amide
- 20 (85) 3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole-5-carboxylic acid (3-hydroxy-propyl)-amide
- (86) {3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyrrolidin-1-yl-methanone
- 25 (87) {3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-piperidin-1-yl-methanone
- (88) 3-(1-Methyl-1H-indazol-6-ylmethyl)-1H-indazole-5-carboxylic acid 2-(2,2,2-trifluoro-ethoxy)-benzylamide
- (89) 5-(1-Methyl-1H-pyrazol-3-yl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole
- 30 (90) 4-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyridin-2-ylamine

- (91) [(S)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- (92) 3-{[4-(1-methyl-1H-pyrazol-4-yl)phenyl]methyl}-N-{[2-(2,2,2-trifluoroethoxy)phenyl]methyl}-1H-indazole-5-carboxamide
- 5 (93) [3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-piperazin-1-yl-methanone
- (94) 5-(1-Methyl-1H-imidazol-2-yl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole
- (95) 2-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyridin-4-ylamine
- 10 (96) 5-(1-Methyl-1H-imidazol-4-yl)-3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazole
- (97) 2-(2-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-imidazol-1-yl)-ethanol
- 15 (98) 4-[3-[(1-methylindazol-5-yl)methyl]-1H-indazol-5-yl]morpholine
- (99) 1-methyl-5-[[5-(1-methylpyrazol-3-yl)-1H-indazol-3-yl]methyl]indazole
- (100) ((S)-3-Hydroxy-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone
- 20 (101) ((R)-3-Hydroxy-pyrrolidin-1-yl)-[3-(1-methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-methanone
- (102) [(R)-2-(4-Chloro-phenyl)-pyrrolidin-1-yl]-{3-[4-(1-methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-methanone
- (103) N-{2-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-ylamino]-ethyl}-acetamide
- 25 (104) [3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-pyridin-4-ylamine
- (105) 1-methyl-5-[[5-(1-methylimidazol-4-yl)-1H-indazol-3-yl]methyl]indazole
- 30 (106) 1-methyl-5-[[5-(1-methylimidazol-2-yl)-1H-indazol-3-yl]methyl]indazole

- (107) 2-{2-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-imidazol-1-yl}-ethanol
- (108) {3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-yl}-pyridin-4-yl-amine
- 5 (109) (3,3-Difluoro-pyrrolidin-1-yl)-(3-{4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazol-5-yl)-methanone
- (110) (3-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazol-5-yl)-pyrrolidin-1-yl-methanone
- (111) (3,3-Difluoro-azetidin-1-yl)-(3-{4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazol-5-yl)-methanone
- 10 (112) 3-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-benzyl}-1H-indazole-5-carboxylic acid methylamide
- (113) N-(2-{3-[4-(1-Methyl-1H-pyrazol-4-yl)-benzyl]-1H-indazol-5-ylamino}-ethyl)-acetamide
- 15 (114) 2-{4-[3-(1-Methyl-1H-indazol-5-ylmethyl)-1H-indazol-5-yl]-imidazol-1-yl}-ethanol.
9. Pharmaceutical composition comprising a compound according to any one of claims 1 to 8, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, as active ingredient together with a pharmaceutically acceptable carrier.
- 20
- 25 10. A compound according to any one of claims 1 to 8, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, for use as a medicament.
- 30 11. A compound according to any one of claims 1 to 8, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including

mixtures thereof in all ratios, for use in the prevention and/or treatment of hyperproliferative, inflammatory or degenerative disorders.

- 5 12. The compound for use according to claim 11, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein the hyperproliferative disorder is cancer.
- 10 13. The compound for use according to any one of claims 11 or 12, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein the hyperproliferative disorder is selected from the group consisting of brain, lung, colon, 15 epidermoid, squamous cell, bladder, gastric, pancreatic, breast, head & neck, renal, kidney, liver, ovarian, prostate, uterine, oesophageal, testicular, gynecological, thyroid cancer; melanoma, acute myelogenous leukemia, multiple myeloma, chronic myelogenous leukemia, myeloid cell leukemia, Kaposi's sarcoma.
- 20 14. The compound for use according to claim 11, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein the inflammatory disorder is 25 selected from multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematoses (SLE) or inflammatory bowel disease.
- 30 15. The compound for use according to claim 11, or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein the degenerative disease is

selected from the group consisting of osteoarthritis or Alzheimer's disease.

