REPUBLIKA E SHQIPËRISË

MINISTRIA E FINANCAVE DHE EKONOMISË
DREJTORIA E PËRGJITHSHME E PRONËSISË INDUSTRIALE

BULETINI I PRONËSISË INDUSTRIALE (Patenta)

Nr. 23/2020
Tiranë më, 20 Korrik 2020

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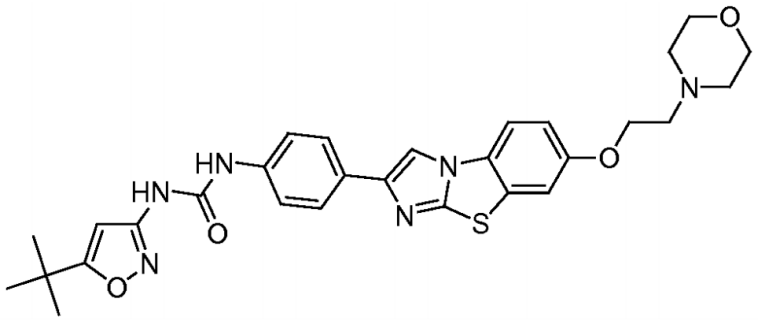
United Arab Emirates /Emiratet e Bashkuara Arabe	AE
United Kingdom/ Mbreteria e Bashkuar	GB
United Republic of Tanzania / Republika e Bashkuar e Tanzanise	TZ
United States of America / Shtetet e Bashkuara te Amerikes	US
Uruguay / Uruguai	UY
Uzbekistan / Uzbekistani	UZ
Vanuatu / Vanuatu	VU
Vatican / Vatikani	VA
Venezuela / Venezuela	VE
Vietnam / Vietnami	VN
Virgin Islands / Ishujt Virxhin	VG

Yemen / Jemeni	YE
Yugoslavia / Jugosllavia	YU
Zaire / Zaireja	ZR
Zambia / Zambia	ZM
Zimbabwe / Zimbabve	ZW

PATENTA TË LËSHUARA

(11) **9191**
(97) EP2429524 / 15/01/2020
(96) 10719218.9 / 14/05/2010
(22) 29/01/2020
(21) AL/P/ 2020/59
(54) **Formulim i thatë me spërkatje i AC220**
30/06/2020
(30) 178472 P 14/05/2009 US and 243977 P 18/09/2009 US
(71) Ambit Biosciences Corporation
, 11080 Roselle StreetSan Diego, CA 92121, US
(72) CORRINGHAM, Robert E. (4215 Sorrento Valley Boulevard, San Diego, CA 92121); O'DONNELL, Patrick B. (4215 Sorrento Valley Boulevard, San Diego, CA 92121) ;JAMES, Joyce K. (4215 Sorrento Valley Boulevard, San Diego, CA 92121)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)
(57) **1.** Një kompozim farmaceutik i thatë me spërkatje që përfshin një përbërje të Formulës I,



ose një kripë farmaceutikisht të pranueshme ose tretës të saj, dhe hidroksipropil-β-ciklodekstrin.
2. Kompozimi farmaceutik i pretendimit 1, ku përbërja është një kripë dihidrokloride.
3. Kompozimi farmaceutik i pretendimit 1, ku tretësi është një tretës metanol.
4. Kompozimi farmaceutik i pretendimit 1 që përfshin përbërjen e Formulës I dhe hidroksipropil-β-ciklodekstrin në një raport prej rreth 1:10 bazuar tek pesha.
5. Kompozimi farmaceutik i pretendimit 1, ku kompozimi është formuluar për administrimin e dozës së vetme.
6. Kompozimi farmaceutik i pretendimit 1, ku kompozimi është formuluar për administrim oral.

(11) **9193**
(97) EP3149031 / 18/12/2019
(96) 15729004.0 / 29/05/2015
(22) 09/03/2020
(21) AL/P/ 2020/148
(54) **RECEPTORËT QELIZORË PAPILLOMAVIRUS ANTI-HUMAN 16 E7 T**
30/06/2020

(30) 201462004335 P 29/05/2014 US
(71) The United States of America, as represented by The Secretary, Department of Health and Human Services
Office of Technology Transfer, National Institute of Health, 6011 Executive Boulevard, Suite 325, MSC 7660, Bethesda, MD 20892-7660, US
(72) ROSENBERG, Steven A. (10104 Iron Gate Road, Potomac, Maryland 20854)
;HINRICHS, Christian S. (5814 Melvern Drive, Bethesda, Maryland 20817)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)
(57) **1.** Një receptor i qelizës T (TCR) që përfshin një rajon të ndryshueshëm human dhe një rajon të pandryshueshëm murinash, ose një variant funksional të TCR, ku TCR-ja dhe varianti funksional përfshijnë rajonin përcaktues të plotësueshmërisë së zinxhirit alfa (CDR) 1 sekuencën aminoacide të SEQ ID NO: 3, zinxhirin alfa CDR2 sekuencën aminoacide të SEQ ID NO: 4, zinxhirin alfa CDR3 sekuencën aminoacide të SEQ ID NO: 5, zinxhirin beta CDR1 sekuencën aminoacide të SEQ ID NO: 6, zinxhirin beta CDR2 sekuencën aminoacide të SEQ ID NO: 7, dhe zinxhirin beta CDR3 sekuencën aminoacide të SEQ ID NO: 8 dhe kanë specifitet antigjenik për papillomavirusin human (HPV) 16 $E7_{11-19}$ SEQ ID NO: 2, në mënyrë opsionale ku TCR-ja përfshin sekuencën aminoacide të (a) SEQ ID NO: 9 dhe (b) SEQ ID NO: 10, ku X në pozicionin 2 është Ala ose Gly.
2. Një receptor i qelizës T i izoluar ose i pastruar (TCR) duke përfshirë zinxhirin alfa CDR1 sekuencën aminoacide të SEQ ID NO: 3, zinxhirin alfa CDR2 sekuencën aminoacide të SEQ ID NO: 4, zinxhirin alfa CDR3 sekuencën aminoacide të SEQ ID NO: 5, zinxhirin beta CDR1 sekuencën aminoacide të SEQ ID NO: 6, zinxhirin beta CDR2 sekuencën aminoacide të SEQ ID NO: 7, dhe zinxhirin beta CDR3 sekuencën aminoacide të SEQ ID NO: 8 dhe që kanë specifitet antigjenik për papillomavirusin human (HPV) 16 $E7_{11-19}$ SEQ ID NO: 2, në mënyrë opsionale ku TCR-ja:

(i) përfshin një rajon të pandryshueshëm human; dhe/ose

(ii) përfshin sekuencën aminoacide të (a) SEQ ID NO: 9 dhe (b) SEQ ID NO: 10, ku X në pozicionin 2 është Ala ose Gly.

3. TCR-ja ose varianti funksional i pretendimit 1 ose TCR-ja e izoluar ose e pastruar e pretendimit 2, duke përfshirë sekuencat aminoacide të

(a) SEQ ID NO: 16, ku

(i) X në pozicionin 48 është Thr ose Cys;

(ii) X në pozicionin 112 është Ser, Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, ose Trp;

(iii) X në pozicionin 114 është Met, Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, ose Trp; dhe

(iv) X në pozicionin 115 është Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, ose Trp; dhe

(b) SEQ ID NO: 18, ku X në pozicionin 56 është Ser ose Cys.

4. TCR-ja ose varianti funksional i pretendimit 1 ose 3 ose TCR-ja e izoluar ose e pastruar e pretendimit 2 ose 3, duke përfshirë sekuencat aminoacide të:

(I)

(a) çdo njëri prej SEQ ID NOs: 14, 17, 21, 24, dhe 25; dhe

(b) çdo njëri prej SEQ ID NOs: 15, 19, dhe 23

(II)

(a) (i) SEQ ID NO: 12, (ii) SEQ ID NO: 22, (iii) SEQ ID NO: 26, (iv) SEQ ID NO: 9 dhe 24, (v) SEQ ID NO: 9 dhe 16, ose (vi) SEQ ID NOs: 9 dhe 17; dhe

(b) (i) SEQ ID NOs: 10 dhe 18 ose (ii) çdo njëri prej SEQ ID NOs: 13, 20, dhe 27; ose

(III) SEQ ID NO: 29 ose 30.

5. Një polipeptid i izoluar ose i pastruar duke përfshirë një pjesë funksionale të (i) TCR-ja ose variant funksional të çdo njëritt prej pretendimeve 1 dhe 3-4 ose (ii) TCR-ja e izoluar ose e pastruar e çdo njërit prej pretendimeve 2-4, ku pjesa funksionale në mënyrë specifike lidhet me HPV 16 $E7_{11-19}$ dhe përfshin zinxhirin alfa CDR1 sekuencën aminoacide të SEQ ID NO: 3, zinxhirin alfa CDR2 sekuencën aminoacide e SEQ ID NO: 4, zinxhirin alfa CDR3 sekuencën aminoacide të SEQ ID NO: 5, zinxhirin beta CDR1 sekuencën aminoacide të SEQ ID NO: 6, zinxhirin beta CDR2 sekuencën aminoacide të SEQ ID NO: 7, dhe zinxhirin beta CDR3 sekuencën aminoacide të SEQ ID NO: 8, në mënyrë opsionale ku pjesa funksionale përfshin sekuencën(at) aminoacide të:

(I) (a) SEQ ID NO: 9, (b) SEQ ID NO: 10, ose (c) SEQ ID NOs: 9 dhe 10, ku X në pozicionin 2 të SEQ ID NO: 10 është Ala ose Gly, dhe kur X në pozicionin 2 të SEQ ID NO: 10 është Gly, polipeptidi është izoluar ose pastruar; ose

(II)

(a) (i) SEQ ID NOs: 9 dhe 24; (ii) SEQ ID NOs: 9 dhe 17; (iii) SEQ ID NO: 9 dhe 16; (iv) SEQ ID NO: 10 dhe 18; ose (v) çdo njëri prej SEQ ID NOs: 12, 13, 20, 22, 26, 27, 29 dhe 30;

(b) SEQ ID NOs: 12 dhe 13;

(c) SEQ ID NOs: 20 dhe 22;

(d) SEQ ID NOs: 26 dhe 27;

(e) SEQ ID NOs: 9, 24, dhe 27;

(f) SEQ ID NOs: 9, 17, dhe 20; ose

(g) SEQ ID NOs: 9, 10, 16, dhe 18,

ku polipeptidi duke përfshirë sekuencën aminoacide të një ose të të dyve SEQ ID NOs: 12 dhe 13 është izoluar ose pastruar.

6. Një proteinë e izoluar ose e pastruar e cila në mënyrë specifike lidhet me HPV 16 $E7_{11-19}$ dhe e cila përfshin një zinxhir të parë polipeptidik duke përfshirë zinxhirin alfa CDR1 sekuencën aminoacide të SEQ ID NO: 3, zinxhirin alfa CDR2 sekuencën aminoacide të SEQ ID NO: 4, dhe zinxhirin alfa CDR3 sekuencën aminoacide të SEQ ID NO: 5, dhe një zinxhir të dytë polipeptidik duke përfshirë zinxhirin beta CDR1 sekuencën aminoacide të SEQ ID NO: 6, zinxhirin beta CDR2 sekuencën aminoacide të SEQ ID NO: 7, dhe zinxhirin beta CDR3 sekuencën aminoacide të SEQ ID NO: 8, në mënyrë opsionale ku proteina:

(i) është një proteinë e shkrirjes ose një antitrup rekombinant;

(ii) përfshin një zinxhir të parë polipeptidik duke përfshirë sekuencën aminoacide të SEQ ID NO: 9 dhe një zinxhir të dytë polipeptidik duke përfshirë sekuencën aminoacide të SEQ ID NO: 10, ku (A) X në pozicionin 2 të SEQ ID NO: 10 është Ala ose Gly, dhe (B) proteina duke përfshirë SEQ ID NOs: 9 dhe 10, ku X në pozicionin 2 të SEQ ID NO: 10 është Gly, është izoluar ose pastruar; ose

(iii) përfshin një zinxhir të parë polipeptidik duke përfshirë sekuencën aminoacide të (i) SEQ ID NO: 12, (ii) SEQ ID NO: 22, (iii) SEQ ID NO: 26, (iv) SEQ ID NO: 9 dhe 16, (v) SEQ ID NO: 9 dhe 17, ose (vi) SEQ ID NO: 9 dhe 24 dhe një zinxhir të dytë polipeptidik duke përfshirë sekuencën aminoacide të (i) SEQ ID NO: 10 dhe 18, ose (ii) çdo njëri prej SEQ ID NOs: 13, 20, dhe 27,

ku proteina duke përfshirë SEQ ID NO: 12 dhe 13 është izoluar ose pastruar.
7. Një proteinë duke përfshirë SEQ ID NO: 29 ose 30.
8. (a) Një acid nukleik duke përfshirë një sekuencë nukleotide që kodon TCR-në ose variantin funksional sipas çdo njërit prej pretendimeve 1 dhe 3-4, polipeptidin sipas pretendimit 5, ose proteinën sipas pretendimit 6 ose 7, ose (b) një acid nukleik i izoluar ose i pastruar duke përfshirë një sekuencë nukleotide që kodon TCR-në sipas çdo njërit prej pretendimeve 2-4, polipeptidin sipas pretendimit 5, ose proteinën sipas pretendimit 6 ose 7, në mënyrë opsionale ku:

(i) acidi nukleik përfshin sekuencën nukleotide të SEQ ID NO: 31, SEQ ID NO: 32, ose të dyja SEQ ID NOs: 31 dhe 32; ose
(ii) acidi nukleik përfshin sekuencën nukleotide të (1) çdo njërit prej 33-36, (2) të dyja SEQ ID NOs: 33 dhe 34, ose (3) të dyja SEQ ID NOs: 35 dhe 36.

9. Një vektor i shprehjes rekombinante duke përfshirë acidin nukleik të pretendimit 8, në mënyrë opsionale ku:

(i) sekuenca nukleotide që kodon zinxhirin beta është pozicionuar 5’ i sekuencës nukleotide që kodon zinxhirin alfa; ose
(ii) vektori i shprehjes rekombinante përfshin SEQ ID NO: 37, 38, 39, ose 40.

10. Një qelizë pritëse duke përfshirë vektorin e shprehjes rekombinante të pretendimit 9, në mënyrë opsionale ku qeliza është humane.
11. Një popullatë qelizash duke përfshirë të paktën një qelizë pritëse të pretendimit 10.
12. Një antitrup, ose një pjesë e lidhjes së antigjenit të tij, e cila në mënyrë specifike lidhet me një epitop të një TCR-je, ku epitopi është formuar nga rajoni përcaktues i plotësueshmërisë së zinxhirit alfa (CDR) 1 sekuenca aminoacide e SEQ ID NO: 3, zinxhiri alfa CDR2 sekuenca aminoacide e SEQ ID NO: 4, zinxhiri alfa CDR3 sekuenca aminoacide e SEQ ID NO: 5, zinxhiri beta CDR1 sekuenca aminoacide e SEQ ID NO: 6, zinxhiri beta CDR2 sekuenca aminoacide e SEQ ID NO: 7, dhe zinxhiri beta CDR3 sekuenca aminoacide e SEQ ID NO: 8.
13. Një kompozim farmaceutik duke përfshirë TCR-në ose variantin funksional sipas çdo njërit prej pretendimeve 1 dhe 3-4, TCR-në e izoluar ose të pastruar të çdo njërit prej pretendimeve 2-4, polipeptidin sipas pretendimit 5, proteinën sipas pretendimit 6 ose 7, acidin nukleik të pretendimit 8, vektorin e shprehjes rekombinante të pretendimit 9, qelizën pritëse të pretendimit 10, ose popullatën e qelizave të pretendimit 11, dhe një mbartës farmaceutikisht të pranueshëm.
14. Një metodë in vitro për të zbuluar praninë e një gjendje në një gjitar, duke përfshirë:

(a) kontaktimin e një mostre duke përfshirë një ose më shumë qeliza nga gjitari me TCR ose variantin funksional sipas çdo njërit prej pretendimeve 1 dhe 3-4, TCR-në e izoluar ose të pastruar të çdo njërit prej pretendimeve 2-4, polipeptidin sipas pretendimit 5, proteinën sipas pretendimit 6 ose 7, qelizën pritëse të pretendimit 10, ose popullatën e qelizave të pretendimit 11, ku qeliza pritëse dhe popullata e qelizave shprehin TCR-në ose variantin funksional, duke formuar kështu një kompleks, dhe
(b) zbulimin e kompleksit, ku zbulimi i kompleksit është tregues i pranisë së gjendjes në gjitarin, ku gjendja është kancer, infeksion HPV 16, ose premalinjësi HPV-pozitive.

15. TCR-ja ose varianti funksional sipas çdo njërit prej pretendimeve 1 dhe 3-4, TCR-ja e izoluar ose e pastruar e çdo njërit prej pretendimeve 2-4, polipeptidi sipas pretendimit 5, proteina sipas pretendimit 6 ose 7, acidi nukleik i pretendimit 8, vektori i shprehjes rekombinante të pretendimit 9, qeliza pritëse e pretendimit 10, popullata e

qelizave të pretendimit 11, ose kompozimi farmaceutik i pretendimit 13, për përdorim në trajtimin ose paralimin e një gjendjeje në një gjitar, ku gjendja është kancer, infeksion HPV 16, ose premalinjësi HPV-pozitive, në mënyrë opsionale ku gjendja është:

(i) kancer i qafës së mitrës, orofaringut, anusit, kanalit anal, anorektumit, vaginës, vulvës ose penisit; ose
(ii) një kancer HPV 16-pozitiv.

(11) **9189**
(97) EP2723023 / 04/03/2020
(96) 12382407.0 / 19/10/2012
(22) 19/03/2020
(21) AL/P/ 2020/176
(54) **Metodë për regjistrimin dhe certifikim e marrjes së postës elektronike**
30/06/2020
(30)
(71) Lleidanetworks Serveis Telemàtics S.A.
Parque Tecnólogico Agroalimentario Edificio H1, 2ª planta, 25003 Lleida, ES
(72) Sapena Soler, Francisco (Parque tecnólogico agroalimentario, edificio H1,2ª planta, 25003 Lleida)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)
(57) **1.** Një metodë për regjistrimin dhe vërtetimin e pranimit të postës elektronike nga një përdorues transmetues (1) te një përdorues marrës në një sistem pritjeje dhe çertifikimi të një emaili të një operatori telekomunikues, sistemi i çertifikimit që përmban të paktën një server të postës hyrëse (2), në të paktën një server me postë dalëse (9, 19, 28), të paktën një bazë të dhënash (16, 17), një server me pullë kohe (32), një njësi për përpunimin e të dhënave (15) dhe një server çertifikimi (13) të cilat janë të ndërlidhura, metoda që përfshin:

• një përdorues transmetues (1), i cili nuk është klient i operatorit telekomunikues, duke dërguar postën elektronike në një adresë destinacioni, kjo adresë është adresa e një përdoruesi marrës (11), i cili është klient i operatorit telekomunikues;
• pritjen, nga të paktën një server i postës hyrëse (2), të postës elektronike të lëshuar nga përdoruesi transmetues (1);
• kalimin e postës elektronike në njësinë e përpunimit të të dhënave (15) që:
  - Shpërbën postën elektronike në komponentë;
  - Gjeneron një numërim unik dhe
  - Fut numërimin unik në të dhënat bazë (16, 17) të pranishme në operatorin e telekomunikacioneve, veç në një bazë të dhënash të largët (16, 17) të përdoruesit marrës (11);

• dërgimi i një kopje të postës elektronike pa modifikime tek përdoruesi marrës (11), posaçërisht në një server të postës së dytë të përdoruesit marrës (11) përmes një serveri të dytë dalës (9, 19, 28);
• duke njoftuar serverin e çertifikimit (13) i cili krijon një skedar (14) me të

dhëna për gjurmueshmërinë e emailit, burimeve, serverave nëpër të cilët ka kaluar, bashkëngjitjet jo të shtypshme, bashkëngjitjet e shtypshme dhe nënshkruan skedarin (14) me nënshkrimin dixhital të operatorit telekomunikues;
• kalimi i skedarit (14) përmes një serveri timestamp (32) për të krijuar një certifikatë (25);
• dorëzimi i certifikatës (25) në një server transmetues të postave të certifikuara dalëse (28) të operatorit telekomunikues; dhe
• marrja e çertifikatës (25) nga serveri i postave të certifikuara dalëse (28) të operatorit telekomunikues në një server të përdoruesit transmetues (1).

2. Metoda për regjistrimin dhe vërtetimin e pranimit të postës elektronike, sipas pretendimit 1, ku pas hapit të pranimit në serverin e postës hyrëse (2) të postës elektronike të lëshuar nga përdoruesi transmetues (1), serveri i postës hyrëse (2) verifikon që posta elektronike përmban një adresë e-mail që duhet të certifikohet dhe se adresa e postës elektronike nuk është postë e dendur dhe as përdoruesi transmetues (1) i përket listës së zezë.

3. Metoda për regjistrimin dhe vërtetimin e pranimit të postës elektronike, sipas pretendimit 2, ku nëse filtri përcakton se posta elektronike nuk është postë e dendur ose përdoruesi transmetues (1) nuk i përket listës së zezë, filtri verifikon nëse përdoruesi marrës (11) ka kredi për vërtetimin e postës elektronike në hyrje.

4. Metoda për regjistrimin dhe vërtetimin e pranimit të postës elektronike, sipas pretendimit 3, ku nëse përdoruesi marrës (11) nuk ka kredi për vërtetimin e postës elektronike hyrëse, gjenerohet mungesa e alarmit të kredisë, e cila paralajmëron dërguar në një server të postës së parë dalëse (9, 19, 28), i cili përpunon postën elektronike dhe dërgon postën elektronike në një server të postës së parë të përdoruesit marrës (11) i cili është përgjegjës për menaxhimin e llogarive në mënyrë që serveri i postës së parë e bën efektiv disponueshmërinë e kredisë që mund të lejojë çertifikimin.

5. Metoda për regjistrimin dhe vërtetimin e pranimit të postës elektronike, sipas pretendimit 3, ku nëse përdoruesi marrës (11) ka kredi për certifikimin e e-mail në hyrje, sistemi fillon procesin e certifikimit të postës në hyrje, së pari duke kaluar në një njësi të përpunimit të të dhënave (15) e cila do të shpërbëjë postën elektronike në përbërësit e saj, gjeneron një numër unik dhe do të fusë numrin unik në një bazë të dhënash (16, 17) e pranishme në operatorin e telekomunikacionit përveç në një bazë të dhënash të largët (16, 17) e përdoruesit marrës (11).

6. Metoda për regjistrimin dhe vërtetimin e pranimit të postës elektronike sipas pretendimit 1, metoda që përfshin më tej përdoruesin marrës (11) që përcakton një dritare kohore në të cilën postat elektronike hyrëse mund të certifikohen.

7. Metoda për regjistrimin dhe vërtetimin e pranimit të postës elektronike, sipas secilit prej pretendimeve të mëparshme, ku çertifikata (25) është krijuar në format PDF.

(11) **9192**
(97) EP3265421 / 12/02/2020
(96) 16758530.6 / 02/03/2016
(22) 19/03/2020
(21) AL/P/ 2020/177
(54) **SISTEM DOZIMI**
30/06/2020

(30) 201562127848 P 04/03/2015 US and 201562127853 P 04/03/2015 US
(71) SodaStream Industries Ltd.
Gilboa Street P.O. Box 280 Airport City, 7019900 Ben Gurion Airport, IL
(72) COHEN, Avi (8/4 Dishon Street, 9695608 Jerusalem) ;BEN SHALOM, Zvi (Lot 206Regional Council Hof Ashkelon, 7910300 Bat Hadar)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)
(57) **1.** Një sistem dozimi që përmban:
një tub shpërndarës (220) për të shpërndarë një lëng viskoz nga një kontejner mbajtës (210) drejt një kontejneri dalës, tubi i përmendur (220) përmban një valvulë të sipërme (222) dhe një valvulë të poshtme (224);
një pompë peristaltike për të shtyrë përkundrejt tubit shpërndarës dhe për të shkaktuar që lëngu viskoz i përmendur të hapë valvulën e poshtme të përmendur (224); dhe **karakterizuar në atë që** një sensor me efekt Hall (230) mat fuqinë e një sensori magnet ballor (240) të pompës së përmendur dhe përcakton praninë e tubit të shpërndarjes së përmendur (220).
2. Sisitemi sipas pretendimit 1 dhe në të cilin tubi i shpërndarjes së përmendur përmban fije për të lidhur kontejnerin mbajtës nëpërmjet fijeve të filetuara.

(11) **9190**
(97) EP3258951 / 29/01/2020
(96) 16707603.3 / 19/02/2016
(22) 24/03/2020
(21) AL/P/ 2020/188
(54) **ANTITRUPAT ANTI-PVRIG DHE METODAT E PËRDORIMIT**
30/06/2020
(30) 201562118208 P 19/02/2015 US; 201562141120 P 31/03/2015 US and 201562235823 P 01/10/2015 US
(71) Compugen Ltd.
26 Harokmim Street, 5885849 Holon, IL
(72) WHITE, Mark (c/o Compugen Ltd.26 Harokmim Street, 5885849 Holon); KUMAR, Sandeep (c/o Compugen Ltd.26 Harokmim Street, 5885849 Holon); CHAN, Christopher (c/o Compugen Ltd.26 Harokmim Street, 5885849 Holon); LIANG, Spencer (c/o Compugen Ltd.26 Harokmim Street, 5885849 Holon); STAPLETON, Lance (c/o Compugen Ltd.26 Harokmim Street, 5885849 Holon); GOZLAN, Yosi (c/o Compugen Ltd.26 Harokmim Street, 5885849 Holon); SAMEAH-GREENWALD, Shirley (c/o Compugen Ltd.26 Harokmim Street, 5885849 Holon); DASSA, Liat (c/o Compugen Ltd.26 Harokmim Street, 5885849 Holon); TIRAN, Zohar (c/o Compugen Ltd.26 Harokmim Street, 5885849 Holon); PRESTA, Leonard (c/o Compugen Ltd.26 Harokmim St., 5885849 Holon); THEOLIS, Richard (c/o Compugen Ltd.26 Harokmim St., 5885849 Holon); DRAKE, Andrew W. (c/o Compugen Ltd.26 Harokmim Street, 5885849 Holon); VAKNIN, IIan (c/o Compugen Ltd.26 Harokmim Street, 5885849 Holon) ;COJOCARU, Gad S. (c/o Compugen Ltd.26 Harokmim Street, 5885849 Holon)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)

(57) **1.** Një antitrup anti-PVRIG (Proteinë që Përmban Fushën Imunoglobuline të Lidhur me Receptorin Poliovirus) për përdorim në trajtimin e kancerit, ku antitrupi aktivizon qelizat T dhe/ose qelizat NK.

2. Një antitrup anti-PVRIG për përdorim sipas pretendimit 1, ku antitrupi anti-PVRIG I sipërpërmendur përfshin: sekuencat vhCDR1, vhCDR2, vhCDR3, vICDR1, vlCDR2 dhe vlCDR3 zgjedhur nga grupi i përbërë prej:

- vhCDR1 siç përcaktohet në SEQ ID NO:877, vhCDR2 siç përcaktohet në SEQ ID NO:878, vhCDR3 siç përcaktohet në SEQ ID NO:879, vlCDR1 siç përcaktohet në SEQ ID NO:881, vlCDR2 siç përcaktohet në SEQ ID NO:882 dhe vlCDR3 siç përcaktohet në SEQ ID NO:883,
- vhCDR1 siç përcaktohet në SEQ ID NO:885, vhCDR2 siç përcaktohet në SEQ ID NO:886, vhCDR3 siç përcaktohet në SEQ ID NO:887, vlCDR1 siç përcaktohet në SEQ ID NO:889, vlCDR2 siç përcaktohet në SEQ ID NO:890 dhe vlCDR3 siç përcaktohet në SEQ ID NO:891,
- vhCDR1 siç përcaktohet në SEQ ID NO:917, vhCDR2 siç përcaktohet në SEQ ID NO:918, vhCDR3 siç përcaktohet në SEQ ID NO:919, vlCDR1 siç përcaktohet në SEQ ID NO:921, vlCDR2 siç përcaktohet në SEQ ID NO:922 dhe vlCDR3 siç përcaktohet në SEQ ID NO:923,
- vhCDR1 siç përcaktohet në SEQ ID NO:941, vhCDR2 siç përcaktohet në SEQ ID NO:942, vhCDR3 siç përcaktohet në SEQ ID NO:943, vlCDR1 siç përcaktohet në SEQ ID NO:945, vlCDR2 siç përcaktohet në SEQ ID NO:946 dhe vlCDR3 siç përcaktohet në SEQ ID NO:947,
- vhCDR1 siç përcaktohet në SEQ ID NO:949, vhCDR2 siç përcaktohet në SEQ ID NO:950, vhCDR3 siç përcaktohet në SEQ ID NO:951, vlCDR1 siç përcaktohet në SEQ ID NO:953, vlCDR2 siç përcaktohet në SEQ ID NO:954 dhe vlCDR3 siç përcaktohet në SEQ ID NO:955,
- vhCDR1 siç përcaktohet në SEQ ID NO:973, vhCDR2 siç përcaktohet në SEQ ID NO:974, vhCDR3 siç përcaktohet në SEQ ID NO:975, vlCDR1 siç përcaktohet në SEQ ID NO:977, vlCDR2 siç përcaktohet në SEQ ID NO:978 dhe vlCDR3 siç përcaktohet në SEQ ID NO:979,
- vhCDR1 siç përcaktohet në SEQ ID NO:997, vhCDR2 siç përcaktohet në SEQ ID NO:998, vhCDR3 siç përcaktohet në SEQ ID NO:999, vlCDR1 siç përcaktohet në SEQ ID NO:1001, vlCDR2 siç përcaktohet në SEQ ID NO:1002 dhe vlCDR3 siç përcaktohet në SEQ ID NO:1003,
- vhCDR1 siç përcaktohet në SEQ ID NO:1037, vhCDR2 siç përcaktohet në SEQ ID NO:1038, vhCDR3 siç përcaktohet në SEQ ID NO:1039, vlCDR1 siç përcaktohet në SEQ ID NO:1041, vlCDR2 siç përcaktohet në SEQ ID NO:1042 dhe vlCDR3 siç përcaktohet në SEQ ID NO:1043.

3. Një antitrup anti-PVRIG për përdorim sipas ndonjë prej pretendimeve 1 deri në 2, ku antitrupi i sipërpërmendur përfshin fushën variable të rëndë siç përcaktohet në SEQ ID NO:884 dhe fushën variable të lehtë siç përcaktohet në SEQ ID NO:888.

4. Një antitrup anti-PVRIG për përdorim sipas ndonjë prej pretendimeve 1 deri në 3, ku antitrupi i sipërpërmendur përfshin fushën variable të rëndë siç përcaktohet në SEQ ID NO:980 dhe fushën variable të lehtë siç përcaktohet në SEQ ID NO:984.

5. Një antitrup anti-PVRIG për përdorim sipas çdo njërit prej pretendimeve 1 deri në 4, ku antitrupi anti-PVRIG është për përdorim në kombinim me një antitrup imunostimulator, një terapi citokine, ose një ilaç imunomodulator.

(11) **9194**
(97) EP3385395 / 29/01/2020
(96) 18173134.0 / 16/08/2016
(22) 06/04/2020
(21) AL/P/ 2020/226
(54) **METODAT E TRAJTIMIT TË PACIENTËVE ME KANCER ME FRENUESIT E TRANSFERAZËS FARNESIL**
30/06/2020
(30) 201562206194 P 17/08/2015 US; 201562218927 P 15/09/2015 US; 201562241019 P 13/10/2015 US; 201662310582 P 18/03/2016 US and 201662372662 P 09/08/2016 US
(71) Kura Oncology, Inc.
3033 Science Park Road, Suite 220, San Diego, CA 92121, US
(72) GUALBERTO, Antonio (8 Larch Road, Acton, MA 01720) ;SCHOLZ, Catherine Rose (8 James Millen Road, North Reading,MA 01864)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)
(57) **1.** Një përbërje për përdorim në një metodë për trajtimin e karcinomës së qelizës skuamoze të kokës dhe qafës (HNSCC) në një pacient, ku pacienti ka një mutacion H-Ras, ku mutacioni H-Ras rezulton në aktivizimin e proteinës H-Ras, ku përbërja është tipifarnib, dhe ku HNSCC është e avancuar, përsëritëse ose metastatike.
2. Përbërja për përdorim sipas pretendimit 1, ku mutacioni H-Ras i pacientit të sipërpërmendur përfshin një zëvendësim amino acidi në një kodon zgjedhur nga grupi i përbërë prej G12, G13, dhe Q61.
3. Përbërja për përdorim sipas pretendimit 1 ose 2, ku metoda përfshin përcaktimin e pranisë së mutacionit H-Ras në një mostër nga pancienti i sipërpërmendur.
4. Përbërja për përdorim sipas pretendimit 3, ku mostra e sipërpërmendur është një biopsi e indit ose një biopsi e tumorit.
5. Përbërja për përdorim sipas pretendimit 3 ose 4, ku mutacioni H-Ras i sipërpërmendur është përcaktuar nga një metodë zgjedhur nga grupi i përbërë prej sekuencës, Reaksionit të Zinxhirit të Polimerazës(PCR), rrjetit të segmenteve të ADN-së, SpektrometriaMasive (MS), analiza e Polimorfizimit të Nukleotideve të Vetme (SNP), denatyrimi i kromatografisë së lëngshme me performance të lartë (DHPLC), dhe analiza e Polimorfizimit të Gjatësisë së Fragmentit të Kufizimit (RFLP).
6. Përbërja për përdorim sipas pretendimit 1 deri në 5, ku metoda përfshin administrimin e tipifarnib në një doze prej 1-1000 mg/kg peshë trupi.
7. Përbërja për përdorim sipas pretendimit 1 deri në 6, ku metoda përfshin administrimin e tipifarnib dy herë në ditë.
8. Përbërja për përdorim sipas pretendimit 7, ku metoda përfshin administrimin e tipifarnib në një dozë prej 600 mg dy herë në ditë ose në një dozë prej 900 mg dy herë në ditë.
9. Përbërja për përdorim sipas çdonjë prej pretendimeve 1 deri në 8, ku metoda përfshin administrimin e tipifarnib për një peridudhë prej një deri në shtatë ditë.
10. Përbërja për përdorim sipas pretendimit 9, ku metoda përfshin administrimin e tipifarnib në ditët 1-7 dhe 15-21 nga një cikël prej 28-ditësh trajtim.
11. Përbërja për përdorim sipas pretendimit 10, ku metoda përfshin administrimin e tipifarnib për të paktën 3 cikle ose për të paktën 6 cikle.

12. Përbërja për përdorim sipas çdonjë prej pretendimeve 1 deri në 11, ku metoda përfshin administrimin e tipifarnib përpara, gjatë, ose pas rrezatimit.
13. Përbërja për përdorim sipas çdonjë prej pretendimeve 1 deri në 12, ku metoda përfshin më tej administrimin e një sasie efektive terapeutike të një agjenti aktiv i dytë ose një terapi kujdesi mbështetëse.
14. Përbërja për përdorim sipas pretendimit 13, ku agjenti aktiv i dytë i sipërpërmendur është zgjedhur nga grupi i përbërë prej një agjenti kimioterapeutik, një agjent ADN-hipometilizimi, një antitrup terapeutik që lidhet në mënyrë specifike te një antigjen kanceri, një faktor i rritjes hematopoietike, një citokine, një antibiotik, një frenues coks-2, një agjent imunomodulator, një globulinë anti-timocite, një agjent imunosupresiv, dhe një derivative kortikosteroid ose një farmakologjikal ose ku agjenti aktiv i dytë i sipërpërmendur është një antitrup anti-PD l ose një antitrup anti-PDLl.

(11) **9196**
(97) EP2690080 / 26/02/2020
(96) 12382306.4 / 27/07/2012
(22) 24/04/2020
(21) AL/P/ 2020/259
(54) **Fekondues të pasuruar me një tretësirë humiko-enzimatike të pasur në enzima fosfati dhe proces i prodhimit të tyre**
30/06/2020
(30)
(71) Fertiberia, S.A.
Torre Espacio, Planta 48 Paseo de la Castellana 259 D, 28046 Madrid, ES
(72) García Izquierdo, Carlos (CEBAS-CSICCampus Universitario de Espinardo, Murcia, 30100 Murcia); Brañas Lasala, Javier (Torre Espacio, Planta 48,Paseo de la Castellana 259 D, 28046 Madrid); Del Campo Novales, Pablo (Torre Espacio, Planta 48, Paseo de la Castellana 259 D, 28046 Madrid) ;Hernández Fernández, María Teresa (CEBAS-CSICCampus Universitario de Espinardo, Murcia, 30100 Murcia)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)
(57) **1.** Një fekondues i karakterizuar në atë që përfshin një fekondues mineral, organik ose organomineral i cili është integruar në të ose është mbuluar nga të paktën një kompleks humicenzimatik ku enzimat janë kryesisht fosfate të cilët janë bllokuar në mënyrë substanciale te substancat humike të kompleksit, ku proporcioni i kompleksit të sipërpërmendur në fekondues renditet ndërmjet 0.01 dhe 5 % të peshës.
2. Një fekondues në lidhje me pretendimin 1, ku fekonduesi është zgjedhur nga grupi i përbërë prej fekondues të nitrogjenizuar, fekondues të fosfatizuar, fekondues të përbërjes NP, fekondues të përbërjes PK, fekondues të përbërjes NK ose fekondues të përbërjes NPK.
3. Një fekondues në lidhje me pretendimet 1 ose 2, ku fekonduesi është një fekondues i nitrogjenizuar kimikisht me një përmbajtje teoretikale të N ndërmjet 10 dhe 46%.
4. Një fekondues në lidhje me pretendimet 1 ose 2, ku fekonduesi është një fekondues i përbërjes kimike NP me një përmbajtje teoretikale të N ndërmjet 3 dhe 30 % dhe P_2O_5 ndërmjet 5 dhe 48 %.

5. Një fekondues në lidhje me pretendimet 1 ose 2, ku fekonduesi është një fekondues i përbërjes kimike NPK me një përmbajtje teoretikale të N ndërmjet 3 dhe 30 % dhe P_2O_5 ndërmjet 5 dhe 50 % dhe një përmbajtje teoretikale të K_2O ndërmjet 5 dhe 50%.
6. Një fekondues në lidhje me pretendimet 1 ose 2 ku fekonduesi është një fekondues kimik i fosfatizuar me një përmbajtje P_2O_5 ndërmjet 5 dhe 48 %.
7. Një fekondues në lidhje me pretendimet 1 ose 2 ku fekonduesi është një fekondues i përbërjes kimike PK me një përmbajtje teoretikale të P_2O_5 ndërmjet 5 dhe 48 % dhe K_2O ndërmjet 5 dhe 50%.
8. Një fekondues në lidhje me pretendimet 1 ose 2 ku fekonduesi është një fekondues i përbërjes kimike NK me një përmbajtje teoretikale të N ndërmjet 3 dhe 30 % dhe K_2O ndërmjet 5 dhe 50%.
9. Një fekondues në lidhje me ndonjë prej pretendimeve të mëparshme ku komplekset humiko-enzimatike mbulojnë fekonduesin.
10. Procesi i prodhimit të një fekonduesi në lidhje me ndonjë prej pretendimeve të mëparshme 1 deri në 9 **karakterizuar në atë që** një tretësirë e kompleksit humik-enzimatik të fosfatit është pluhurizuar mbi fekonduesin mineral, organik ose organomineral në një pikë ndërmjet përzierjes së lëndës së parë dhe fundit të linjës prodhuese.
11. Procesi i prodhimit në lidhje me pretendimin 10, ku tretësira e komplekseve humiko-enzimatike të fosfateve është pluhurizuar gjithashtu përpara ftohësit ose në pikën e daljes të së njëjtën në seksionin e mbulimit.
12. Procesi i prodhimit të një fekonduesi në lidhje me çdo njërin prej pretendimeve 1 deri në 8 si më sipër ku komplekset humiko-enzimatike janë integruar në fekondues nga inkorporimi i tyre në procesin e grimcimit së bashku me lëndën e parë të fekonduesit.

(11) **9195**
(97) EP3064572 / 12/02/2020
(96) 13896647.8 / 01/11/2013
(22) 28/04/2020
(21) AL/P/ 2020/270
(54) **METODË PËR PRODHIMIN E QELIZËS STAMINALE PLURIPOTENTE TË INDUKTUAR NGA QELIZA STAMINALE MESENKIMALE DHE QELIZA STAMINALE PLURIPOTENTE E INDUKTUAR E PRODHUAR NGA METODA**
30/06/2020
(30)
(71) BBHC Co. Ltd.
72 UN village-gil Yongsan-gu, Seoul 140-884, KR
(72) LEE, Sang Yeon (9-6 Minbaek-gil, Uiwang-siGyeonggi-do 437-081); JUNG, Won Ju (102-901 468 Hangaram-roSongpa-gu, Seoul 138-873); KIM, Ho Bin (1-906 12 Bulgwang-ro 8-gilEunpyeong-gu, Seoul 122-857); OH, Min Sun (115-1008 Sinbanpo Hanshin Apt.37-48 Jamwon-roSeocho-gu, Seoul 137-030) ;LEE, Kye Ho (72 UN village-gilYongsan-gu, Seoul 140-884)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)

(57) **1.** Metodë për prodhimin e një qelize staminale pluripotente të induktuar, metoda që përfshin:

shtimin e një ekstrakti *Ecklonia cava* në një mjedis kulutivimi qelize; dhe dediferencimin e një qelize staminale mesenkimale në një qelizë staminale pluripotente të induktuar në mjedis.

2. Metoda sipas pretendimit 1, ku mjedisi i kultivimit të qelizës përfshin Mjedisin e Shqiponjave të Modifikuar Dulbecco (DMEM), Mjedisin Esencial Minimal (MEM), Mjedisin Themelor të Shqiponjës (BME), RPMI 1640, F-10, F12, DMEM-F12, Mjedisin Esencial α-Minimal (aMEM), Mjedisin Esencial Minimal Glasgow (GMEM), Mjedisin Dulbecco të Modifikuar Iscove (IMDM), Mjedisin MacCoy 5A, Mjedisin e plotë AMINOMAX, Mjedisin e plotë AMINOMAX II, Mjedisin CHANG ose Mjedisin MESENCULT-XF.

3. Metoda sipas çdo njërit prej pretendimeve 1 ose 2, ku ekstrakti *Ecklonia cava* është përfshirë në mjedis në një sasi prej 100 deri në 400mg/mL në lidhje me kompozimin e mjedisit.

4. Metoda sipas çdo njërit prej pretendimeve 1 deri në 3, ku mjedisi përfshin më tej 0.01 deri në 10 v/v% të ujit të energjisë, ku uji i energjisë konsiston në ujë të dejonizuar të pastruar që përmban SiO_2, Al_2O_3, TiO_3, Fe_2O_3, CaO, Na_2O, K_2O, dhe LiO.

(11) **9163**
(97) EP2825727 / 25/03/2020
(96) 12871543.0 / 12/12/2012
(22) 14/05/2020
(21) AL/P/ 2020/307
(54) **MENAXHUES I RRJEDHJES SË LËNGUT**
22/06/2020
(30) 201213446195 13/04/2012 US and 201261611543 P 15/03/2012 US
(71) Osborne, Lawrence
4375 Escondido Canyon Road, Acton, CA 93510, US
(72) Osborne, Lawrence (4375 Escondido Canyon Road, Acton, CA 93510)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)
(57) 1. Një menaxhues i rrjedhjes së lëngut (100) për një pus hidrokarburesh,

menaxhuesi i rrjedhjes së lëngut përmban:

një valvul (108, 300A; 400A) që ka një trup valvule (302; 402) me një portë derdhjeje (328; 428), një transportues (310; 410) të ndodhur brenda trupit të valvulës dhe një sustë (308; 408) për të nxitur tranportuesin në një drejtim brenda trupit të valvules; dhe një pjesë tërheqjeje (354; 411);

valvula është e konfiguruar për t'u përdorur si pjesë e një vargu prodhimi të pusit të hidrokarbureve (200A) përfshi një pompë (104) dhe një varg tubacioni të sipërm (204),

valvula për përdorim është ndërvendosur ndërmjet pompës dhe vargut të tubacionit të sipërm;

në të cilin:

trupi i valvulës përfshin një trup të mesëm (305; 405) me portën e derdhjes, trupi i mesëm ndëvendosur ndërmjet trupave të sipërm (304; 404) dhe të poshtëm (306;406) përgjatë një linje qendrore të valvulave (Y-Y);

një zgavër e trupit të valvulës (369, 371,373; 469, 471, 473) çifton në mënyrë të lëngshme trupat e mesëm, të sipërm dhe të poshtëm;

një hundë e brendshme (330; 430) që shtrihet së brendshmi nga trupi i valvulës, hunda është e vendosur brenda zgavrës së trupit të valvulës;

transportuesi është transportues me diametër substancialisht konstant (310; 410) i ndodhur në zgavrën e trupit të valvulës dhe i lëvizshëm në lidhje me trupin e valvulës përgjatë linjës qendrore, transportuesi ka një mbyllje të fundit të sipërm të transportuesit (314; 414) dhe një diametër të brendshëm të transportuesit (352; 452) përgjatë linjës qendrore;

një xhunto rrëshqitës (335; 435) është vendosur ndërmjet transportuesit dhe një muri (339; 439) të zgavrës së trupit të valvulës, xhuntoja rrëshqitëse e përmendur bllokon rrjedhjen ndërmjet transportuesit dhe murit të përmendur të zgavrës së trupit të valvulës;

susta (308; 408)) nxit mbylljen eë fundit të sipërm të transportuesit të takohet me një ulëse të brendshme të hundës (332; 432) për të formuar një ulëse stacionare (331; 431);

pjesa e tërheqjes (354; 411) takohet me ulësen e transportuesit (326; 481) për të formuar një xhunto të lëvizshme që bllokon rrjedhjen nëpërmjet diametrit të brendshëm të transportuesit, kur forcat e tërheqjes të shkaktuara nga rrjedha e sipërme që veprojnë në pjesën e tërheqjes të përmendur tejkalohen nga forcat e gravitacionit që veprojnë në pjesën e tërheqjes së përmendur;

porta e derdhjes është në komunikim të lëngshëm me zgavrën e trupit të sipërm të valvulës kur xhuntoja stacionare është e hapur dhe zhuntoja e lëvizshme është e mbyllur;

porta e derdhjes është e izoluar në mënyrë të lëngshme prej zgavrës së trupit të sipërm të valvulës kur xhuntoja e lëvizshme është e hapur dhe xhuntoja stacionare është e mbyllur;

valvula kaon një rrjedhje në vargun e tubacionit të sipër ku rrjedhja hyn në valvul nëpërmjet trupit të poshtëm të valvulës; dhe,
valvula devijon një rrjedhje nëpërmjet protës së derdhjes kur rrjedha hyn në valvul nëpërmjet trupit të sipërm të valvulës;
susta ka një fund suste të mbështetur në një xhep të trupit të valvulës (363; 463), fundi i sustës së përmendur rrethon një xhep të paretit (342; 442);
karakterizuar në atë që ana e murit ka një ose më shumë porta (356; 456) për shpëlarjen e xhepit dhe ne paretin formues lateral të përmendur të trupit të (302; 402).

2. Menaxhuesi i rrjedhjes së lëngut sipas pretendimit 1 gjithashtu përmban unaza xhuntoje (520, 530) të mbështetura në brazda (525, 527) formuar në pjesërisht në një fishek xhuntoje (522) të transportuesit.

3. Menaxhuesi i rrjedhjes së lëngut i pretendimit 1 ose pretendimit 2 gjithashtu përmban pjesë të transportuesit (351) për mbajtjen e pjesës së tërheqjes brenda transportuesit.

4. Menaxhuesi i rrjedhjes së lëngut i pretendimit 3 gjithashtu përmban një sipërfaqe të pjesës së tërheqjes (355) për takimin me ulësen e transportuesit.

5. Menaxhuesi i rrjedhjes së lëngut i pretendimit 4 në të cilin pjesa e tërheqjes ka një sipërfaqe të jashtme në formë sferike (355).

6. Menaxhuesi i rrjedhjes së lëngut i çdo pretendimi të mëparshëm që është ndërvendosur në mënyrë të lëngshme ndërmjet vargut të tubacionit (204) për marrjen e daljes së rrjedhjes nga valvula nëpërmjet trupit të sipërm të valvulvës dhe pompës (104), pompa është një pompë elektrike submersibël për furnizimin e rrjedhjes drejt trupit të poshtëm të valvulës.

7. Menaxhuesi i rrjedhjes së lëngut e pretendimit 1 ose pretendimit 2 që gjithashtu përmban:
një ose më shumë dimensione të zgavrave të trupit të valvulvës të mjaftueshme për të lejuar një shufër drejtimi të pompes (250) për t’u shtrirë përgjatë valvulës; dhe,

një element të pjesës së tërheqjes (418) për të angazhuar në mënyrë të rrëshqitshme shufrën e drejtimit të pompës.

8. Menaxhuesi i rrjedhjes së lëngut e pretendimit 7 gjithashtu përmban:
një adaptor të sipërm (403) për kufizimin e udhëtimit të pjesës së tërheqjes; dhe,
në të cilin trupi i sipërm i valvulës përfshin ose është i lidhur me një bllokues (404) për drejtimin e shufrës së drejtimit, bllokuesi ka një gjatësi rreth 4 deri 20 herë gjatësinë e valvulës.

9. Menaxhuesi i rrjedhjes së lëngut e çdo pretendimi 7 ose 8 gjithashtu përmban unazë periferike të pjesës së tërheqjes (413) që bashkon mbylljen e pjesës së tërheqjes për takimin me ulësen e transportuesit.

10. Menaxhuesi i rrjedhjes së lëngut e pretendimit 9 në të cilin unaza e pjesës së tërheqjes është vendosur ndërmjet fundeve të mprehtë të pjesës së tërheqjes (411).

11. Menaxhuesi i rrjedhjes së lëngut sipas çdo pretendimi 7 deri 10 të ndërvendosur në mënyrë të lëngshme ndërmjet vargut të tubacionit (204) për marrjen e largimit të rrjedhjes nga valvula nëpërmjet trupit të sipërm të valvulës dhe pompës, pompa është e një pompë e drejtuar ngan jë shufër për furnizimin e rrjedhjes drejt trupit të poshtëm të valvulës.