16. Set (kit) consisting of separate packs of

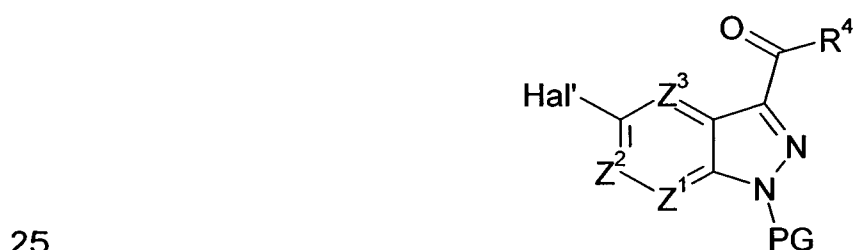
- 5 a) an effective amount of a compound according to any one of claims 1 to 8, or or derivatives, prodrugs, solvates, tautomers or stereoisomers thereof as well as the physiologically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, and
- 10 b) an effective amount of a further medicament active ingredient.

17. Process for manufacturing a compound of formula (I)



(I)

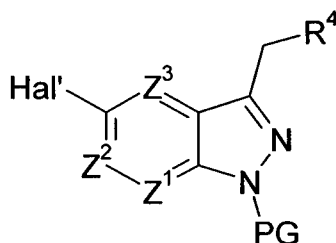
with Z¹, Z², Z³, R¹, R², R³, R⁴ being defined as in claim 1,
20 wherein a compound of formula (II)



(II)

with Z¹, Z², Z³, R⁴ being as defined above, Hal' being Cl, Br or I and PG being a suitable protecting group,
is reacted in a
30 step (a) with a suitable reduction means to form a compound of formula (III)

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(III)

with Z^1 , Z^2 , Z^3 , R^4 , Hal' and PG being as defined above, which compound of formula (III) is further transformed either in a step (b1) by means of a C-C-coupling reaction utilizing a compound of

 $R^1\text{-Hal}''$

(IV)

with R^1 being Heter¹ or Hetcyc¹ that are defined as in claim 1, wherein that Heter¹ or Hetcyc¹ is connected to Hal'' via a ring carbon atom, and Hal'' being Cl, Br or I,

or

in a step (b2) by means of a C-N-coupling reaction utilizing a compound of formula (V)

 $R^1\text{-H}$

(V)

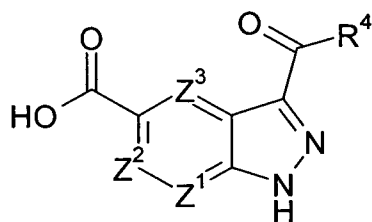
with R^1 being -NHR^7 or Hetcyc¹ wherein Hetcyc¹ is defined as in claim 1 and is connected to the hydrogen atom H in formula (V) via a ring nitrogen atom,

and subsequent removal of PG into a compound of formula (I) with Z^1 , Z^2 , Z^3 , R^1 , R^2 , R^3 , R^4 being defined as above;

or

wherein said compound of formula (II) above is reacted in a step (c) with potassium acetate in the presence of carbon monoxide and a suitable catalyst and subsequently a strong base to form a compound of formula (VI)

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(VI)

with Z^1 , Z^2 , Z^3 and R^4 being as defined above; which compound of formula (VI) is reacted in a step (d) with a suitable reduction means and subsequently in a step (e) with a compound of formula VII

 R^6-H

(VII)

with R^6 being as defined in claim 1, in the presence of a suitable base and a suitable catalyst to form a compound of formula (I) with R^1 being $-C(=O)R^6$.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/001732

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D413/14 C07D235/12 C07D403/06 C07D403/10 C07D403/14 A61K31/416 A61P25/00 ADD. According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/143646 A1 (OSI PHARMACEUTICALS, LLC, USA) 17 November 2011 (2011-11-17) p. 56 and 57, examples 13 and 14; -----	1-3
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2009, COOPER, ALAN B. ET AL: "Polycyclic indazole derivatives that are ERK inhibitors and their preparation, pharmaceutical compositions and use in the treatment of cancer", XP002749283, retrieved from STN Database accession no. 2009:556608 compounds: RN 942189-53-9, RN 942189-69-7 ----- -/--	1-3
☒ 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 "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 30 October 2015		Date of mailing of the international search report 27/11/2015
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Wolf, Claudia

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/001732

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 2011/034441 A1 (HOOD JOHN [US] ET AL) 10 February 2011 (2011-02-10) claims 1, 31 -----	1-17

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Information on patent family members

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