12. Menaxhuesi i rrjedhjes së lëngut sipas çdo pretendimi të mëparshëm në të cilin xhepi i trupit të valvulës është një xhep unazor (363).

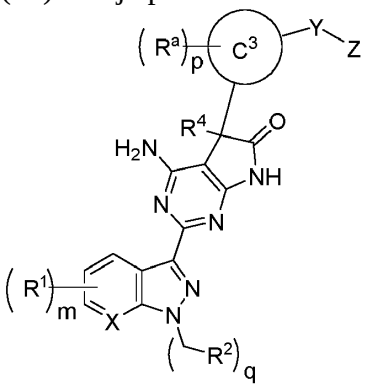
13. Menaxhuesi i rrjedhjes së lëngut sipas çdo pretendimi të mëparshëm në të cilin një ose më shumë porta të përmendura (356, 456) të xhepit të pareteve laterale (342,442) shtrihet ndërmjet xhepit të trupit të valvulës dhe zgavrës së trupit të valvulës (373) të trupit të poshtëm.

14. Menaxhuesi i rrjedhjes së lëngut sipas çdo pretendimi të mëparshëm në të cilin veprimi i sustës (310) shkakton shpëlarjen e xhepit të trupit të valvulës nëpërmjet një ose më shumë portave të përmendura të paretit lateral.

15. Një metodë e menaxhimit të rrjedhjes së lëngut për një pus hidrokarburesh që përmban hapat e:
sigurimin e një menaxhuesi të rrjedhjes në pus (100) sipas pretendimit 1 të ndërvendoesur ndërmjet një tubacioni të sipërm (204) dhe një pompe (104) në pusin e hidrokarbureve;
sigurimin e lëngut që të do të ngrihet nga një rezervuar i pusit;
kalimin e lëngut që hyn në valvul nëpërmjet trupit të poshtëm të valvulës; dhe
devijimin e rrjedhjes nëpërmjet portës së derdhjes kur rrjedhja hyn në valvul nëpërmjet trupit të sipërm të valvulës.

(11) **9164**
(97) EP3394067 / 01/04/2020
(96) 16823455.7 / 20/12/2016
(22) 18/05/2020
(21) AL/P/ 2020/309
(54) **PREJARDHËSIT E 4-AMINO-2-(1H-PIRAZOL[3,4-B] PIRIDIN-3-IL)-6-OKSO-6,7-DIHIDRO-5H-PIRROL[2,3-D]PIRIMIDINËS DHE PREJARDHËSIT PËRKATËS TË (1H-INDAZOL-3-IL) SI MODULATORË TË CGMP PËR MJEKIMIN E SËMUNDJEVE KARDIOVASCULARE**
22/06/2020
(30) PCT/CN2015/098251 22/12/2015 WO
(71) Merck Sharp & Dohme Corp.
126 East Lincoln Avenue, Rahway, NJ 07065-0907, US
(72) RAGHAVAN, Subharekha (2000 Galloping Hill Road, Kenilworth, New Jersey 07033); LI, Guoqing (2000 Galloping Hill Road, Kenilworth, New Jersey 07033); BERGER, Raphelle (126 East Lincoln Avenue, Rahway, New Jersey 07065-0907); CHEN, Yi-Heng (126 East Lincoln Avenue, Rahway, New Jersey 07065-0907); GARFUNKLE, Joie (600 Coporate Drive, Lebanon, New Jersey 08833); LI, Hong (126 East Lincoln Avenue, Rahway, New Jersey 07065-0907); MIAO, Shouwu (295 Prestwick Way, Edison, New Jersey 08820); SMITH, Cameron, J. (9004 Snowford Court, Montgomery Village, Maryland 20886-4017); STELMACH, John (228 Seneca Place, Westfield, New Jersey 07090); WHITEHEAD, Alan (126 East Lincoln Avenue, Rahway, New Jersey 07065-0907); ZHANG, Rui (2000 Galloping Hill Road, Kenilworth, New Jersey 07033); ZHANG, Yong (126 East Lincoln Avenue, Rahway, New Jersey 07065-0907); FU, Jianmin (6 Tai-He Road BDA, Beijing 100176); JI, Gang (6 Tai-He Road BDA, Beijing 100176) ;JIANG, Falong (6 Tai-He Road BDA, beijing 100176)
(74) Fatos DEGA
Rr."Nikolla Tupe", N.2, H.4, A.30, Tiranë, Tiranë

(57) **1.** Një përbërës me Formulë (I)



(I)

ose një kripë farmaceutikisht e pranueshme e tij, ku:

X është C(H) ose N;

çdo R^1 është në mënyrë të pavarur halo, hidroksi, C_1-C_3 alkil, C_3-C_6 cikloalkil ose -O-C_1-C_3 alkil;

R^2 është:

(a.) C_1-C_6 alkil, ku ky C_1-C_6 alkil i R^2 është i pazëvendësuar ose i zëvendësuar me 1 deri 6 pjesë të përzgjedhura në mënyrë të pavarur nga fluor ose -O-C_1-C_3 alkil;

(b.) unazë C^2, ku unaza C^2 është:

(i.) C_3-C_{12} cikloalkil;

(ii.) fenil;

(iii.) një heteroaril monociklik 5- ose 6-anëtarësh që përmban 1 deri 2 heteroatome të përzgjedhur nga N, O, ose S; ose

(iv.) një heterociklil monociklik 5- ose 6-anëtarësh që përmban 1 deri 2 heteroatome të përzgjedhur nga N, O, ose S;

ku unaza C^2 është e pazëvendësuar ose e zëvendësuar me 1 deri 3 pjesë të përzgjedhura në mënyrë të pavarur nga halo, ciano, C_1-C_3 alkil, -O-C_1-C_3 alkil, ose okso;

R^4 është C_1-C_6 alkil, CF_3, ose C_3-C_6 cikloalkil;

unaza C3 është:

(a.) fenil;

(b.) një heteroaril monociklik 5- ose 6-anëtarësh ose një heteroaril biciklik 9- deri 10-anëtarësh që përmban 1 deri 3 heteroatome të përzgjedhur nga N, O, ose S;

(c.) një heterociklil monociklik 5- ose 6-anëtarësh që përmban 1 deri 3 heteroatome të përzgjedhur nga N, O, ose S; ose

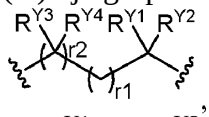
(d.) C_3-C_6 cikloalkil;

çdo R^a përzgjidhet në mënyrë të pavarur nga halo, ciano, C_1-C_3 alkil, -O-C_1-C_3 alkil, okso, ose hidroksi;

Y është:

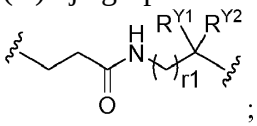
(a.) një lidhje;

(b.) një grup me formulë

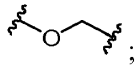


ku R^{Y1} dhe R^{Y2}, janë në mënyrë të pavarur H, C_1-C_3 alkil, hidroksi, fluor, C_1-C_3 hidroksialkil, ose amino; ose alternativisht R^{Y1} dhe R^{Y2}, së bashku me atomin e karbonit tek i cili ata bashkohen formojnë një C_3-C_6 cikloalkil;

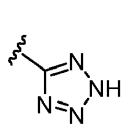
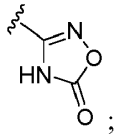
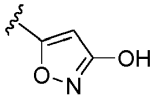
R^{Y3} dhe R^{Y4} janë në mënyrë të pavarur H, C_1-C_3 alkil, hidroksi, fluor, ose C_1-C_3 hidroksialkil; ose alternativisht R^{Y3} dhe R^{Y4}, së bashku me atomin e karbonit tek i cili ata bashkohen formojnë një C_3-C_6 cikloalkil;
(c.) një grup me formulë


;

(d.) unazë AH, ku unaza AH është C_3-C_6 cikloalkil ose fenil, ku unaza AH është e pazëvendësuar ose e zëvendësuar me 1 deri 3 pjesë të përzgjedhura në mënyrë të pavarur nga halo ose C_1-C_3 alkil;
(e.) një grup -CH=CH-; ose
(f.) një grup

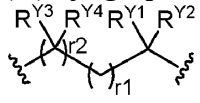

;

Z është:
(a.) $-CO_2H$; (b.) -C(O)N(H)OH; (c.)


; (d.)

; (e.)

;

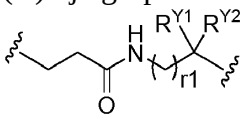
(f.) $-SO_3H$; (g.) $-P(=O)(OH)_2$; ose (h.) $-C(O)N(H)S(O)_2CH_3$;
indeksi m është 0, 1, ose 2;
indeksi p është 0, 1, 2, ose 3;
indeksi q është 0 ose 1;
indeksi r1 është 0, 1, 2, 3, ose 4; dhe
indeksi r2 është 0 ose 1.

2. Përbërësi sipas pretendimit 1 ose një kripë farmaceutikisht e pranueshme e tij, ku:
unaza C^3 është:
(a.) fenil;
(b.) një heteroaril monociklik 5- ose 6-anëtarësh që përmban 1 deri 3 heteroatome të përzgjedhur nga N, O, ose S;
(c.) një heterociklil monociklik 5- ose 6-anëtarësh që përmban 1 deri 3 heteroatome të përzgjedhur nga N, O, ose S; ose
(d.) C_3-C_6 cikloalkil;
çdo R^a përzgjidhet në mënyrë të pavarur nga halo, ciano, C_1-C_3 alkil, -O-C_1-C_3 alkil, ose okso;
Y është:
(a.) një lidhje;
(b.) një grup me formulë


,

ku R^{Y1} dhe R^{Y2} janë në mënyrë të pavarur H, C_1-C_3 alkil, hidroksi, fluor, ose C_1-C_3 hidroksialkil; ose alternativisht R^{Y1} dhe R^{Y2}, së bashku me atomin e karbonit tek i cili ata bashkohen formojnë një C_3-C_6 cikloalkil;
R^{Y3} dhe R^{Y4} janë në mënyrë të pavarur H, C_1-C_3 alkil, hidroksi, fluor, ose C_1-C_3 hidroksialkil; ose alternativisht R^{Y3} dhe R^{Y4}, së bashku me atomin e karbonit tek i cili ata bashkohen formojnë një C_3-C_6 cikloalkil;

(c.) një grup me formulë



; or

(d.) unazë AH, ku unaza AH është C_3-C_6 cikloalkil ose fenil, ku unaza AH është e pazëvendësuar ose e zëvendësuar me 1 deri 3 pjesë të përzgjedhura në mënyrë të pavarur nga halo ose C_1-C_3 alkil.

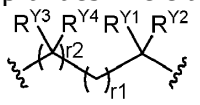
3. Përbërësi sipas pretendimit 2 ose një kripë farmaceutikisht e pranueshme e tij, ku indeksi q është 1, dhe R^2 është C_2-C_3 alkil i cili është i pazëvendësuar ose i zëvendësuar me 1 deri 5 fluor.

4. Përbërësi sipas pretendimit 2 ose një kripë farmaceutikisht e pranueshme e tij, ku indeksi q është 1;
R^2 është unazë C^2;

unaza C^2 është fenil, cikloheksil, adamantil, piridil, ose tetrahidropiranil;
ku unaza C^2 është e pazëvendësuar ose e zëvendësuar me 1 deri 3 fluor ose metil.

5. Përbërësi sipas cilitdo prej pretendimeve 1 deri 4 ose një kripë farmaceutikisht e pranueshme e tij, ku unaza C^3 është fenil, tiazolil, oksazolil, oksadiazolil, triazolil, ose piridil.

6. Përbërësi sipas cilitdo prej pretendimeve 1 deri 5 ose një kripë farmaceutikisht e pranueshme e tij, ku Y është grupi me formulë



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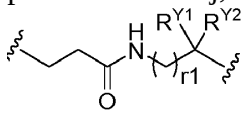
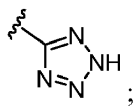
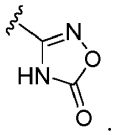
7. Përbërësi sipas cilitdo prej pretendimeve 1 deri 5 ose një kripë farmaceutikisht e pranueshme e tij, ku Y është grupi me formulë



.

8. Përbërësi sipas pretendimit 6 ose një kripë farmaceutikisht e pranueshme e tij, ku indeksi r1 është 1;
indeksi r2 është 0; dhe
R^{Y1} dhe R^{Y2} janë në mënyrë të pavarur H ose C_1-C_3 alkil.

9. Përbërësi sipas cilitdo prej pretendimeve 1 deri 8 ose një kripë farmaceutikisht e pranueshme e tij, ku Z është (a.) $-CO_2H$; (b.) -C(O)N(H)OH;

(c.)  ; or (d.)  .

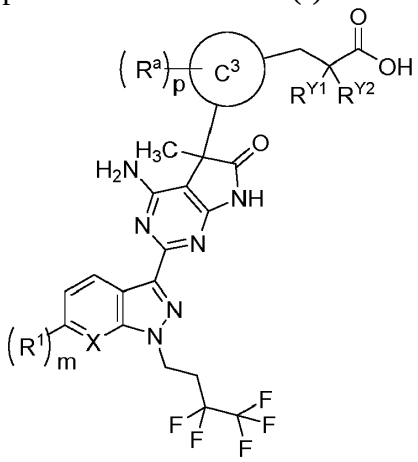
10. Përbërësi sipas pretendimit 9 ose një kripë farmaceutikisht e pranueshme e tij, ku Z është $-CO_2H$.

11. Përbërësi sipas cilitdo prej pretendimeve 1 deri 10, ku X është C(H).

12. Përbërësi sipas cilitdo prej pretendimeve 1 deri 10, ku X është N.

13. Përbërësi sipas cilitdo prej pretendimeve 1 deri 12, ku R^4 është metil ose ciklopropil.

14. Përbërësi sipas pretendimit 2 ose një kripë farmaceutikisht e pranueshme e tij, ku përbërësi me Formulë (I) ka Formulën (IA)

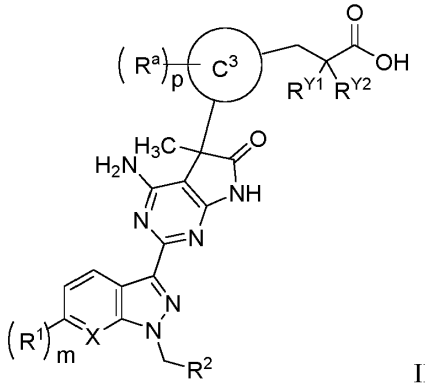


IA

ku

X është C(H) ose N;
R^1 është metil ose halo;
C^3 është fenil ose tiazolil;
R^a është metil, ciano, ose halo;
R^{Y1} dhe R^{Y2} janë në mënyrë të pavarur H ose metil;
indeksi m është 0 ose 1; dhe
indeksi p është 0 ose 1.

15. Përbërësi sipas pretendimit 2 ose një kripë farmaceutikisht e pranueshme e tij, ku përbërësi me Formulë (I) ka Formulën (IB)



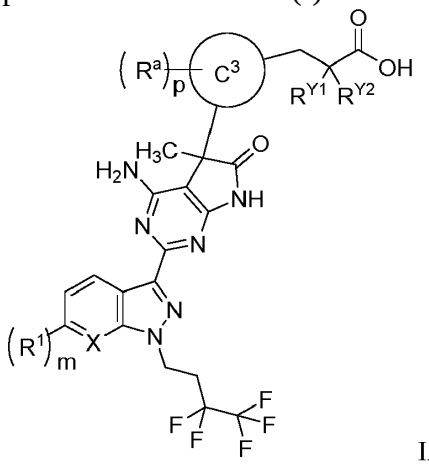
IB

ku

X është C(H) ose N;
R^1 është metil ose halo;
R^2 është unazë C^2, ku unaza C^2 është:
(i.) C_3-C_{12} cikloalkil;
(ii.) fenil;

(iii.) një heteroaril monociklik 5- ose 6-anëtarësh që përmban 1 deri 2 heteroatome të përzgjedhur nga N, O, ose S; ose
(iv.) një heterociklil monociklik 5- ose 6-anëtarësh që përmban 1 deri 2 heteroatome të përzgjedhur nga N, O, ose S;
ku unaza C^2 është e pazëvendësuar ose e zëvendësuar me 1 deri 3 pjesë të përzgjedhura në mënyrë të pavarur nga halo, ciano, C_1-C_3 alkil, -O-C_1-C_3 alkil, or okso C^3 is fenil, tiazolil, ose oksazolil;
R^a është metil, ciano, ose halo;
R^{Y1} dhe R^{Y2} janë në mënyrë të pavarur H ose metil;
indeksi m është 0 ose 1; dhe
indeksi p është 0 ose 1.

16. Përbërësi sipas pretendimit 1 ose një kripë farmaceutikisht e pranueshme e tij, ku përbërësi me Formulë (I) ka Formulën (IA)



IA

ku

X është C(H) ose N;
R^1 është halo;
C^3 është fenil, tiazolil, oksazolil, ose benzotiazolil;
R^a është metil, ciano, ose halo;
R^{Y1} dhe R^{Y2} janë në mënyrë të pavarur H, metil, ose amino;
indeksi m është 0 ose 1; dhe
indeksi p është 0 ose 1.

17. Përbërësi sipas pretendimit 1 ose një kripë farmaceutikisht e pranueshme e tij, ku përbërësi është:

3-(2-{4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5H-pirrol[2,3-d]pirimidin-5-il}oksazol-4-il)-2,2-dimetilpropanoik acid;
3-(2-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}oksazol-4-il)-2,2-dimetilpropanoik acid;
3-(2-{4-amino-2-[6-klor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il)oksazol-4-il}-2,2-dimetilpropanoik acid;

3-(4-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-2-bromofenil)propanoik acid;
3-{4-[4-amino-2-{6-klor-1-[(4-metilcikloheksil)metil]-1*H*-indazol-3-il}-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il]fenil}propanoik acid;
3-{4-[4-amino-2-{6-klor-1-[tetrahidro-2*H*-piran-2-ilmetil]-1*H*-indazol-3-il}-5-metil-6-okso-6,7-dihidro-5H-pirrol[2,3-*d*]pirimidin-5-il]fenil}propanoik acid;
3-(4-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(6-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}piridin-3-il)-2,2-dimetilpropanoik acid;
3-(4-{4-amino-5-metil-6-okso-2-(1-(3,3,4,4,4-pentafluorbutil)-2,3-dihidro-1*H*-pirazol[3,4-*b*]piridin-3-il)-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)-2,2-dimetilpropanoik acid;
3-(4-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(3-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)-2,2-dimetilpropanoik acid;
3-(4-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1*H*-1,2,3-triazol-1-il)propanoik acid;
3-(4-{4-amino-2-(1-butil-6-klor-1*H*-pirazol[3,4-*b*]piridin-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-(1-butil-1*H*-pirazol[3,4-*b*]piridin-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-5-metil-6-okso-2-[1-(4,4,4-trifluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-5-metil-6-okso-2-[1-(4,4,4-trifluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)-2,2-dimetilpropanoik acid;
3-(4-{4-amino-5-metil-6-okso-2-[1-(4,4,4-trifluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}fenil)-2-metilpropanoik acid;
3-(4-{4-amino-2-[5-fluor-1-(4,4,4-trifluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-[6-klor-1-(4,4,4-trifluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-5-metil-2-[6-metil-1-(4,4,4-trifluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(3-(4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-[5-fluor-1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;

3-(3-{4-amino-2-[5-fluor-1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-[1-(2,3-difluor-4-metilbenzil)-6-metil-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}benzoik acid;
3-(3-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)-2,2-dimetilpropanoik acid;
(4-(4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1*H*-1,2,3-triazol-1-il)acid acetic;
3-(4-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5H-pirrol[2,3-*d*]pirimidin-5-il}-1*H*-1,2,3-triazol-1-il)propanoik acid;
2-(4-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}-1*H*-1,2,3-triazol-1-il)-2-metilpropanoik acid;
3-(4-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1*H*-1,2,3-triazol-1-il)-2,2-dimetilpropanoik acid;
1-[(4-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1*H*-1,2,3-triazol-1-il)metil] acid ciklopropankarboksilic;
3-(4-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)-2,2-dimetilpropanoik acid;
3-(4-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)-2-metilpropanoik acid;
2-{4-[4-amino-2-(1-butil-6-klor-1*H*-indazol-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il]-1*H*-1,2,3-triazol-1-il}acid acetic;
3-{4-[4-amino-2-(1-butil-6-klor-1*H*-indazol-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il]-1*H*-1,2,3-triazol-1-il}propanoik acid;
3-(4-[4-amino-2-(1-butil-6-klor-1*H*-indazol-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il]fenil}-2,2-dimetilpropanoik acid;
3-{4-[4-amino-2-(1-butil-6-klor-1*H*-indazol-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il]fenil}propanoik acid;
3-(3-{4-amino-2-[6-klor-1-(2-methoksietil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)-2,2-dimetilpropanoik acid;
3-(4-{4-amino-2-[6-klor-1-(2-methoksietil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-[6-klor-1-(4,4,4-trifluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-[6-klor-1-(4,4,4-trifluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5H-pirrol[2,3-d]pirimidin-5-il}fenil)-2,2-dimetilpropanoik acid;
3-{4-[4-amino-2-(6-klor-1-pentil-1*H*-indazol-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il]fenil}propanoik acid;

3-(4-{4-amino-2-[6-klor-1-(cikloheksilmetil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-{4-[4-amino-2-(6-klor-1-heksil-1*H*-indazol-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il]fenil}propanoik acid;
3-(4-{4-amino-2-[6-fluor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5H-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-[6-klor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}fenil)propanoik acid;
3-(3-{4-amino-2-(6-klor-1-(2-fluorbenzil)-1*H*-indazol-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}fenil)propanoik acid;
4-(2-{4-amino-2-(6-klor-1-(2-fluorbenzil)-1*H*-indazol-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}tiazol-4-il)acid butanoik;
3-(2-{4-amino-2-(6-klor-1-(2-fluorbenzil)-1*H*-indazol-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}oksazol-4-il)propanoik acid;
2-(2-{ 4-amino-2-(6-klor-1-(2-fluorbenzil)-1*H*-indazol-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}oksazol-4-il)acid acetic;
3-(4- {4-amino-2-[6-klor-1-(4,4-dimetilpentil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(3-{4-amino-2-[1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(2-(4-amino-2-[1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}oksazol-4-il)propanoik acid;
4-(2-{4-amino-2-[1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}tiazol-4-il)acid butanoik;
3-(2-{4-amino-2-[1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}oksazol-4-il)-2,2-dimetilpropanoik acid;
3-(4-[4-amino-2-{6-klor-1-[(3-fluorpiridin-2-il)metil]-1*H*-indazol-3-il}-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il]fenil)propanoik acid;
3-(4-[4-amino-2-{6-klor-1-[(4,4-difluorcikloheksil)metil]-1*H*-indazol-3-il}-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il]fenil)propanoik acid;
3-(4-{4-amino-2-[1-(2-fluorbenzil)-6-metil-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-[6-fluor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}fenil)propanoik acid;
3-(3-{4-amino-2-[6-fluor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}fenil)propanoik acid;
3-(2-{4-amino-2-[6-fluor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)-2,2-dimetilpropanoik acid;
3-(2-{4-amino-2-[6-fluor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}oksazol-4-il)-2,2-dimetilpropanoik acid;
3-(4- {4-amino-2-[6-klor-1-(2,6-difluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-[6-klor-1-(4-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-[6-klor-1-(3-metilbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}fenil)propanoik acid;

3-(4-{4-amino-2-[6-klor-1-(4-metilbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-[6-klor-1-(2-metilbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{4-amino-2-[6-klor-1-(3-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-{2-[1-(adamantan-1-ilmetil)-6-klor-1*H*-indazol-3-il]-4-amino-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-(4-amino-2-[5-fluor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5H-pirrol[2,3-d]pirimidin-5-il}fenil)propanoik acid;
3-(2-{4-amino-2-[5-fluor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}oksazol-4-il)-2,2-dimetilpropanoik acid;
3-(4-{4-amino-2-[5-klor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5H-pirrol[2,3-d]pirimidin-5-il}fenil)propanoik acid;
3-(2-{4-amino-2-[5-klor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}oksazol-4-il)-2,2-dimetilpropanoik acid;
3-(2-{4-amino-2-[1-(2,3-difluor-4-metilbenzil)-6-metil-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}tiazol-4-il)-2,2-dimetilpropanoik acid;
3-(4-{4-amino-2-[1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(2-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)-2,2-dimetilpropanoik acid;
(2-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-b]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)acid acetic;
3-(2-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)-3-metil acid butanoik;
2-(2-{-4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)acid ciklopropankarboksilic;
1-[(2-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)metil]acid ciklopropankarboksilic;
3-(2-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)propanoik acid;
(2-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-4-metil-1,3-tiazol-5-il)acid acetic;
3-(2-(4-amino-2-[5-fluor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazo1-4-il)-2,2-dimetilpropanoik acid;
3-(2-{4-amino-2-[5-fluor-1-(3,3,3-trifluorpropil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)-2,2-dimetilpropanoik acid;

3-(2-[4-amino-2-(1-butil-1*H*-pirazol[3,4-*b*]piridin-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il]-1,3-tiazol-4-il}-2,2-dimetilpropanoik acid;
3-(2-{4-amino-5-metil-6-okso-2-[1-(4,4,4-trifluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)-2,2-dimetilpropanoik acid;
3-(2-{4-amino-5-metil-6-okso-2-[1-(4,4,4-trifluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)propanoik acid;
3-(2-{4-amino-2-[6-klor-1-(4,4,4-trifluorbutil)-1*H*-pirazol[3,4-b]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)-2,2-dimetilpropanoik acid;
3-(2-(4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)-2,2-dimetilpropanoik acid;
3-(2-4{-amino-2-[5-fluor-1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)-2,2-dimetilpropanoik acid;
3-(2-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazo1-4-il)-2,2-dimetilpropanoik acid;
3-(2-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)benzoik acid;
4-(2-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-5-metil-1,3-tiazol-4-il)benzoik acid;
3-(2-{4-amino-2-[6-klor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)-2,2-dimetilpropanoik acid;
3-(2-{4-amino-5-ciklopropil-2-[5-fluor-1-(4,4,4-trifluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6-okso-6,7-dihidro-5H-pirrol[2,3-d]pirimidin-5-il}tiazol-4-il)-2,2-dimetilpropanoik acid;
3-(2-{4-ammo-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)-N-hidroksi-2,2-dimetilpropanamid;
[5-(4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-2-okso-1,3,4-oksadiazol-3(2*H*)-il]acid acetic;
2-[5-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-2-okso-1,3,4-oksadiazo1-3(2*H*)-il]-2-metilpropanoik acid;
(3-(4- (4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5H-pirrol[2,3-d]pirimidin-5-il}fenil)propanoil)glicin;
2-(3-(4-{4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanamido)-2-metilpropanoik acid;
(3-(4-(4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5H-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoil)-D-alanin;

(3-(4-(4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5H-pirrol[2,3-d]pirimidin-5-il}fenil)propanoil)-L-alanin;
(2*R*)-2-(3-(4-{4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanamido)acid butanoik;
(2*S*)-2-(3-(4-{4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanamido)acid butanoik;
(3-(4-{4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoil)-D-serin;
(3-(4-{4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-d]pirimidin-5-il}fenil)propanoil)-D-treonin;
N-((2*H*-tetrazol-5-il)metil)-3-(4-{4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanamid;
3-(4-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-2*H*-1,2,3-triazol-2-il)propanoik acid;
3-(4-{4-amino-2-[6-klor-1-(2-fluorbenzil)-5-hidroksi-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;
3-(4-[4-amino-2-(1-butil-6-metil-1*H*-pirazol[3,4-*b*]piridin-3-il)-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il]fenil}propanoik acid;
4-amino-2-[6-klor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-5-{4-[2-(2*H*-tetrazol-5-il)etil]fenil}-5,7-dihidro-6*H*-pirrol[2,3-*d*]pirimidin-6-një;
4-(4-{4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)acid butanoik;
(4-{4-amino-2-[1-(2-fluorbenzil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)acid acetic;
4-(4-{4-amino-2-[6-klor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)acid butanoik;
4-(4-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il)-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)acid butanoik;
2-(4-{4-amino-2-[6-klor-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)acid acetic;
2-(4-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)acid acetic;
3-(6-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}piridin-3-il)propanoik acid;
3-(4-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-2-cianofenil)propanoik acid;
3-(4-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-2-metilfenil)propanoik acid;
ose
3-(4-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-2-hidroksifenil)propanoik acid.

18. Përbërësi sipas pretendimit 1 ose një kripë farmaceutikisht e pranueshme e tij, ku përbërësi është:

3-(2- {4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}oksazol-4-il)-2,2-dimetilpropanoik acid;

3-(4-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)propanoik acid;

3-(3-{4-amino-2-[6-klor-1-(3,3,4,4,4-pentafluorbutil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}fenil)-2,2-dimetilpropanoik acid;

3-(2-{4-amino-2-[6-1-(2-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)-2,2-dimetilpropanoik acid;

3-(2-{4-amino-5-metil-6-okso-2-[1-(3,3,4,4,4-pentafluorbutil)-1*H*-pirazol[3,4-*b*]piridin-3-il]-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-tiazol-4-il)-2,2-dimetilpropanoik acid;

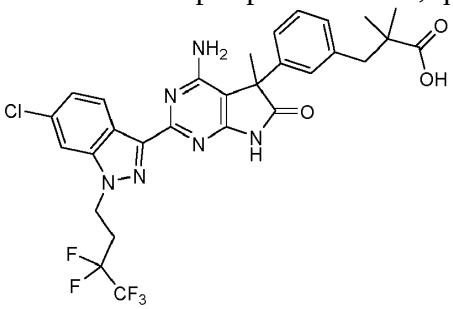
3-{2-[4-amino-2-{6-klor-1-[(3-fluorpiridin-2-il)metil]-1*H*-indazol-3-il}-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il]-1,3-oksazol-4-il}-2,2-dimetilpropanoik acid;

3-(2-(4-amino-2-[6-klor-1-(3-fluorbenzil)-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-5-metil-1,3-oksazol-4-il)-2,2-dimetilpropanoik acid;

3-(2-{4-amino-2-[1-(2,3-difluorbenzil)-6-fluor-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-oksazol-4-il)-2,2-dimetilpropanoik acid; ose

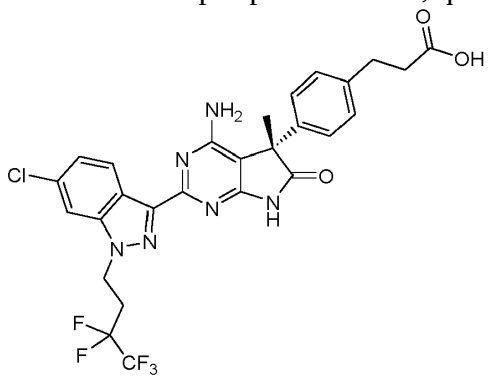
3-(2-{4-amino-2-[1-(cikloheksilmetil)-6-fluor-1*H*-indazol-3-il]-5-metil-6-okso-6,7-dihidro-5*H*-pirrol[2,3-*d*]pirimidin-5-il}-1,3-oksazol-4-il)-2,2-dimetilpropanoik acid.

19. Përbërësi sipas pretendimit 1, që është



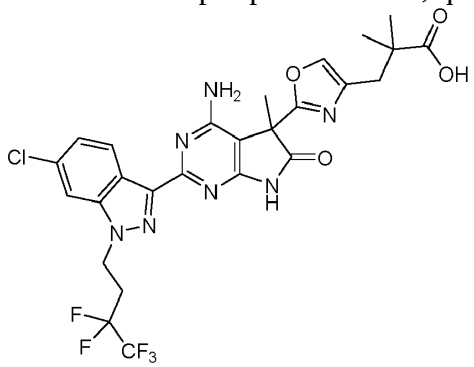
ose një kripë farmaceutikisht e pranueshme e tij.

20. Përbërësi sipas pretendimit 1, që është



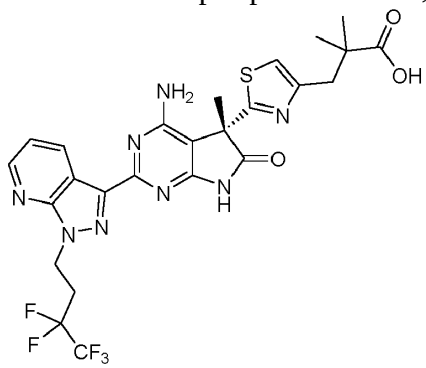
ose një kripë farmaceutikisht e pranueshme e tij.

21. Përbërësi sipas pretendimit 1, që është



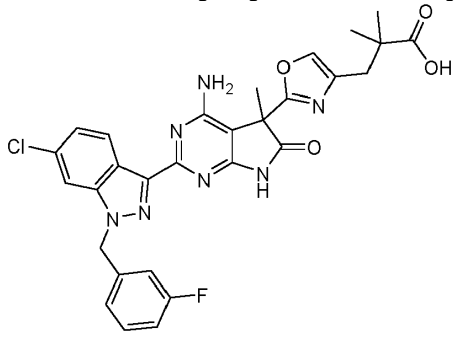
ose një kripë farmaceutikisht e pranueshme e tij.

22. Përbërësi sipas pretendimit 1, që është



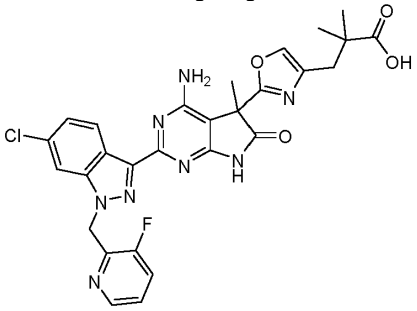
ose një kripë farmaceutikisht e pranueshme e tij.

23. Përbërësi sipas pretendimit 1, që është



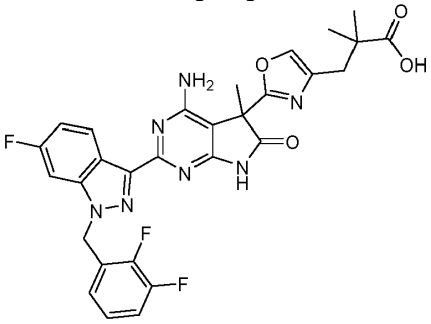
ose një kripë farmaceutikisht e pranueshme e tij.

24. Përbërësi sipas pretendimit 1, që është



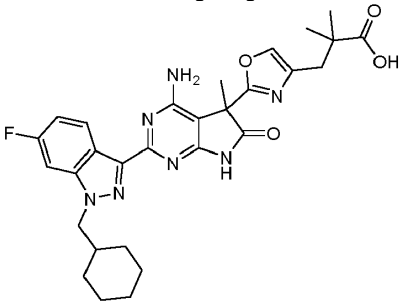
ose një kripë farmaceutikisht e pranueshme e tij.

25. Përbërësi sipas pretendimit 1, që është



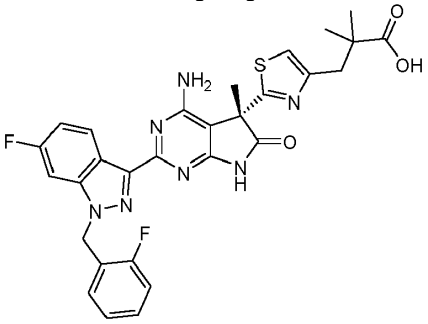
ose një kripë farmaceutikisht e pranueshme e tij.

26. Përbërësi sipas pretendimit 1, që është



ose një kripë farmaceutikisht e pranueshme e tij.

27. Përbërësi sipas pretendimit 1, që është



ose një kripë farmaceutikisht e pranueshme e tij.

28. Një përbërje farmaceutike, që përmban përbërësin sipas cilitdo prej pretendimeve 1 deri 27 ose një kripë farmaceutikisht e pranueshme të tij, dhe një transportues (bartës) farmaceutikisht të pranueshëm.

29. Përbërja farmaceutike sipas pretendimit 28, që përmban edhe një ose më shumë agjentë aktivë shtesë të përzgjedhur nga një frenues i enzimës konvertuese të angiotensinës, një antagonist i receptorit të angiotensinës II, një frenues neutral i endopeptidazës, një antagonist aldosteron, një frenues i reninës, një antagonist i receptorit endotelin, një frenues i sintazës aldosterone, një frenues i fosfodiesterazës-5, një vazodilatator, një bllokues i kanalit të kalciumit, një aktivizues i kanalit të kaliumit, një diuretik, një simpatolitik, një ilaç bllokues beta-adrenergjik, një ilaç bllokues alfa-adrenergjik, një agonist alfa- adrenergjik qendror, një vazodilatator periferik, një agjent ulës i lipideve ose një agjent ndryshimesh metabolike.

30. Përbërësi sipas cilitdo prej pretendimeve 1 deri 27, ose një kripë farmaceutikisht e pranueshme e tij, për përdorim në mjekimin e një kondicioni të përzgjedhur nga sëmundja kardiovaskulare, mosfunksionimi endotelial, mosfunksionimi diastolik, ateroskleroza, hipertensioni, infarkti, hipertensioni pulmonar (grupet I, II, III, IV sipas WHO), angina pektoris, tromboza, restenoza, infarkti miokardial, goditja (stroke), insufiçenca kardiake, fibroza, hipertonia pulmonare, mosfunksionimi erektil, azma, sindromi i distresit akut respirator (ARDS), sëmundja kronike e veshkës, fibroza cistike, anemia qelizore drapore, skleroderma, sindromi i Raynaud-it, diabeti, retinopatia diabetike, cirrhoza e mëlçisë, sëmundja pulmonare obstruktive kronike (COPD), dëmtimi akut i mushkërive, fibroza pulmonare, ose sëmundja intersticiale e mushkërive.

31. Përbërësi sipas cilitdo prej pretendimeve 1 deri 27, ose një kripë farmaceutikisht e pranueshme e tij, për përdorim në mjekimin e hipertensionit pulmonar.

32. Përdorimi sipas pretendimit 31, ku kondicioni është hipertensioni arterial pulmonar.

33. Përdorimi sipas pretendimit 31, ku kondicioni është hipertensioni pulmonar Grupi III WHO.

34. Përdorimi sipas pretendimit 31, ku kondicioni është hipertensioni pulmonar Grupi IV WHO.

(11) **9184**
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(96) 13783852.0 / 28/10/2013
(22) 27/05/2020
(21) AL/P/ 2020/339
(54) **NXITËSI PR13.5 PËR PËRGJIGJET E FORTA TË QELIZËS-T DHE ANTITRUPIT**
30/06/2020
(30) 201261719429 P 28/10/2012 US

(71) Bavarian Nordic A/S
Hejreskovvej 10A, 3490 Kvistgaard, DK
(72) STEIGERWALD, Robin (Klenzestrasse 97, 80469 München) ;BRINKMANN, Kay (Gebsattelstrasse 10, 81541 München)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)

(57) **1.** Një virus rekombinant i modifikuar i Vaksinës Ankara (MVA) për përdorim në induktimin e një përgjigje të fortë të qelizës CD8 T kundër një neoantigjeni në një njeri që përfshin administrimin e një ose më shumë administratorëve të virusit rekombinant të modifikuar të Vaksinës Ankara (MVA) të sipërpërmendur te njeriu;
ku rekombinanti MVA përfshin një nxitës Pr13.5 të lidhur në mënyrë të operueshme te një sekuencë nukleotidi që kodon neoantigjenin,
ku nxitësi Pr13.5 përfshin të paktën 1 kopje të një sekuence acidi nukleik prej të paktën 40 bazash që kanë të paktën 95% ngjashmëri me SEQ ID NO:1, dhe të paktën 1 kopje të një sekuence nukleotide të dytë prej të paktën 31 nukleotidesh që ka të paktën 95% ngjashmëri me SEQ ID NO:1, dhe
ku nxitësi i sipërpërmendur gjeneron të paktën 1.5-fish më shumë neoantigjen-specifik të qelizës CD8 T më pas ato janë gjeneruar me një ndërtim MVA korrespondues në të cilën nxitësi është zëvendësuar nga nxitësi PrS i përcaktuar nga SEQ ID NO:6 pas një imunizimi të vetëm.
2. MVA për përdorim e pretendimit 1, ku nxitësi Pr13.5 përfshin të paktën 2 kopje të një sekuence acidi nukleik prej të paktën 40 bazave që kanë të paktën 98% ngjashmëri me SEQ ID NO:1.
3. MVA për përdorim e pretendimeve 1-2, ku nxitësi Pr13.5 përfshin të paktën 2 kopje të një sekuence acidi nukleik prej të paktën 40 bazave që kanë 100% ngjashmëri me SEQ ID NO:1.
4. MVA për përdorim e pretendimit 1, ku nxitësi Pr13.5 përfshin 2 kopje të një sekuence prej të paktën 40 nukleotiesh që ka 100% ngjashmëri me SEQ ID NO:1.
5. MVA për përdorim e pretendimit 1, ku nxitësi Pr13.5 përfshin nukleotidet 15878-15755 në Figurën 1.
6. Një virus rekombinant i modifikuar i Vaksinës Ankara (MVA) që përfshin një nxitës Pr13.5 të lidhur në mënyrë të operueshme te një sekuencë nukleotidi që kodon një neoantigjen,
ku nxitësi Pr13.5 përfshin të paktën 1 kopje të një sekuence acidi nukleik prej të paktën 40 bazash që kanë të paktën 95% ngjashmëri me SEQ ID NO:1, dhe të paktën 1 kopje të një sekuence nukleotide të dytë prej të paktën 31 nukleotidesh që ka të paktën 95% ngjashmëri me SEQ ID NO:1, dhe
ku nxitësi i sipërpërmendur gjeneron të paktën 1.5-fish më shumë neoantigjen-specifik të qelizës CD8 T më pas ato janë gjeneruar me një ndërtim MVA korrespondues në të cilin nxitësi është zëvendësuar nga nxitësi PrS i përcaktuar nga SEQ ID NO:6 pas një imunizimi të vetëm.
7. Rekombinanti MVA i pretendimit 6, ku nxitësi Pr13.5 përfshin të paktën 2 kopje të një sekuence acidi nukleik prej të paktën 40 bazash që kanë të paktën 98% ngjashmëri me SEQ ID NO:1.
8. Rekombinanti MVA i pretendimeve 6-7, ku nxitësi Pr13.5 përfshin të paktën 2 kopje të një sekuence acidi nukleik prej të paktën 40 bazash që kanë 100% ngjashmëri me SEQ ID NO:1.

9. Rekombinanti MVA i pretendimit 6, ku nxitësi Pr13.5 përfshin 2 kopje të një sekuence nukleotide prej të paktën 40 nukleotidesh që ka 100% ngjashmëri me SEQ ID NO:1.
10. Rekombinanti MVA i pretendimit 6, ku nxitësi Pr13.5 përfshin nucleotidet 15878-15755 në Figurën 1.

(11) **9166**
(97) EP2745839 / 11/03/2020
(96) 13198744.8 / 20/12/2013
(22) 01/06/2020
(21) AL/P/ 2020/346
(54) **PERBERJE FARMACEUTIKE NE FORME PLUHURI NGA GOJA QE PERMBAN FRAKSION FLAVONID DHE MPIKES KSANTAN**
22/06/2020
(30) 1203579 21/12/2012 FR
(71) Les Laboratoires Servier
35, rue de Verdun, 92284 Suresnes Cedex, FR
(72) Pean, Jean-Manuel (12, rue Adolphe Crespin, 45000 Orleans) ;Marsas, Stéphanie (6, allée des Chartreux, 45430 Checy)
(74) Vladimir NIKA
Bul " Bajram CURRI", Pall.2, Shk.3, Ap.4, Tiranë
(57) 1. Përbërje farmaceutike në formën pluhuri në qese që pihet nga goja, që përmban si përbërës aktiv një fraksion flavonoid të pastruar të mikronizuar, që përmban nga 87% në 93% diosminë, nga 2.5% në 5.0% hesperidinë, nga 0.9% në 2.8% izorhoifolinë, nga 0.9 % deri në 2.8% linarinë dhe më pak se 1% diosmetinë, madhësia e grimcave e së cilës është rreptësisht më e vogël se 5 mm, dhe mpikës ksantan (xanthan gum) si ekcipient.
2. Përbërje farmaceutike sipas pretendimit 1, ku sasia e fraksionit flavonoid është midis 7% m/m dhe 20% m/m.
3. Përbërja farmaceutike sipas pretendimit 1, ku përqëndrimi i mpikësit ksantan është 0,5% m/v.
4. Përbërja farmaceutike sipas pretendimit 1, ku sasia e mpikësit ksantan është midis 0.30% m/m dhe 0.60% m/m.
5. Përbërja farmaceutike sipas pretendimit 1, që përmban një ose më shumë ekcipientë farmaceutikisht të pranueshëm të zgjedhur nga ëmbëlsues, aromatizues, konservues ose korrigjues të pH-it.
6. Përbërja farmaceutike sipas secilit prej pretendimeve 1 deri në 5 për përdorim në trajtimin e insuficencës venoze.
The present invention relates to a high-dose drinkable oral suspension in a sachet, comprising as active ingredient a micronised purified flavonoid fraction comprising from 87% to 93% diosmin, from 2.5% to 5.0% hesperidin, from 0.9% to 2.8% isorhoifolin, from 0.9% to 2.8% linarin and less than 1% diosmetin, the particle size of which is strictly less than 5 μm, and xanthan gum as excipient, and to the use thereof in the treatment of venous insufficiency.

The flavonoid fraction is derived from a Rutaceae extract. The micronised purified flavonoid fraction used in the invention contains from 87% to 93% of diosmin and other flavonoids concomitantly. These other flavonoids in an amount of approximately 10% comprise from 2.5% to 5.0% hesperidin, from 0.9% to 2.8% isorhoifolin, from 0.9% to 2.8% linarin and less than 1% diosmetin. The particle size of the micronised flavonoid fraction is strictly less than 5 μm, or even less than 4 μm, 3 μm, 2 μm and even 1.6 μm.
The flavonoid fraction according to the invention is administered in daily doses ranging from 1000 mg to 3000 mg in order to treat the symptoms of chronic venous insufficiency of the lower limbs. Owing to significant metabolisation of the flavonoid fraction in the gastrointestinal tract, this active ingredient must be given in a high dose each time it is administered. Moreover, treatments based on flavonoid fraction are long-term treatments which must be easy to take in order to encourage compliance with the treatment on the part of patients. Consequently, it is preferable to develop galenic forms which can be taken easily by elderly persons and without the addition of water for patients who consume them away from the home.
The therapeutic use of the flavonoid fraction extracted from Rutaceae according to the invention has been described in patent specification EP 0 711 560. That patent specification describes a composition of effervescent granules containing a high dose of 1000 mg of flavonoid fraction. However, these effervescent granules are to be dispersed in water prior to consumption.

Drinkable solutions containing flavonoids and xanthan gum have been described in patent specification US 5,240,732. That patent specification discloses a solution in which the flavonoids have been dissolved in an alcohol, in contrast to the present invention, which relates to an aqueous suspension in which the flavonoid fraction is homogeneously dispersed.
Drinkable suspensions containing polyphenols and stabilisers for the dispersion have been described in patent application US 2012/0070475. The suspensions according to application US 2012/0070475 contain a low dose of quercetin and use only gellan gum as stabiliser for the dispersion.
Finally, document FR 6967M discloses a drinkable suspension of diosmin comprising 0.5% tragacanth, which suspension must be stirred before use.

The present invention relates to a pharmaceutical composition in the form of a high-dose drinkable oral suspension in a sachet, comprising as active ingredient a micronised purified flavonoid fraction comprising from 87% to 93% diosmin, from 2.5% to 5.0% hesperidin, from 0.9% to 2.8% isorhoifolin, from 0.9% to 2.8% linarin and less than 1% diosmetin, the particle size of which is strictly less than 5 μm, and comprising xanthan gum as excipient.

The percentage of flavonoid fraction in the pharmaceutical composition is between 7% m/m and 20% m/m.
The quantity of flavonoid fraction in the pharmaceutical composition is between 1000 mg and 3000 mg, including 2000 mg, 1500 mg, 2500 mg.
The oral suspension containing a high dose of active ingredient of the present invention must have a viscosity which is suitable on the one hand for allowing the suspension to flow in the manufacturing machines and out of the sachet on

administration and on the other hand for allowing the flavonoid fraction not to settle in the sachet and to be stable over time.
In order to comply with all these functional properties, the oral suspension must have specific rheological properties.
The viscosity of the suspension must not be dependent on the time during which it is subjected to shear forces. It is necessary that the suspension regains its initial viscosity after application of a stress, whatever the duration of its application. The viscosity of the suspension must therefore be reversible over the shear range 0.01 and 1000 s^{-1}. This rheological property, i.e. the suspension regains its viscosity entirely during rest times, is essential in the steps of pumping, pre-packaging through transport and storage to use by the end consumer of the oral suspension in a sachet.
Moreover, it appears necessary for the viscosity of the suspension to be independent of the temperature over the range 15°C-60°C, the *ad hoc* temperature range at the end of production and during the steps of transport, processing and packaging of the final product.
Viscosity measurements are performed on an Anton Paar rheometer or on a Brookfield rheometer. The results obtained with these two types of rheometer are wholly comparable.
The rheological properties and the stability required by the oral suspension according to the invention are obtained by thickening the pharmaceutical composition. Thickening of the pharmaceutical composition is obtained by the use of a thickening agent.

The thickening agent according to the invention is xanthan gum. Xanthan gum is a high molecular weight anionic polysaccharide composed of D-glucoses and D-mannoses as dominant hexoses. In solution, the xanthan gum molecules combine to form a network of entangled molecules.

The concentration of xanthan gum in the pharmaceutical composition according to the invention is between 0.45% m/v and 0.55% m/v. The concentration of xanthan gum may be 0.50% m/v, 0.47% m/v, 0.53% m/v.

The quantity of xanthan gum in the pharmaceutical composition is between 0.30% m/m and 0.60% m/m.

The pharmaceutical composition in the form of an oral suspension having a high content of flavonoid fraction according to the invention is free of surfactants. Surfactants are generally used in oral suspensions in order to improve the dispersion and wettability of the particles in suspension.

In addition to the flavonoid fraction and the xanthan gum, the pharmaceutical composition according to the invention comprises one or more pharmaceutically acceptable excipients such as preservatives, flavourings, sweeteners or pH correctors.

There may be mentioned as examples of excipients:

for the preservatives: sodium benzoate, benzalkonium chloride, methyl parahydroxybenzoate, propyl parahydroxybenzoate;

for the flavourings: orange flavouring, lemon flavouring, soft caramel flavouring, vanilla/lemon flavouring;
for the sweeteners: maltitol, sorbitol, aspartame, xylitol, potassium acesulfame, sodium saccharin;
for the pH correctors: citric acid, ascorbic acid, tartaric acid.

The pharmaceutical composition according to the invention is in the form of a drinkable suspension in a sachet. The sachet or stick preferably has a unit volume of 10 ml containing the daily dose of flavonoid fraction. For better compliance by the patient, the unit volume of the sachet must not be too great, for example 10 ml, 12 ml, 15 ml, 17 ml, not more than 20 ml.
The present invention relates also to the use of the pharmaceutical compositions according to the invention in the treatment of venous disease, more particularly of venous insufficiency. These pharmaceutical compositions are used as veinotonic and vasoprotective agents.

The examples below illustrate the invention in a non-limiting manner.

Example 1: Pharmaceutical composition for a sachet containing a suspension of 1 g of flavonoids

Sodium benzoate	0.015 g/10 ml
Citric acid	0.0125 g/10 ml
Orange flavouring	0.015 g/10 ml
Maltitol	1.8 g/10 ml
Flavonoid fraction	1.0 g/10 ml
Xanthan gum	0.05 g/10 ml
Purified water	q.s. 10 ml

Preparation of the suspension of Example 1:

For approximately 100,000 sachets:
700 litres of purified water and 1.5 kg of sodium benzoate are mixed carefully at 20°C until dissolution is complete. 1.25 kg of citric acid and 1.5 kg of orange flavouring are added to the solution. 180 kg of maltitol powder are added to the solution and mixed carefully. 100 kg of the flavonoid fraction are added very slowly to the mixture until a homogeneous suspension has formed. 5 kg of xanthan gum are introduced very slowly directly into the suspension. Purified water is added in a quantity sufficient to obtain a final volume of 1100 litres.

Example 2: Stability of the oral suspension of Example 1 (batch LP02)

The stability of the pharmaceutical composition of Example 1 according to the invention in a sachet was tested under different conditions of temperature and humidity.

The sachets are composed of a multilayer complex (polyethylene PET12/aluminium AL12/extruded polyethylene complex PE50).

T	Sachet			
	Density (Eur. Ph.)			
	25°C/60% RH	30°C/65% RH	30°C/75% RH	40°C/75% RH
T0	1.11			
T0 + 1 month	1.10	1.10	1.10	1.10
T0 + 3 months	1.10	1.10	1.10	1.10

The table above relating to the evolution of the density of the suspension in the sachet shows that the density is wholly stable even under conditions of high temperature and humidity (40°C/75% RH). This stability of the density shows that the suspension does not separate into phases over time under conditions of high temperature and humidity.

T	Sachet			
	Particle size of the flavonoid fraction			
	25°C/60% RH	30°C/65% RH	30°C/75% RH	40°C/ 75% RH
T0	d10 0.658 d50 2.581 d90 6.642			
T0 + 1 month	d10 0.723 d50 2.679 d90 6.969	d10 0.741 d50 2.692 d90 6.675	d10 0.739 d50 2.694 d90 6.698	d10 0.760 d50 2.726 d90 6.685
T0 + 3 months	d10 0.726 d50 2.663 d90 6.670	d10 0.746 d50 2.779 d90 6.862	d10 0.751 d50 2.708 d90 6.690	d10 0.798 d50 2.818 d90 6.739

The particle size distribution of the flavonoid fraction is expressed as the d10, d50 and d90 diameter, where

d10 = d(v,0.1) corresponds to the value at 10% of the cumulative particle size distribution curve by volume;

d50 = d(v,0.5) corresponds to the value at 50% of the cumulative particle size distribution curve by volume;

d90 = d(v,0.9) corresponds to the value at 90% of the cumulative particle size distribution curve by volume.

The table above shows that the particle size of the flavonoid fraction according to the invention does not increase over time under conditions of high temperature and humidity. The particles of the micronised flavonoid fraction do not agglomerate or form a sediment in the oral suspension according to the invention.

T	Sachet			
	Viscosity in CP			
	25°C/60% RH	30°C/65% RH	30°C/75% RH	40°C/75% RH
T0	321			
T0 + 1 month	293	298	294	296
T0 + 3 months	293	293	294	298

The table above relating to the viscosity of the suspension in the sachet shows that the viscosity is extremely stable over time under conditions of high temperature and humidity.

Finally, a visual check of the suspension under the different conditions of temperature and humidity after 1 month and 3 months of evaluation shows an absence of lumps and bubbles in the sachets.

Example 3: Uniformity of content of the pharmaceutical composition according to Example 1

The test is performed on 10 sachets. The contents of each sachet are metered; a reference solution of diosmin is used as control.

The average content X_m is expressed as follows:

$$X_m = (\Sigma X_i)/10$$

The acceptance value (AV), expressed as a percentage of the theoretical value, is given by the following formula:

$$AV = (M\text{-}X_m) + k \times s$$

where:
X_m is the average content, expressed as a percentage of the theoretical value;
M is the reference value, expressed as a percentage of the theoretical value: M = 98.5 if $X_m < 98.5$; M = X_m if $98.5 \leq X_m \leq 101.5$; M = 101.5 if $X_m > 101.5$;
k is the acceptability constant (k = 2.4 for 10 sachets);
s is the standard deviation of the contents X_i.

Parameters of uniformity of content (diosmin)	Batch LP02 1000 litres (sachet) according to Example 1	
	Start of filling into sachets	End of filling into sachets
Average content	100.5	102.1
Standard deviation	0.9	0.7
Acceptance value (AV)	2.2	2.3

According to the European Pharmacopoeia, article 2.9.40, an acceptance value below 15 means that the uniformity of content meets requirements (level L1). The table above therefore shows that the diosmin contained in the formulation according to the invention has a uniformity of content which complies with the statutory requirements.

CLAIMS

1. Pharmaceutical composition in the form of a drinkable oral suspension in a sachet, comprising as active ingredient a micronised purified flavonoid fraction comprising from 87% to 93% diosmin, from 2.5% to 5.0% hesperidin, from 0.9% to 2.8% isorhoifolin, from 0.9% to 2.8% linarin and less than 1% diosmetin, the particle size of which is strictly less than 5 μm, and xanthan gum as excipient.

2. Pharmaceutical composition according to claim 1, wherein the quantity of the flavonoid fraction is between 7% m/m and 20% m/m.

3. Pharmaceutical composition according to claim 1, wherein the concentration of xanthan gum is 0.5% m/v.

4. Pharmaceutical composition according to claim 1, wherein the quantity of xanthan gum is between 0.30% m/m and 0.60% m/m.

5. Pharmaceutical composition according to claim 1, comprising one or more pharmaceutically acceptable excipients chosen from sweeteners, flavourings, preservatives or pH correctors.

6. Pharmaceutical composition according to any one of claims 1 to 5 for use in the treatment of venous insufficiency.

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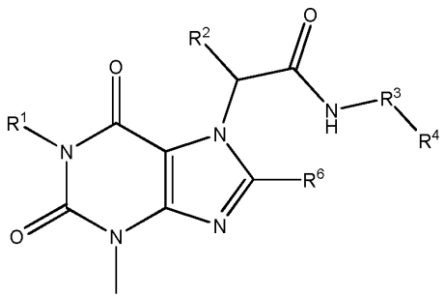
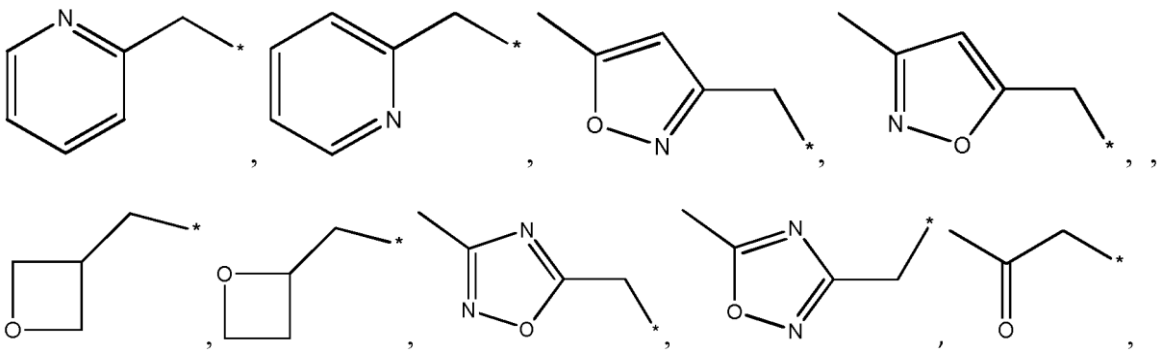
(54) **FRENIMI I KANALIT JONIK A1 ME POTENCIAL TË RECEPTORIT RASTËSOR**
30/06/2020
(30) 201462052678 P 19/09/2014 US
(71) Eli Lilly and Company
Lilly Corporate Center, Indianapolis, IN 46285, US
(72) CHENARD, Bertand, L. (7 Whaling Drive, Waterford, CT 06385) ;WU, Xinyuan (35 Travis Drive, Newton, MA 02467)
(74) Ela SHOMO PANIDHA
Euromarkpat Albania LTD , Rr. Pjeter BOGDANI, P.20/4, Ap.7/5, Tirane, 100
(57) **1.** Një komponim i Formulës (I):

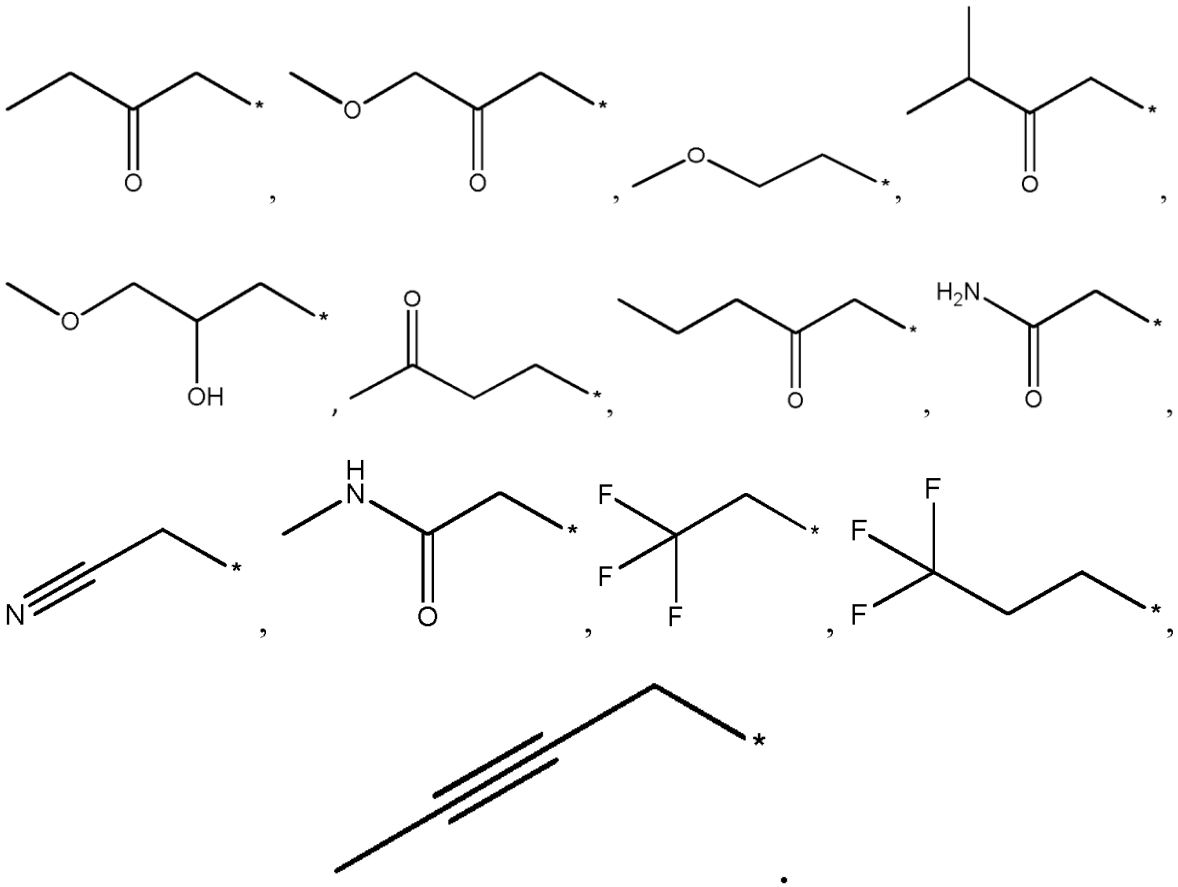


ose një kripë e tij farmaceutikisht e pranueshme, ku:

R^1 është hidroksipropil, hidroksietil, ketopentil, hidroksimetil, piridinilmetil, oksazolilmetil, metilizoksazolilmetil, oksetanilmetil, oksadiazolilmetil, metiloksadiazolilmetil, metoksietil, hidroksimetoksipropil, metoksiketopropil, ketometilbutil, ketopropil, ketobutil, acetamido, cianometil, metilacetamido, trifluoroetil, trifluoropropil, ose butinil;
R^2 është H ose C_1-C_6 alkil;
R^3 është fenil, piridil, pirimidinil, pirazinil, ose tiazolil, ku secili prej tyre është i zëvendësuar me $(R^4)_{1-2}$;
R^4 është në mënyrë të pavarur H, C_1-C_3 alkil, C_1-C_3 alkoksi, C_l-C_3 haloalkil,
-$N(R^8)_2$, cikloalkil 3 deri në 8-elementësh, aril, heterociklil, heteroaril, ciano, ose halo, ose dy R^4 sëbashku me atomet tek të cilët ata janë bashkuar mund të formojnë një unazë 3 deri në 7-elementëshe të zëvendësuar opsionalisht ku secila prej tyre është opsionalisht e zëvendësuar me $(R^5)_{1-3}$;
R^5 është në mënyrë të pavarur H, C_3-C_{10} heterociklil, C_1-C_3 alkil, C_1-C_3 alkoksi,
-C_1-C_6 alkil-O-C_0-C_6 alkil, -C_0-C_6 alkil-O-C_1-C_6 alkil, -$N(C_1$-C_3 alkil$)_2$, C_1-C_6 haloalkil, -C_1-C_3 alkil-$N(R^8)_2$, heterociklilalkil, halo, ciano, ose keto,
ku secili prej tyre është opsionalisht i zëvendësuar me $(R^7)_{1-3}$;
R^6 është H ose C_1-C_6 alkil;
R^7 është në mënyrë të pavarur H, C_1-C_6 alkil, C_2-C_6 alkenil, C_2-C_6 alkinil, C_1-C_6 alkoksi, C_1-C_6 haloalkil, hidroksi, aril, heteroaril, heterociklil, arilalkil, ariloksi, heteroariloksi, arilalkoksi, heteroarilalkoksi, heterarilalkil, haloalkil, keto, ciano, ose halo, ose dy R^7 sëbashku me atomet tek të cilët ata janë bashkuar mund të formojnë një unazë 3 deri në 7-elementëshe opsionalisht të zëvendësuar; dhe
R^8 është H, C_1-C_6 alkil, ose C_1-C_6 haloalkil.

2. Komponimi i secilit prej pretendimeve të mëparshme, ku R^1 është

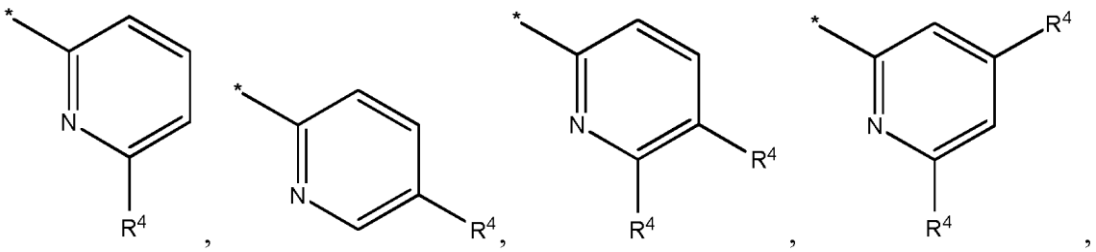


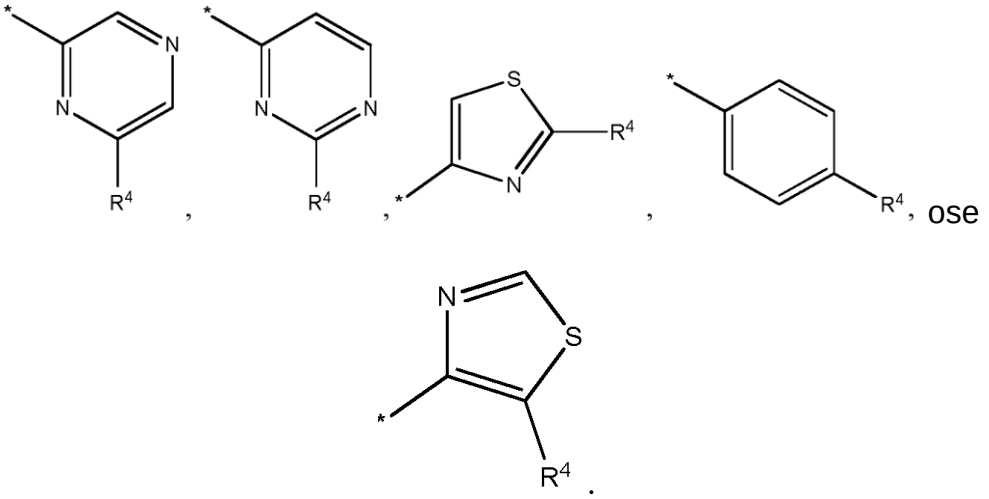


3. Komponimi i secilit prej pretendimeve të mëparshme, ku

a) R^2 është metil; ose:
b) R^2 është H.

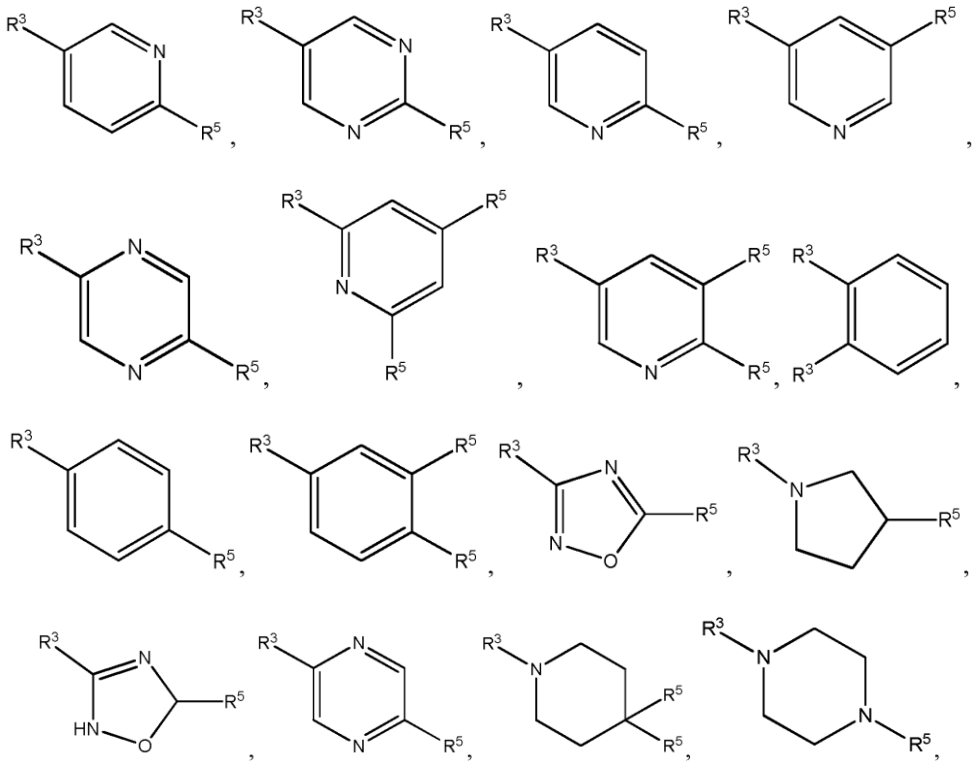
4. Komponimi i secilit prej pretendimeve të mëparshme, ku R^3 është

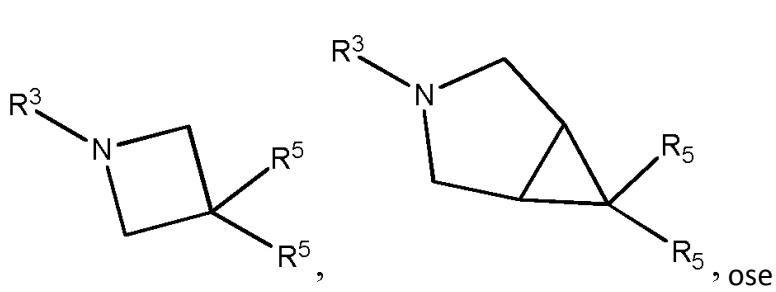



, ose

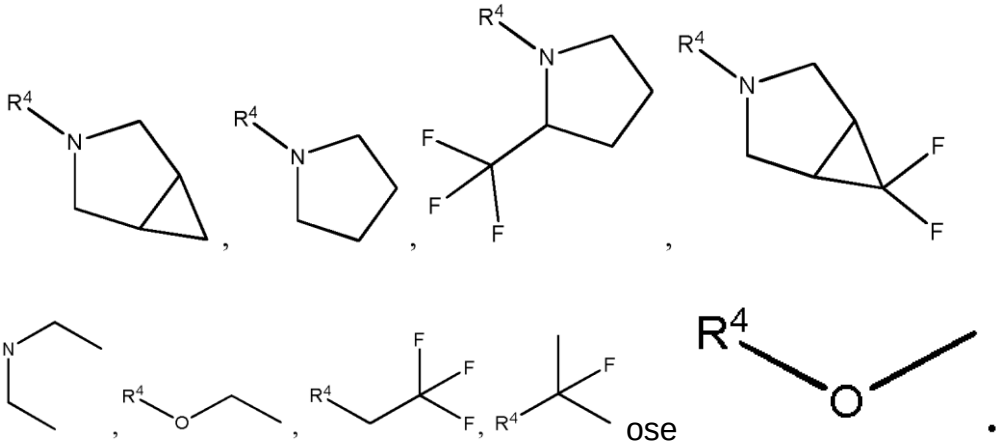
5. Komponimi i secilit prej pretendimeve të mëparshme, ku R^4 është në mënyrë të pavarur H, metil, etil, propil, -N(R^8)$_2$, fenil, halo, ciano, haloalkil, metoksi, piridinil, pirimidinil, oksadiazolil, piperidinil, azetidinil, pirazinil, azabiciklohekzil, piperazinil, ose pirrolidinil, ku secili prej tyre është i zëvendësuar me (R^5)$_{1-2}$.

6. Komponimi i secilit prej pretendimeve të mëparshme, ku R^4 është në mënyrë të pavarur H, metil, etil, propil, ciano, metoksi, klor, fluor, brom, -CF_3, -CF_2,




, ose .

7. Komponimi i secilit prej pretendimeve të mëparshme, ku R^5 është në mënyrë të pavarur H, pirrolidinil, trifluorometil, trifluoroetil, halo, metil, izopropil, ciano, propil, etil, azabiciklohekzil, difluoroazabiciklohekzil, keto, metoksi, metoksietil, dialkilamino, ose etoksi, ku secili prej tyre është opsionalisht i zëvendësuar me $(R^6)_{1-3}$; opsionalisht ku R^5 është në mënyrë të pavarur H, $-CF_3$, cianometil, brom, klor, fluor, metil, etil, izopropil, ciano, keto,

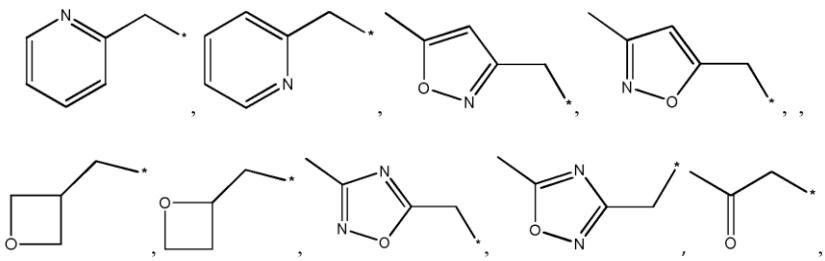

ose .

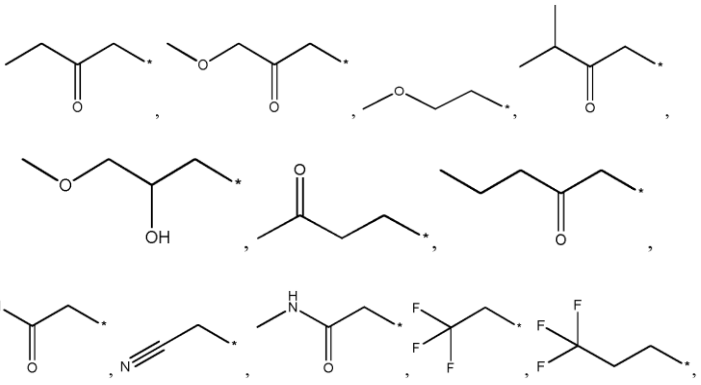
8. Komponimi i secilit prej pretendimeve të mëparshme, ku

a) R^6 është H; ose:
b) R^6 është metil.

9. Komponimi i secilit prej pretendimeve të mëparshme, ku R^8 është H, metil, etil, ose CF_3.

10. Komponimi i secilit prej pretendimeve të mëparshme, ku R^1 është





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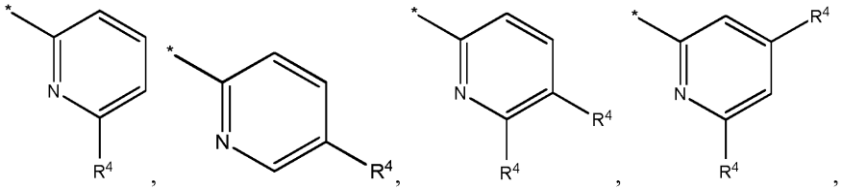
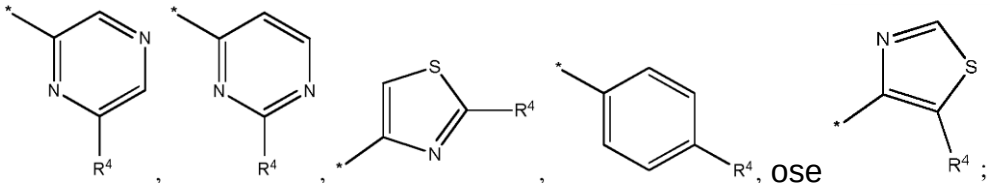
;

R^2 është H ose metil;
R^3 është

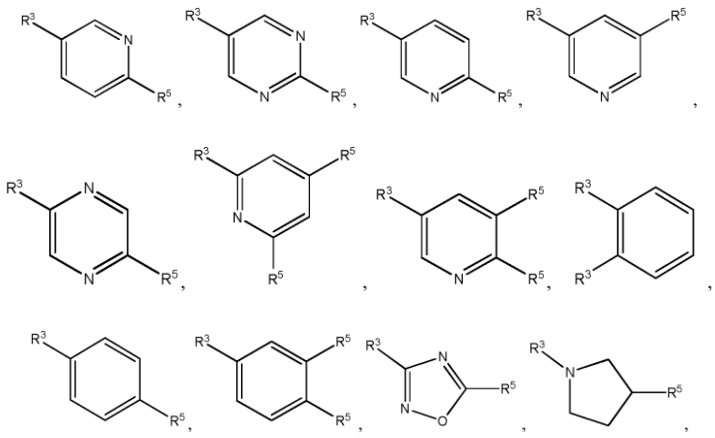


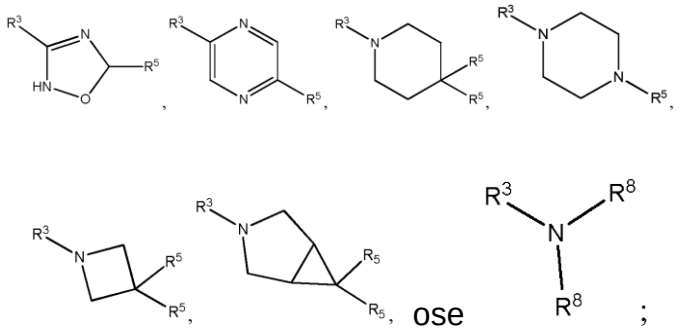


ose

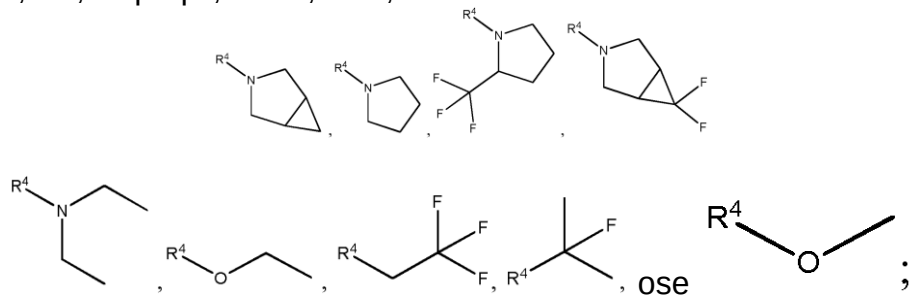
;

R^4 është në mënyrë të pavarur H, metil, etil, propil, ciano, metoksi, klor, fluor, brom,
$-CF_3$, $-CF_2$,



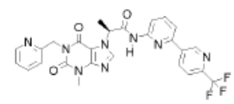
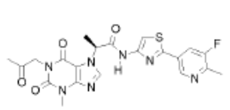
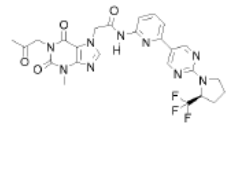


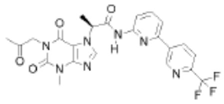
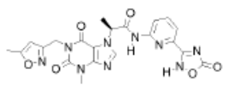
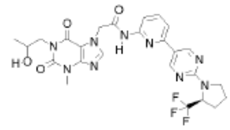
R^5 është në mënyrë të pavarur H, -CF_3, cianometil, brom, klor, fluor, metil, etil, izopropil, ciano, keto,

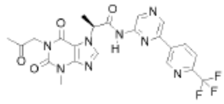
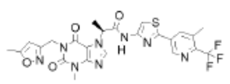
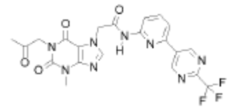


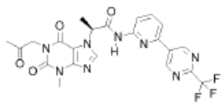
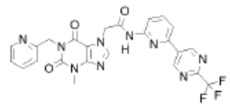
R^6 është H ose metil; dhe
R^8 është H, metil, etil, ose CF_3.

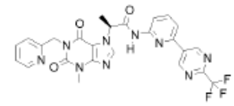
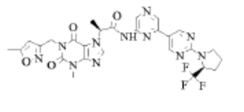
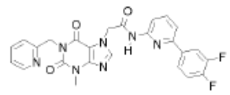
11. Komponimi i secilit prej pretendimeve të mëparshme, ku komponimi është përz- gjedhur nga grupi që konsiston në:

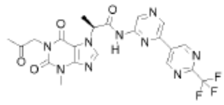
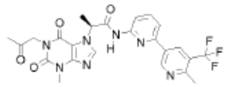
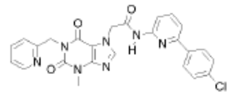
  ,  ,

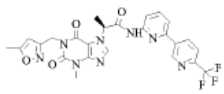
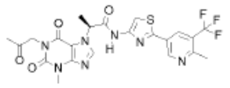
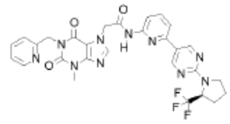
  ,  ,

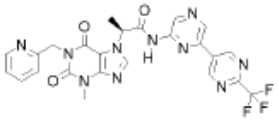
  ,  ,

  ,

  ,  ,

  ,  ,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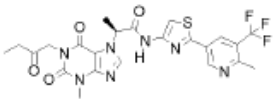
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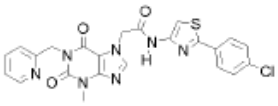
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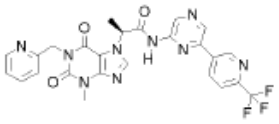
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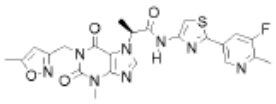
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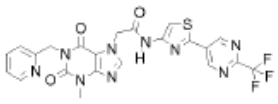
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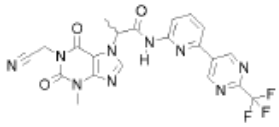
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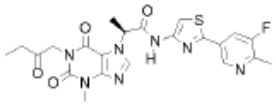
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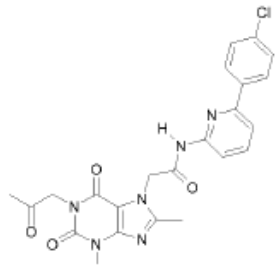
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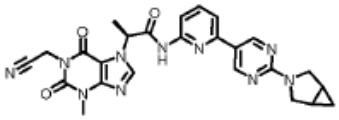
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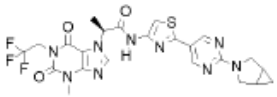
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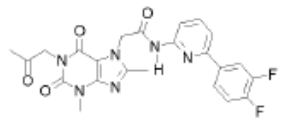
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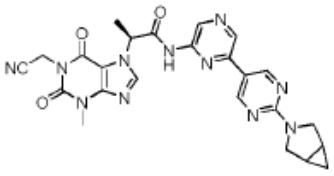
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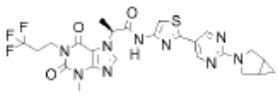
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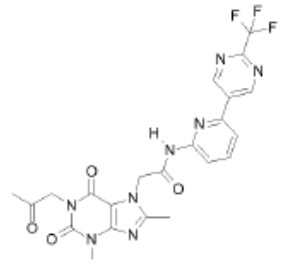
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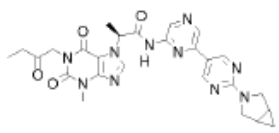
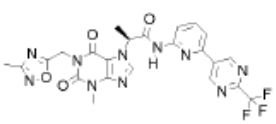
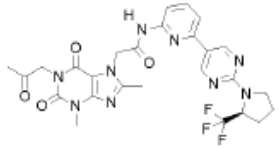

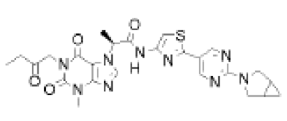

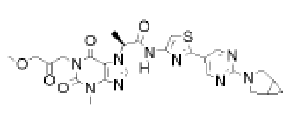

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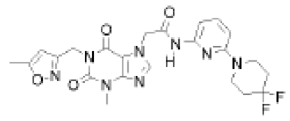

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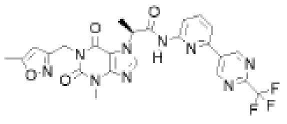

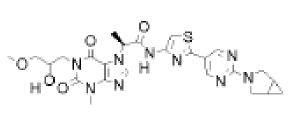

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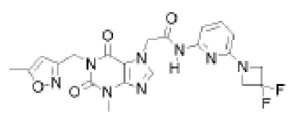

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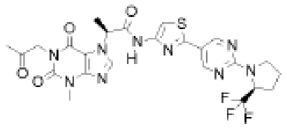

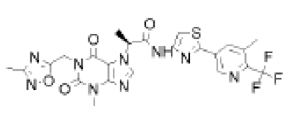

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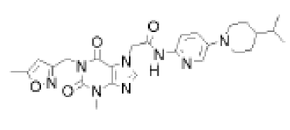

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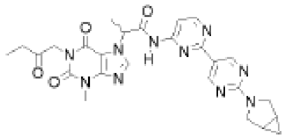

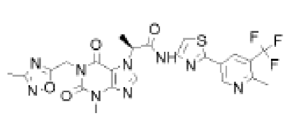

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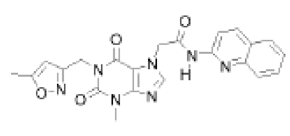

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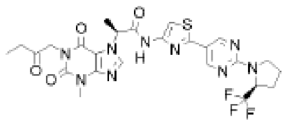

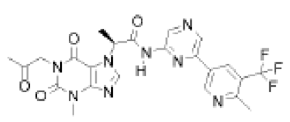

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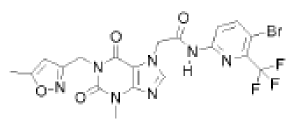

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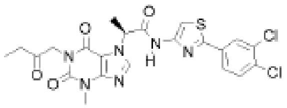

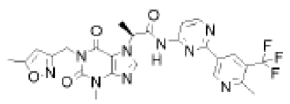

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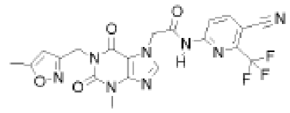

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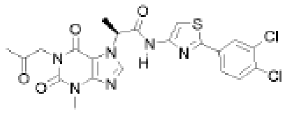

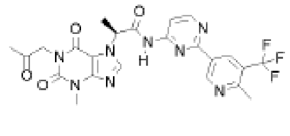

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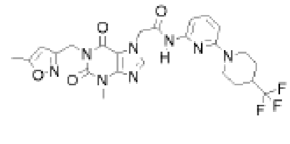

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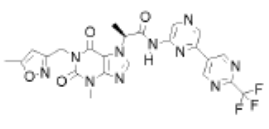

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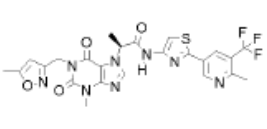

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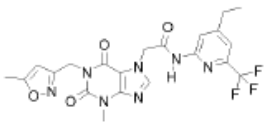

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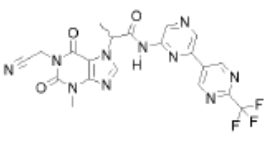

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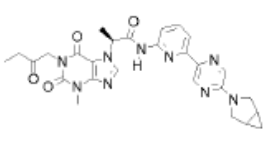

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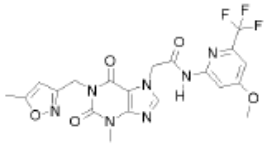

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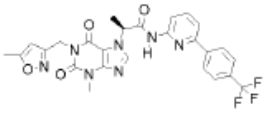

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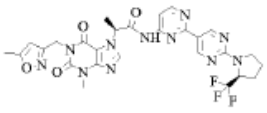

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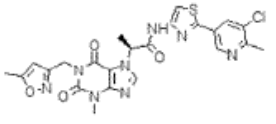

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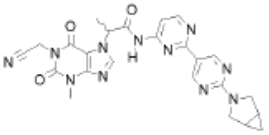

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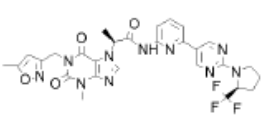

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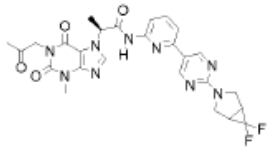

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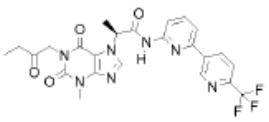

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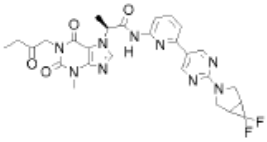

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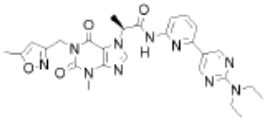

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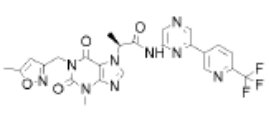

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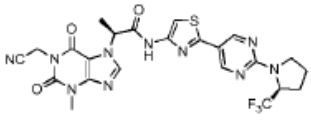

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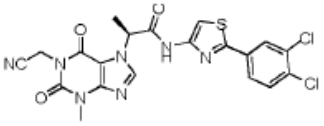

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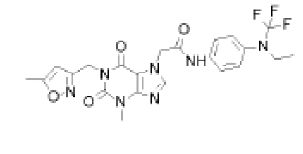

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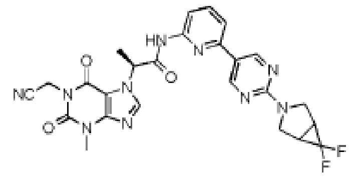

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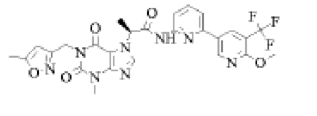

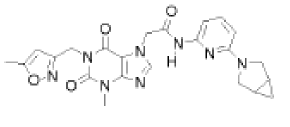

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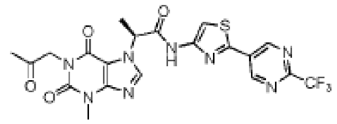

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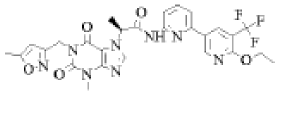

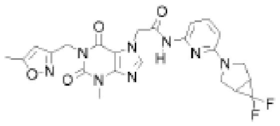

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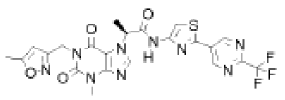

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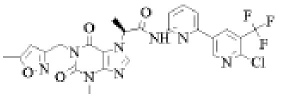

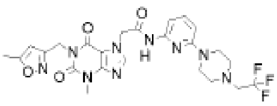

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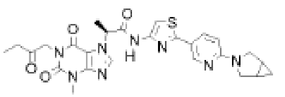

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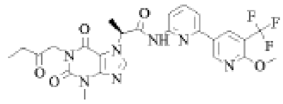

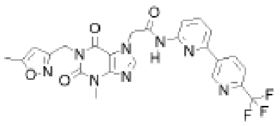

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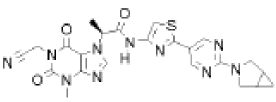

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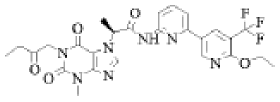

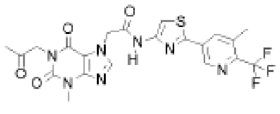

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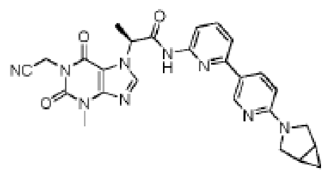

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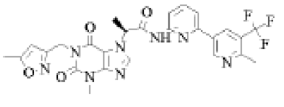

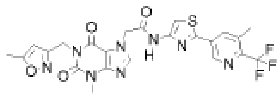

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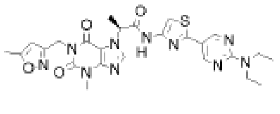

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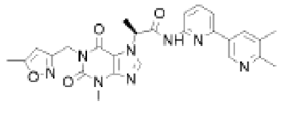
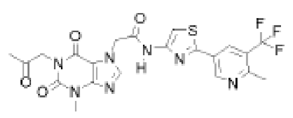
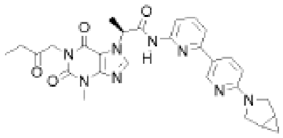
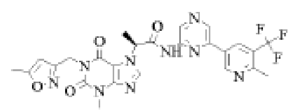
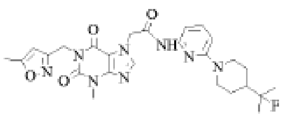
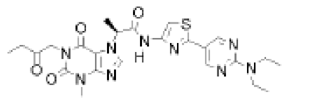


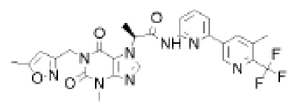
 ,

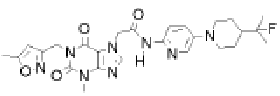
 ,

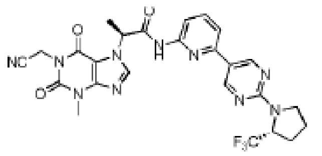


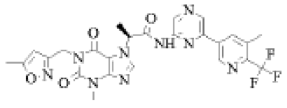
 ,

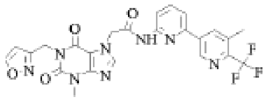
 ,

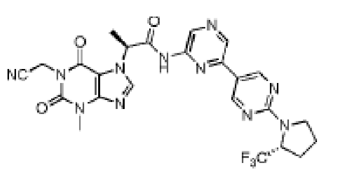


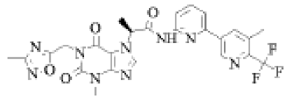
 ,

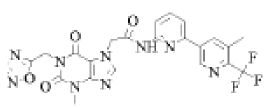
 ,

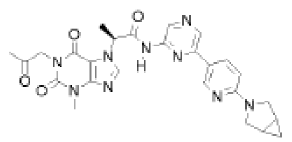


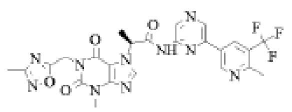
 ,

 ,



 ,

 ,



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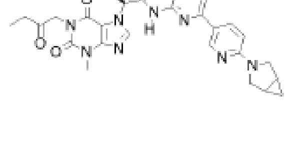
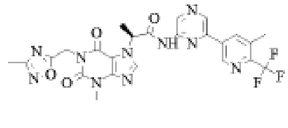
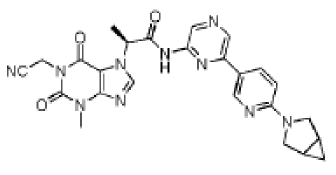
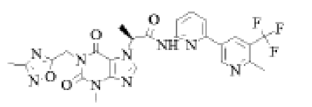
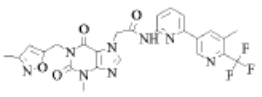
 ,



 ,

 ,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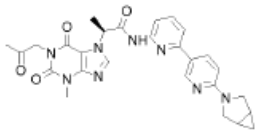
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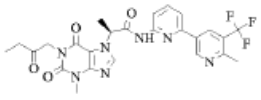
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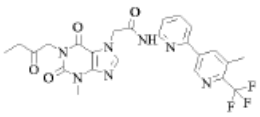
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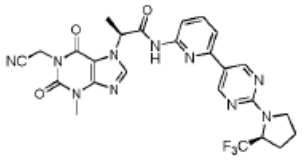
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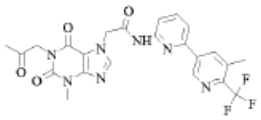
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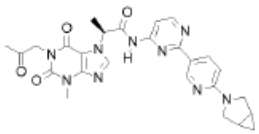
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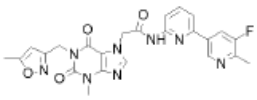
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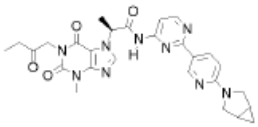
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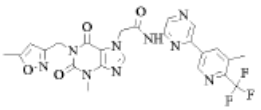
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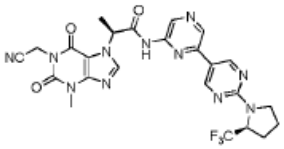
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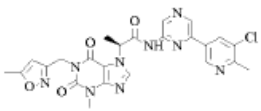
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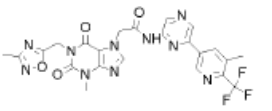
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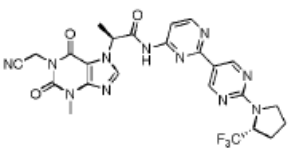
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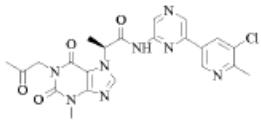
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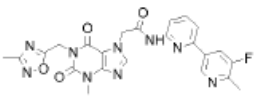
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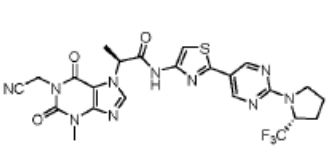
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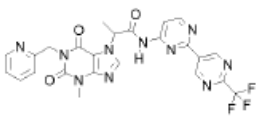
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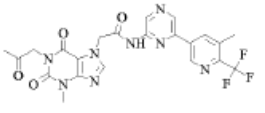
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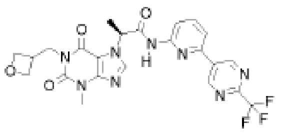

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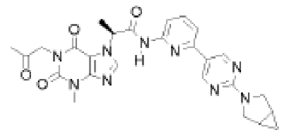

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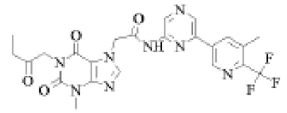

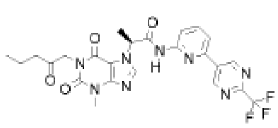

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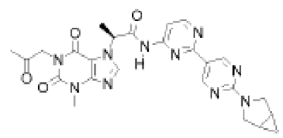

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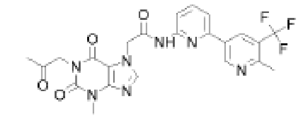

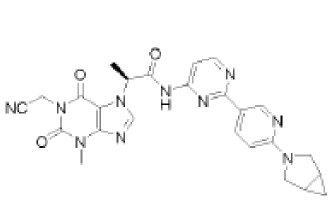

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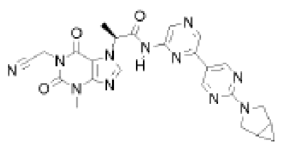

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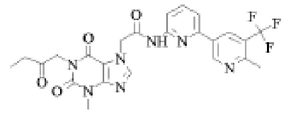

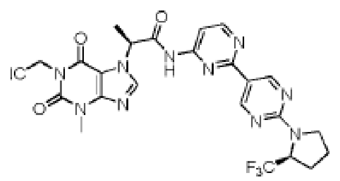

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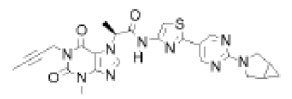

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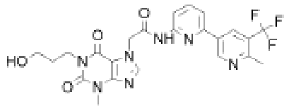

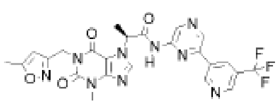

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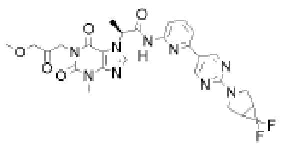

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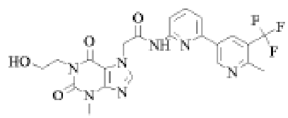

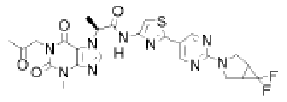

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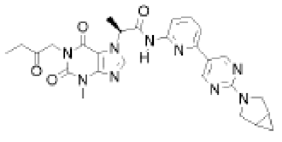

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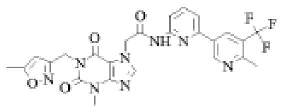

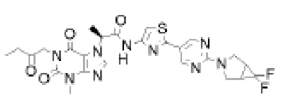

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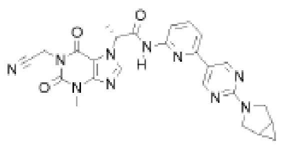

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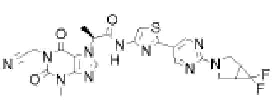

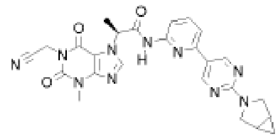

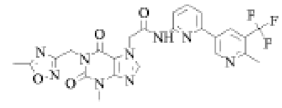

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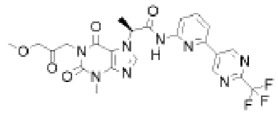

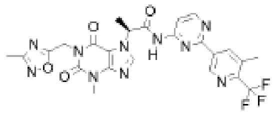

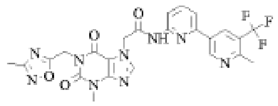

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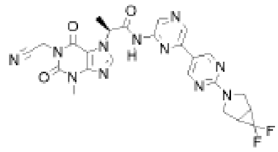

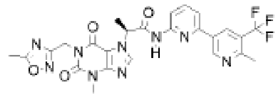

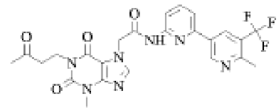

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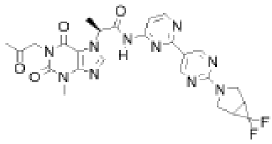

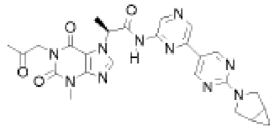

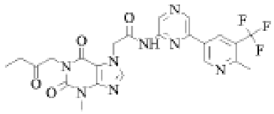

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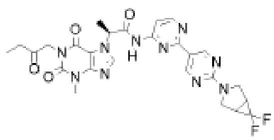

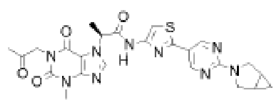

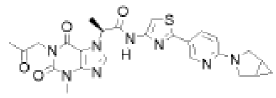

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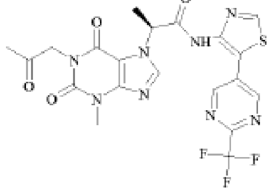

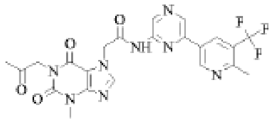

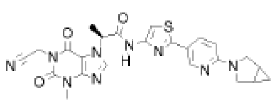

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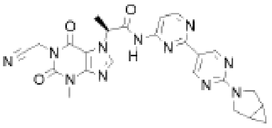

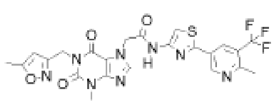

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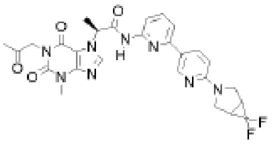

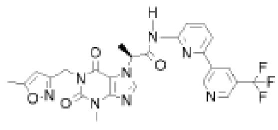

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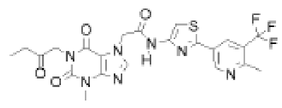

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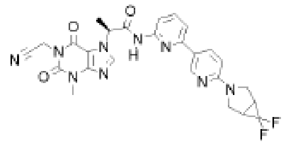

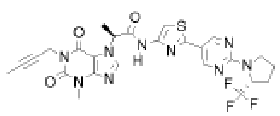

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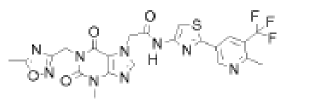

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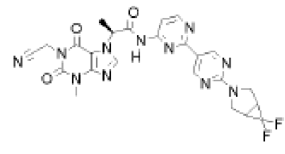

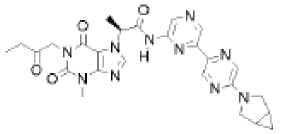

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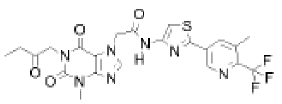

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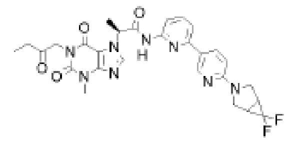

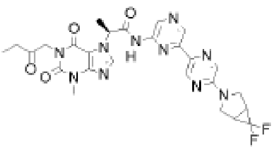

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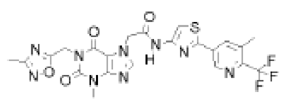

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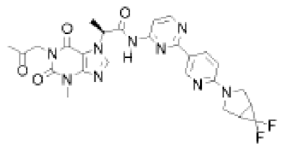

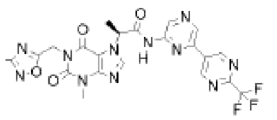

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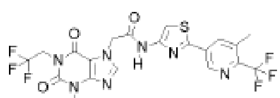

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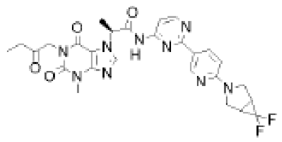

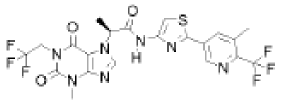

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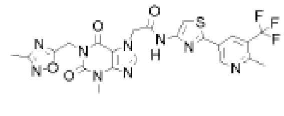

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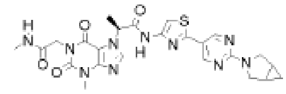

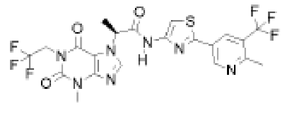

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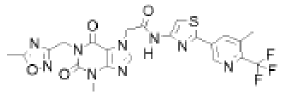

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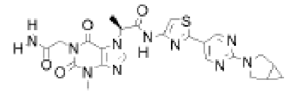

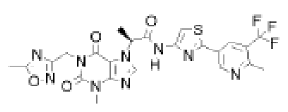

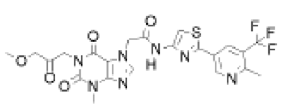

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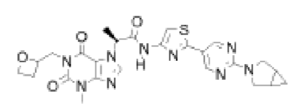

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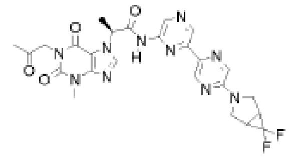

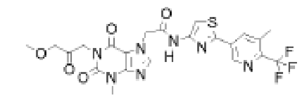

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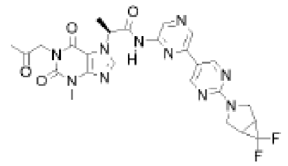

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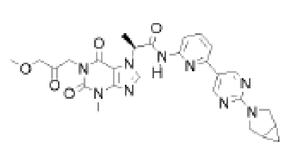

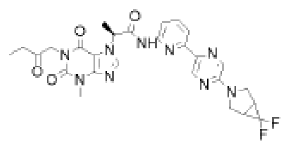

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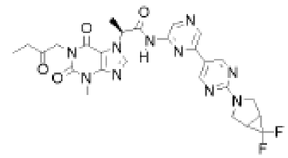

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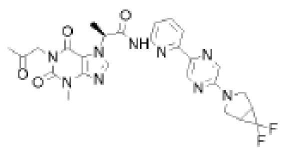

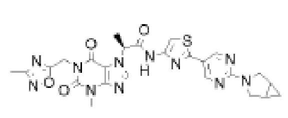

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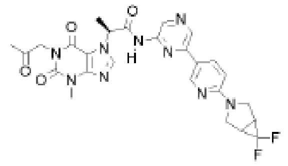

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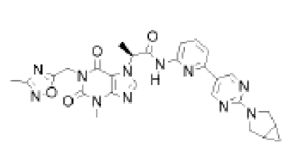

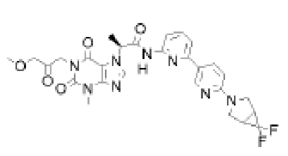

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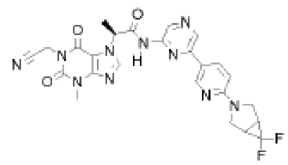

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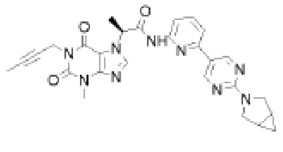

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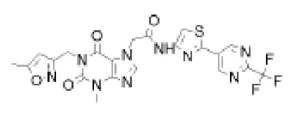

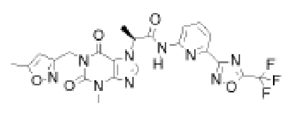

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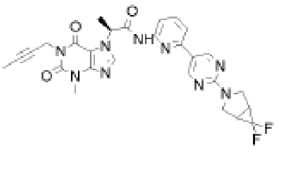

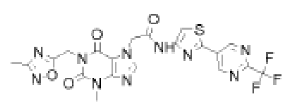

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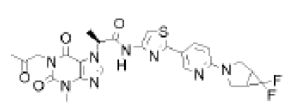

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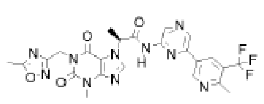
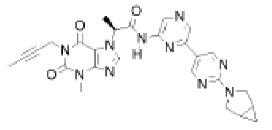
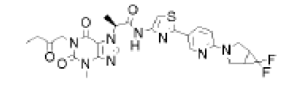

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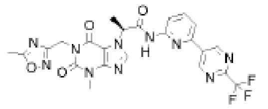
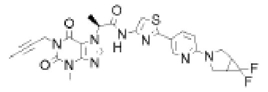
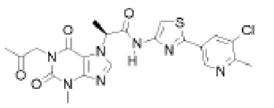

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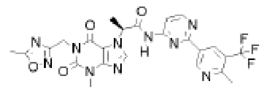
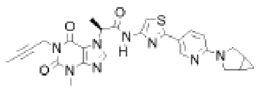
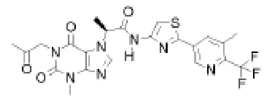

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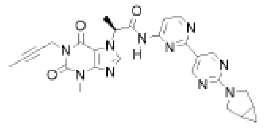
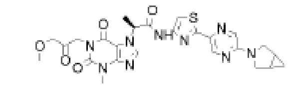
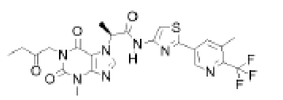

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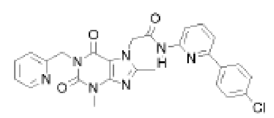
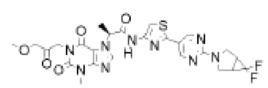
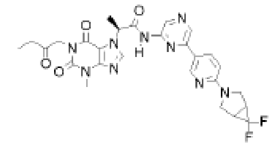

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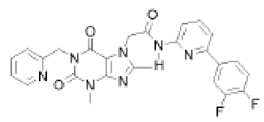
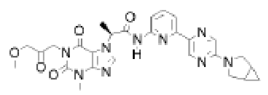
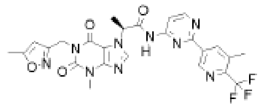

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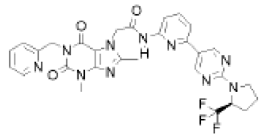
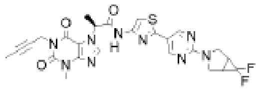
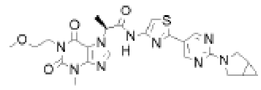

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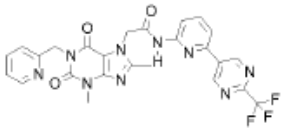
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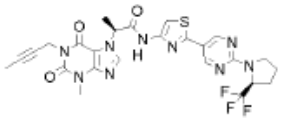
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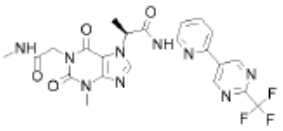
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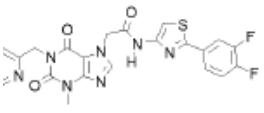
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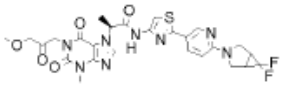
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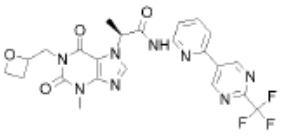
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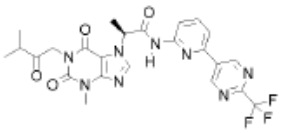
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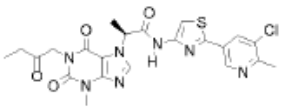
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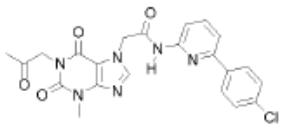
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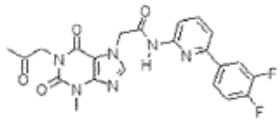
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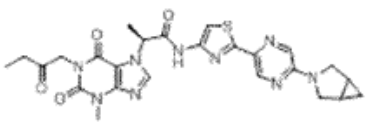
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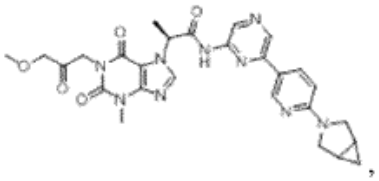
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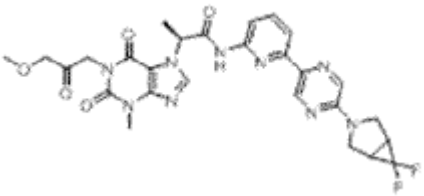
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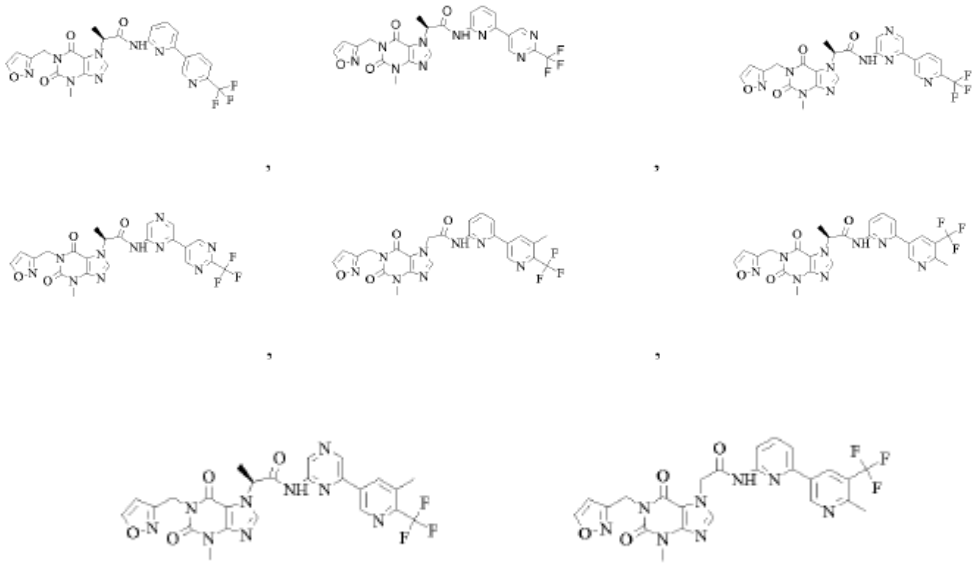
12. Një komponim i përzgjedhur nga grupi që konsiston në:



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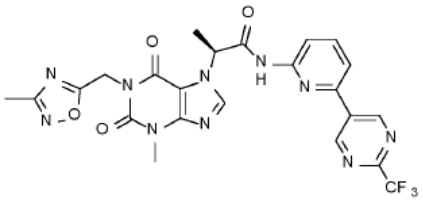
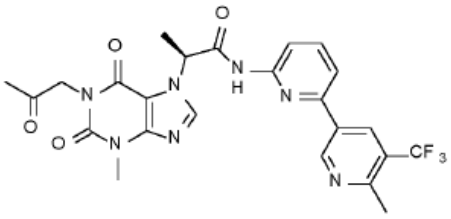
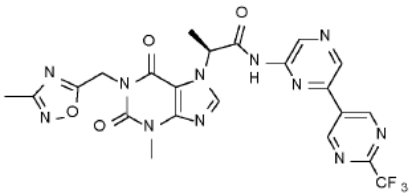
13. Komponimi sipas pretendimit 11 i cili është:



14. Komponimi sipas pretendimit 11 i cili është:



15. Komponimi sipas pretendimit 11 i cili është:



16. Një përbërje farmaceutike që përmban të paktën një komponim sipas secilit prej pretendimeve të mëparshme ose një kripë e tij farmaceutikisht e pranueshme në një përzierje me një mbushës, tretës ose transportues farmaceutikisht të pranueshëm.

17. Një komponim sipas secilit prej pretendimeve të mëparshme për tu përdorur si një medikament.

18. Një komponim sipas secilit prej pretendimeve të mëparshme, ose një kripë e tij farmaceutikisht e pranueshme për tu përdorur në trajtimin e një çrregullimi të shkaktuar nga TRPA1 tek një subjekt, ku çrregullimi i shkaktuar nga TRPA1 është përzgjedhur nga grupi që konsiston në: dhimbje, sëmundje inflamatore, çrregullim dermatologjik, ose gjendje respiratore.

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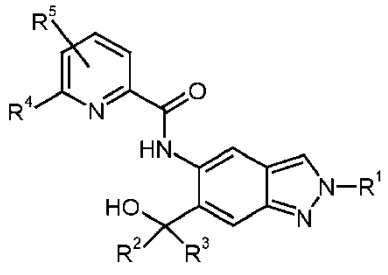
(96) 15800828.4 / 25/11/2015
(22) 05/06/2020
(21) AL/P/ 2020/367
(54) **INDAZOLE TË ZËVENDËSUARA, PROCESI PËR PËRGATITJEN E TYRE, FORMULIME FARMACEUTIKE QË I PËRMBAJNË ATO, DHE PËRDORIMI I TYRE PËR PËRGATITJEN E MEDIKAMENTEVE**
30/06/2020
(30) 14195032 26/11/2014 EP
(71) Bayer Pharma Aktiengesellschaft
Müllerstrasse 178, 13353 Berlin, DE
(72) BÖMER, Ulf (Leipziger Str. 49, 16548 Glienicke); BOTHE, Ulrich (Kavalierstr. 15, 13187 Berlin); SIEBENEICHER, Holger (Kruppstr. 18, 10557 Berlin); SCHMIDT, Nicole (455 Mission Bay Blvd. South, San Francisco, CA 94158); GÜNTHER, Judith (Parkstr. 60, 13187 Berlin); STEUBER, Holger (Hannoversche Strasse 19A, 10115 Berlin); LANGE, Martin (Straßburger Str. 9K, 10405 Berlin); NUBBEMEYER, Reinhard (Moorweg 96, 13509 Berlin); STEGMANN, Christian (Schliemannstr. 39, 10437 Berlin); SUTTER, Andreas (Pistoriusstr. 7, 13086 Berlin); RAUSCH, Alexandra (Schönhauser Str. 54C, 13158 Berlin); HAUFF, Peter (Erich-Nehlhans-Str. 30, 10247 Berlin) ;FRIEDRICH, Christian (Altstädtische Fischerstr. 17, 14770 Brandenburg)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)

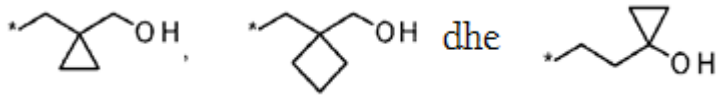
1. (57) Përbërjet e formulës së përgjithshme (I)



(I)

në të cilën:

R^1 është C_1-C_6-alkil, ku grupi C_1-C_6-alkil është i pazëvendësuar ose mono- ose shumë i zëvendësueshëm në mënyrë identike ose të ndryshme nga halogjen, hidroksil, një grup i pazëvendësuar ose mono- ose poli-halogjen-i zëvendësuar C_3-C_6-cikloalkil, ose një R6 ose R^8O, ose një grup i zgjedhur nga:



ku * përfaqëson vendin e lidhje se grupit me pjesën e mbetur të molekulës;

R^2 dhe R^3 gjithmonë kanë të njëjtin përkufizim dhe të dyja janë ose hidrogjen ose C_1-C_6-alkil;

R^4 është halogjen, ciano, i pazëvendësuar ose i vetëm ose i shumëfishtë, në mënyrë identike ose të ndryshme të zëvendësuar C_1-C_6-alkil ose i pazëvendësuar ose i vetëm ose i shumëfishtë, në mënyrë identike ose të ndryshme të zëvendësuar C_3-C_6-cikloalkil, dhe zëvendësuesit janë zgjedhur nga grupi i halogjen dhe hidroksil;

R^5 është hidrogjen, halogjen ose i pazëvendësuar ose mono- ose poli-halogjen-i zëvendësuar C_1-C_6-alkil;

R^6 është një heterocikël i pazëvendësuar ose mono- ose di-metil-i zëvendësuar monociklik i saturuar që ka 4 deri në 6 unaza atomesh, e cila përmban një heteroatom ose një heterogrup nga grupi i O, S, SO dhe SO_2;

R^8 është C_1-C_6-alkil, ku grupi C_1-C_6-alkil është i pazëvendësuar ose mono- ose shumëfish i zëvendësuar në mënyrë identike ose të ndryshme nga halogjen;

dhe diastereomer, enantiomer, kripëra, tretësa ose tretësat e kripërave të tyre.

2. Përbërjet sipas Pretendimit 1, ku

R^1 është C_1-C_6-alkil, ku grupi C_1-C_6-alkil është i pazëvendësuar ose mono- ose shumëfish i zëvendësuar në mënyrë identike ose të ndryshme nga fluorine, hidroksil ose një grup R^6 ose R^8O;

R^2 dhe R^3 gjithmonë kanë të njëjtin përkufizim dhe janë të dyja ose hidrogjen ose C_1-C_3-alkil;

R^4 është halogjen, ciano ose C_1-C_3-alkil, ku grupi C_1-C_3-alkil është i pazëvendësuar ose mono- ose shumëfish i zëvendësuar në mënyrë identike ose të ndryshme nga halogjen ose hidroksil;

R^5 është hidrogjen, fluorine, klorine ose C_1-C_3-alkil;

R^6 është oksetanil ose tetrahidrofuranil;

R^8 është një grup i pazëvendësuar C_1-C_4-alkil ose një grup tri-fluorine-i zëvendësuar C_1-C_4-alkil.

3. Përbërjet sipas Pretendimit 1 ose 2, ku R^4 është difluorometil, trifluorometil ose metil.

4. Përbërjet sipas Pretendimit 1, 2 ose 3, ku R^5 është hidrogjen ose fluorine.

5. Përbërjet sipas Pretendimit 1, 2, 3 ose 4, ku R^2 dhe R^3 janë së bashku ose hidrogjen ose metil.

6. Përbërjet sipas Pretendimit 2, ku

R^1 është C_2-C_6-alkil, ku grupi C_2-C_6-alkil është i pazëvendësuar, ose grupi C_2-C_6-alkil është mono-, di- ose tri-fluorine-e zëvendësuar ose grupi C_2-C_6-alkil është i zëvendësuar vetëm nga hidroksil, R^6, ose R^8O, ose R^1 është një grup oksetanil-i zëvendësuar C_1-C_3-alkil;

R^2 dhe R^3 gjithmonë kanë të njëjtin përkufizim dhe janë që të dyja ose hidrogjen ose metil;

R^4 është një grup i pazëvendësuar ose mono- ose poli-halogjen-i zvëndësuar C_1-C_3-alkil ose një grup C_1-C_3-alkil i zëvendësuar nga një grup hidroksil ose një grup C_1-C_3-alkil i zëvendësuar nga një grup hidroksil dhe tre atome fluorine;

R^5 është hidrogjen, fluorine ose C_1-C_3-alkil;

R^8 është C_1-C_4-alkil, ku grupi C_1-C_4-alkyl është i pazëvendësuar ose mono-, di- ose tri-fluorine-i zëvendësuar.

7. Përbërjet sipas Pretendimit 6, në të cilin

R^1 është një grup C_2-C_5-alkil i zëvendësuar nga hidroksil ose C_1-C_3-alkoksi ose trifluorometoksi ose 2,2,2-trifluoroetoksi ose trifluorometil ose është një grup oksetan-3-il-i zëvendësuard C_1-C_2-alkil;

R^2 dhe R^3 gjithmonë kanë të njëjtin përkufizim dhe janë që të dyja ose hidrogjen ose metil;

R^4 është metil, etil, trifluoro-C_1-C_3-alkil, difluoro-C_1-C_3-alkil, hidroksimetil, 1-hidroksietil, 2-hidroksipropan-2-il dhe 2,2,2-trifluoro-1-hidroksietil;

R^5 është hidrogjen, fluorine ose metil.

8. Përbërjet sipas Pretendimit 7, në të cilin

R^1 është 4,4,4-trifluorobutil, 3-hidroksi-3-metilbutil, 3-hidroksibutil, 3-metoksipropil, 3-hidroksipropil, 3-hidroksi-2-metilpropil, 3-hidroksi-2,2-dimetilpropil, 3-trifluorometoksipropil, 2-metoksietil ose 2-hidroksietil;

R^2 dhe R^3 janë që të dyja metil ose hidrogjen;

R^4 është difluorometil, trifluorometil ose metil;

R^5 është hidrogjen ose fluorine.

9. Përbërjet sipas Pretendimit 8, në të cilin

R^1 është 3-hidroksi-3-metilbutil, 3-hidroksibutil, 3-hidroksi-2-metilpropil ose 3-hidroksi-2,2-dimetilpropil;

R^2 dhe R^3 janë që të dyja metil;

R^4 është difluorometil ose trifluorometil;

R^5 është hidrogjen.

10. Përbërjet sipas Pretendimit 8, në të cilin

R^1 është 3-hidroksi-3-metilbutil, 3-hidroksibutil, 3-hidroksi-2-metilpropil ose 3-hidroksi-2,2-dimetilpropil;

R^2 dhe R^3 janë që të dyja metil;

R^4 është metil;

R^5 është fluorine, ku R^5 është në pozicion orto ndaj R^4.

11. Përbërjet sipas Pretendimit 1-10 si më poshtë:

1) N-[6-(2-Hidroksipropan-2-il)-2-(2-metoksietil)-2H-indazol-5-il]-6-(trifluorometil)piridine-2-karboksamide

2) N-[6-(Hidroksimetil)-2-(2-metoksietil)-2H-indazol-5-il]-6-(trifluorometil)piridine-2-karboksamide

3) N-[6-(2-Hidroksipropan-2-il)-2-(3-metoksipropil)-2H-indazol-5-il]-6-(trifluorometil)piridine-2-karboksamide

4) N-[6-(Hidroksimetil)-2-(3-metoksipropil)-2H-indazol-5-il]-6-(trifluorometil)piridine-2-karboksamide

5) N-[2-(2-Hidroksietil)-6-(2-hidroksipropan-2-il)-2H-indazol-5-il]-6-(trifluorometil)piridine-2-karboksamide

6) N-[6-(2-Hidroksipropan-2-il)-2-(3-hidroksipropil)-2H-indazol-5-il]-6-(trifluorometil)piridine-2-karboksamide

7) N-[2-(2-Hidroksietil)-6-(hidroksimetil)-2H-indazol-5-il]-6-(trifluorometil)piridine-2-karboksamide

8) N-[6-(2-Hidroksipropan-2-il)-2-(oksetan-3-ilmetil)-2H-indazol-5-il]-6-(trifluorometil)piridine-2-karboksamide

9) N-[6-(Hidroksimetil)-2-(oksetan-3-ilmetil)-2H-indazol-5-il]-6-(trifluorometil)piridine-2-karboksamide

10) N-[2-(3-Hidroksi-3-metilbutil)-6-(2-hidroksipropan-2-il)-2H-indazol-5-il]-6-(trifluorometil)piridine-2-karboksamide

11) 6-(Difluorometil)-N-[2-(3-hidroksi-3-metilbutil)-6-(2-hidroksipropan-2-il)-2H-indazol-5-il]piridine-2-karboksamide

12) 6-(Difluorometil)-N-[6-(2-hidroksipropan-2-il)-2-(3-hidroksipropil)-2H-indazol-5-il]piridine-2-karboksamide

13) N-[6-(2-Hidroksipropan-2-il)-2-(4,4,4-trifluorobutil)-2H-indazol-5-il]-6-(trifluorometil)piridine-2-karboksamide

14) N-{6-(2-Hidroksipropan-2-il)-2-[3-(trifluorometoksi)propil]-2H-indazol-5-il}-6-(trifluorometil)piridine-2-karboksamide

15) N-{6-(2-Hidroksipropan-2-il)-2-[3-(2,2,2-trifluoroetoksi)propil]-2H-indazol-5-il}-6-(trifluorometil)piridine-2-karboksamide

16) 5-Fluoro-N-[2-(3-hidroksi-3-metilbutil)-6-(2-hidroksipropan-2-il)-2H-indazol-5-il]-6-metilpiridine-2-karboksamide

17) N-[2-(3-Hidroksi-3-metilbutil)-6-(2-hidroksipropan-2-il)-2H-indazol-5-il]-6-metilpiridine-2-karboksamide

18) 6-(2-Hidroksipropan-2-il)-N-[6-(2-hidroksipropan-2-il)-2-(4,4,4-trifluorobutil)-2H-indazol-5-il]piridine-2-karboksamide

19) N-{2-[2-(1-Hidroksikikloprropil)etil]-6-(2-hidroksipropan-2-il)-2H-indazol-5-il}-6-(trifluorometil)piridine-2-karboksamide.

12. Përbërja e formulës së përgjithshme (I) sic përcaktohet në cdonjë prej Pretendimeve 1 deri në 11 për trajtimin dhe/ose profilaksinë e sëmundjeve.

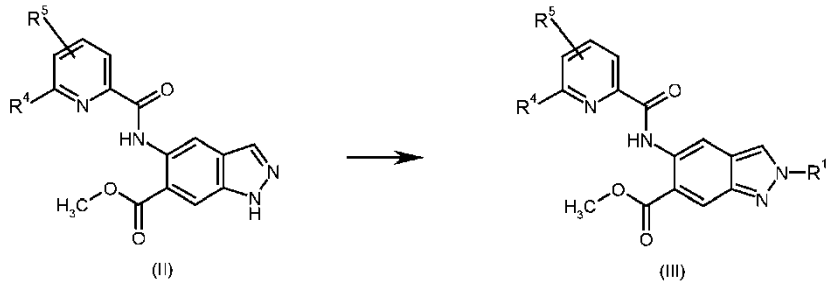
13. Përbërja e formulës së përgjithshme (I) sic përcaktohet në cdonjë prej Pretendimeve 1 deri në 11 për përdorim në një metodë përtrajtimin dhe/ose profilaksinë e çrregullimeve neoplastike, çrregullimeve dermatologjike, çrregullimeve gjinekoligjike, çrregullimeve kardiovaskulare, sëmundjeve pulmonare, çrregullimeve oftalmologjike, çrregullimeve neurologjike, çrregullimeve metabolike, çrregullimeve hepatike, çrregullimeve inflamatore, çrregullimeve dhe dhimbjes autoimune.

14. Përbërja e formulës së përgjithshme (I) sic përcaktohet në cdonjë prej Pretendimeve 1 deri në 11 për përdorim në një metodë për trajtimin dhe/ose profilaksinë e limfomës, degjenerimit makular, psoriazës, lupus eritematosus, skleroza e shumëfishtë, COPD, cermë, NASH, fibrozat hepatike, rezistenca e insulinës, sindroma metabolike, spondilo artrit dhe artriti rheumatid, endometrioza dhe dhimbja e lidhur me endometriozën dhe simptoma shoqëruese të endometriozës si, dismenorrhea, dispareunia, disuria dhe dishezia.

15. Përbërja e formulës së përgjithshme (I) sic përcaktohet në cdonjë prej Pretendimeve 1 deri në 11 për përdorim në një metodë për trajtimin dhe/ose profilaksinë e dhimbjes duke përfshirë dhimbjen akute, kronike, inflamatore dhe neuropatike, në mënyrë të preferuar të hiperalgjezia, alodinia, dhimbje nga artriti (si psh. osteoartriti, artriti rheumatid dhe spondilo artitrit), dhimbje para menstruale, dhimbje shoqëruese-endometriozës, dhimbje post-operacion, dhimbje nga cistiti interstitial, CRPS (sindroma e dhimbjes rajonale komplekse), trigeminal neuralgjia, dhimbje nga prostata, dhimbje e shkaktuar nga dëmtime të shtyllës kurrizore, dhimbje e inflamacionit-të induktuar, dhimbje të kurrizit, dhimbje nga kanceri, dhimbje e shoqëruar-nga kimioterapia, neuropatia -e induktuar nga trajtimi HIV, dhimbje e induktuar -nga djegia dhe dhimbja kronike.

16. Medikament që përfshin një përbërje të formulës (I) sic përcaktohet në cdonjë prej Pretendimeve 1 deri në 11 në kombinim me një përshpejtues inert, jo-toksik, farmaceutikisht të përshtatshëm.

17. Procesi për përgatitjen e përbërjeve të formulës së përgjithshme (III) nga përbërjet e formulës së përgjithshme (II)



ku

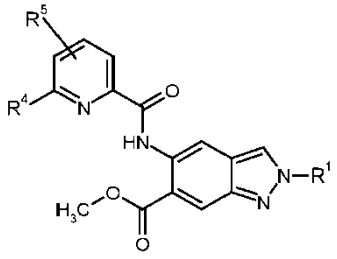
R^1 është 4,4,4-trifluorobutil, 3-hidroksi-3-metilbutil, 3-metoksipropil, 3-hidroksipropil, 3-hidroksi-2-metilpropil, 3-hidroksi-2,2-dimetilpropil, 3-trifluorometoksipropil, 2-metoksietil ose 2-hidroksietil;

R^4 është difluorometil, trifluorometil ose metil;

R^5 është hydrogen ose fluorine;

nga reaksoni i (II) me halide alkil të zëvendësuar në mënyrë të përshtatshme ose sulfonate alkil 4-metil benzene në prezencë të karbonate kaliumi.

18. Përbërjet e formulës së përgjithshme (III)



(III)

në të cilën

R^1 është 4,4,4-trifluorobutil, 3-hidroksi-3-metilbutil, 3-metoksipropil, 3-hidroksipropil, 3-hidroksibutil, 3-hidroksi-2-metilpropil, 3-hidroksi-2,2-dimetilpropil, 3-trifluorometoksipropil, 2-metoksietil, 2-hidroksietil, ose 2-(1-hidroksiciklopropil) etil;

R^4 është difluorometil, trifluorometil ose metil; dhe

R^5 është hidrogjen ose fluorine;

dhe diastereomere, enantiomere, kripëra, tretësit ose tretësit e kripërave të tyre.

19. Përbërjet e formulës së përgjithshme (III), si më poshtë:

metil 5-{[(5-fluoro-6-metilpiridin-2-il)karbonil]amino}-2-(3-hidroksi-3-metilbutil)-2H-indazole-6-karboksilate dhe

metil 2-(3-hidroksi-3-metilbutil)-5-({[6-(trifluorometil)piridin-2-il]karbonil}amino)-2H-indazole-6-karboksilate.

The present application relates to novel substituted indazoles, to processes for preparation thereof, to intermediates for use in the preparation of the novel compounds, to the use of the novel substituted indazoles for treatment and/or prophylaxis of diseases and to the use thereof for production of medicaments for treatment and/or prophylaxis of diseases, especially of proliferative disorders such as autoimmune disorders, of metabolic and inflammatory disorders, for example rheumatoid arthritis, spondyloarthritis (especially psoriatic spondyloarthritis and Bekhterev's disease), chronic obstructive pulmonary disease (abbreviation: COPD), multiple sclerosis, systemic lupus erythematosus, gout, metabolic syndrome, fatty liver hepatitis, insulin resistance, endometriosis and inflammation-induced or chronic pain, and of lymphoma.

The present invention relates to novel substituted indazoles of the general formula (I) which inhibit interleukin-1 receptor-associated kinase 4 (IRAK4).

Human IRAK4 (interleukin-1 receptor-associated kinase 4) plays a key role in the activation of the immune system. Therefore, this kinase is an important therapeutic target molecule for the development of inflammation-inhibiting substances. IRAK4 is expressed by a multitude of cells and mediates the signal transduction of Toll-like receptors (TLR), except for TLR3, and receptors of the interleukin (IL)-1β family consisting of the IL-1R (receptor), IL-18R, IL-33R and IL-36R (Janeway and Medzhitov, Annu. Rev. Immunol., 2002; Dinarello, Annu. Rev. Immunol., 2009; Flannery and Bowie, Biochemical Pharmacology, 2010).
Neither IRAK4 knockout mice nor human cells from patients lacking IRAK4 react to stimulation by TLRs (except for TLR3) and the IL-1β family (Suzuki, Suzuki, et al., Nature, 2002; Davidson, Currie, et al., The Journal of Immunology, 2006; Ku, von Bernuth, et al., JEM, 2007; Kim, Staschke, et al., JEM, 2007).
The binding of the TLR ligands or the ligands of the IL-1β family to the respective receptor leads to recruitment and binding of MyD88 [Myeloid differentiation primary response gene (88)] to the receptor. As a result, MyD88 interacts with IRAK4, resulting in the formation of an active complex which interacts with and activates the kinases IRAK1 or IRAK2 (Kollewe, Mackensen, et al., Journal of Biological Chemistry, 2004; Precious et al., J. Biol. Chem., 2009). As a result of this, the NF (nuclear factor)-κB signalling pathway and the MAPK (mitogen-activated protein kinase) signal pathway is activated (Wang, Deng, et al., Nature, 2001). The activation both of the NF-κB signal pathway and of the MAPK signal pathway leads to processes associated with different immune processes. For example, there is increased expression of various inflammatory signal molecules and enzymes such as cytokines, chemokines and COX-2 (cyclooxygenase-2), for example, and increased mRNA stability of inflammation-associated genes, for example COX-2, IL-6 (interleukin-6), IL-8 (Holtmann, Enninga, et al., Journal of Biological Chemistry, 2001; Datta, Novotny, et al., The Journal of Immunology, 2004). Furthermore, these processes may be associated with the proliferation and differentiation of particular cell types, for example monocytes, macrophages, dendritic cells, T cells and B cells (Wan, Chi, et al., Nat Immunol, 2006; McGettrick and J. O'Neill, British Journal of Haematology, 2007).

The central role of IRAK4 in the pathology of various inflammatory disorders had already been shown by direct comparison of wild-type (WT) mice with genetically modified animals having a kinase-inactivated form of IRAK4 (IRAK4 KDKI). IRAK4 KDKI animals have an improved clinical picture in the animal model of multiple sclerosis, atherosclerosis, myocardial infarction and Alzheimer's disease (Rekhter, Staschke, et al., Biochemical and Biophysical Research Communication, 2008; Maekawa, Mizue, et al., Circulation, 2009; Staschke, Dong, et al., The Journal of Immunology, 2009; Kim, Febbraio, et al., The Journal of Immunology, 2011; Cameron, Tse, et al., The Journal of Neuroscience, 2012). Furthermore, it was found that deletion of IRAK4 in the animal model protects against virus-induced myocarditis by virtue of an improved anti-viral reaction with simultaneously reduced systemic inflammation (Valaperti, Nishii, et al., Circulation, 2013). It has also been shown that the expression of IRAK4 correlates with the degree of Vogt-Koyanagi-Harada syndrome (Sun, Yang, et al., PLoS ONE, 2014). In addition, the high relevance of IRAK4 for immune complex-mediated IFNα (interferon-alpha) production by plasmacytoid dendritic cells, a key process in the pathogenesis of systemic lupus erythematosus (SLE), has been shown (Chiang et al., The Journal of Immunology, 2010). Furthermore, the signalling pathway is associated with obesity (Ahmad, R., P.

Shihab, et al., Diabetology & Metabolic Syndrome, 2015).
As well as the essential role of IRAK4 in congenital immunity, there are also hints that IRAK4 influences the differentiation of what are called the Th17 T cells, components of adaptive immunity. In the absence of IRAK4 kinase activity, fewer IL-17-producing T cells (Th17 T cells) are generated compared to WT mice. The inhibition of IRAK4 enables the prophylaxis and/or treatment of atherosclerosis, type 1 diabetes mellitus, rheumatoid arthritis, spondyloarthritis (especially psoriatic spondyloarthritis and Bekhterev's disease), lupus erythematosus, psoriasis, vitiligo, giant cell arteritis, chronic inflammatory bowel disorder and viral disorders, for example HIV (human immunodeficiency virus), hepatitis virus (Staschke, et al., The Journal of Immunology, 2009; Marquez, et al., Ann Rheum Dis, 2014; Zambrano-Zaragoza, et al., International Journal of Inflammation, 2014; Wang, et al., Experimental and Therapeutic Medicine, 2015; Ciccia, et al., Rheumatology, 2015).

Owing to the central role of IRAK4 in the MyD88-mediated signal cascade of TLRs (except for TLR3) and the IL-1 receptor family, the inhibition of IRAK4 can be utilized for the prophylaxis and/or treatment of disorders mediated by the receptors mentioned. TLRs and also components of the IL-1 receptor family are involved in the pathogenesis of rheumatoid arthritis, psoriasis, arthritis, myasthenia gravis, vasculitis, for example Behçet's disease, granulomatosis with polyangiitis and giant cell arteritis, pancreatitis, systemic lupus erythematosus, dermatomyositis and polymyositis, metabolic syndrome including, for example, insulin resistance, hypertension, dyslipoproteinaemia and obesity, diabetes mellitus (type 1 and type 2), diabetic nephropathy, osteoarthritis, Sjögren syndrome and sepsis (Yang, Tuzun, et al., J Immunol, 2005; Candia, Marquez et al., The Journal of Rheumatology, 2007; Scanzello, Plaas, et al. Curr Opin Rheumatol, 2008; Deng, Ma-Krupa, et al., Circ Res, 2009; Roger, Froidevaux, et al, PNAS, 2009; Devaraj, Tobias, et al., Arterioscler Thromb Vasc Biol, 2011; Kim, Cho, et al., Clin Rheumatol, 2010; Carrasco et al., Clinical and Experimental Rheumatology, 2011; Gambuzza, Licata, et al., Journal of Neuroimmunology, 2011; Fresno, Archives Of Physiology And Biochemistry, 2011; Volin and Koch, J Interferon Cytokine Res, 2011; Akash, Shen, et al., Journal of Pharmaceutical Sciences, 2012; Goh and Midwood, Rheumatology, 2012; Dasu, Ramirez, et al., Clinical Science, 2012; Ouziel, Gustot, et al., Am J Patho, 2012; Ramirez and Dasu, Curr Diabetes Rev, 2012, Okiyama et al., Arthritis Rheum, 2012; Chen et al., Arthritis Research & Therapy, 2013; Holle, Windmoller, et al., Rheumatology (Oxford), 2013; Li, Wang, et al., Pharmacology & Therapeutics, 2013; Sedimbi, Hagglof, et al., Cell Mol Life Sci, 2013; Caso, Costa, et al., Mediators of Inflammation, 2014; Cordiglieri, Marolda, et al., J Autoimmun, 2014; Jialal, Major, et al., J Diabetes Complications, 2014; Kaplan, Yazgan, et al., Scand J Gastroenterol, 2014; Talabot-Aye, et al., Cytokine, 2014; Zong, Dorph, et al., Ann Rheum Di, 2014; Ballak, Stienstra, et al., Cytokine, 2015; Timper, Seelig, et al., J Diabetes Complications, 2015). Skin diseases such as psoriasis, atopic dermatitis, Kindler's syndrome, bullous pemphigoid, allergic contact dermatitis, alopecia areata, acne inversa and acne vulgaris are associated with the IRAK4-mediated TLR signalling pathway or the IL-1R family (Schmidt, Mittnacht, et al., J Dermatol Sci, 1996; Hoffmann, J Investig Dermatol Symp Proc, 1999; Gilliet, Conrad, et al., Archives of Dermatology, 2004; Niebuhr, Langnickel, et al., Allergy, 2008; Miller, Adv Dermatol, 2008; Terhorst, Kalali, et al., Am J Clin Dermatol, 2010; Viguier, Guigue, et al., Annals of Internal Medicine, 2010; Cevikbas, Steinhoff, J Invest Dermatol, 2012;

Minkis, Aksentijevich, et al., Archives of Dermatology, 2012; Dispenza, Wolpert, et al., J Invest Dermatol, 2012; Minkis, Aksentijevich, et al., Archives of Dermatology, 2012; Gresnigt and van de Veerdonk, Seminars in Immunology, 2013; Selway, Kurczab, et al., BMC Dermatology, 2013; Sedimbi, Hagglof, et al., Cell Mol Life Sci, 2013; Wollina, Koch, et al. Indian Dermatol Online, 2013; Foster, Baliwag, et al., The Journal of Immunology, 2014).

Pulmonary disorders such as pulmonary fibrosis, obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), acute lung injury (ALI), interstitial lung disease (ILD), sarcoidosis and pulmonary hypertension also show an association with various TLR-mediated signal pathways. The pathogenesis of the pulmonary disorders may be either infectiously mediated or non-infectiously mediated processes (Ramirez Cruz, Maldonado Bernal, et al., Rev Alerg Mex, 2004; Jeyaseelan, Chu, et al., Infection and Immunity, 2005; Seki, Tasaka, et al., Inflammation Research, 2010; Xiang, Fan, et al., Mediators of Inflammation, 2010; Margaritopoulos, Antoniou, et al., Fibrogenesis & Tissue Repair, 2010; Hilberath, Carlo, et al., The FASEB Journal, 2011; Nadigel, Prefontaine, et al., Respiratory Research, 2011; Kovach and Standiford, International Immunopharmacology, 2011; Bauer, Shapiro, et al., Mol Med, 2012; Deng, Yang, et al., PLoS One, 2013; Freeman, Martinez, et al., Respiratory Research, 2013; Dubaniewicz, A., Human Immunology, 2013). TLRs and also IL-1R family members are also involved in the pathogenesis of other inflammatory disorders such as allergy, Behçet's disease, gout, lupus erythematosus, adult-onset Still's disease, pericarditis and chronic inflammatory bowel disorders such as ulcerative colitis and Crohn's disease, transplant rejection and graft-versus-host reaction, and so inhibition of IRAK4 here is a suitable prophylactic and/or therapeutic approach (Liu-Bryan, Scott, et al., Arthritis & Rheumatism, 2005; Piggott, Eisenbarth, et al., J Clin Inves, 2005; Christensen, Shupe, et al., Immunity, 2006; Cario, Inflammatory Bowel Diseases, 2010; Nickerson, Christensen, et al., The Journal of Immunology, 2010; Rakoff-Nahoum, Hao, et al., Immunity, 2006; Heimesaat, Fischer, et al., PLoS ONE, 2007; Heimesaat, Nogai, et al., Gut, 2010; Kobori, Yagi, et al., J Gastroenterol, 2010; Schmidt, Raghavan, et al., Nat Immunol, 2010; Shi, Mucsi, et al., Immunological Reviews, 2010; Leventhal and Schroppel, Kidney Int, 2012; Chen, Lin, et al., Arthritis Res Ther, 2013; Hao, Liu, et al., Curr Opin Gastroenterol, 2013; Kreisel and Goldstein, Transplant International, 2013; Li, Wang, et al., Pharmacology & Therapeutics, 2013; Walsh, Carthy, et al., Cytokine & Growth Factor Reviews, 2013; Zhu, Jiang, et al., Autoimmunity, 2013; Yap and Lai, Nephrology, 2013; Vennegaard, Dyring-Andersen, et al., Contact Dermatitis, 2014; D'Elia, Brucato, et al., Clin Exp Rheumatol, 2015; Jain, Thongprayoon, et al., Am J Cardiol., 2015; Li, Zhang, et al., Oncol Rep., 2015).

Gynaecological disorders mediated by TLR and the IL-1R family, such as adenomyosis, dysmenorrhoea, dyspareunia and endometriosis, especially endometriosis-associated pain and other endometriosis-associated symptoms such as dysmenorrhoea, dyspareunia, dysuria and dyschezia, can be positively influenced by the prophylactic and/or therapeutic use of IRAK4 inhibitors (Akoum, Lawson, et al., Human Reproduction, 2007; Allhorn, Boing, et al., Reproductive Biology and Endocrinology, 2008; Lawson, Bourcier, et al., Journal of Reproductive Immunology, 2008; Sikora, Mielczarek-Palacz, et al., American Journal of Reproductive Immunology, 2012; Khan, Kitajima, et al., Journal of Obstetrics and Gynaecology Research, 2013; Santulli, Borghese, et al., Human Reproduction, 2013). The prophylactic and/or therapeutic use of IRAK4 inhibitors can also have a positive

influence on atherosclerosis (Seneviratne, Sivagurunathan, et al., Clinica Chimica Acta, 2012; Falck-Hansen, Kassiteridi, et al., International Journal of Molecular Sciences, 2013; Sedimbi, Hagglof, et al., Cell Mol Life Sci, 2013).
In addition to the disorders already mentioned, IRAK4-mediated TLR processes have been described in the pathogenesis of eye disorders such as retinal ischaemia, keratitis, allergic conjunctivitis, keratoconjunctivitis sicca, macular degeneration and uveitis (Kaarniranta and Salminen, J Mol Med (Berl), 2009; Sun and Pearlman, Investigative Ophthalmology & Visual Science, 2009; Redfern and McDermott, Experimental Eye Research, 2010; Kezic, Taylor, et al., J Leukoc Biol, 2011; Chang, McCluskey, et al., Clinical & Experimental Ophthalmology, 2012; Guo, Gao, et al., Immunol Cell Biol, 2012; Lee, Hattori, et al., Investigative Ophthalmology & Visual Science, 2012; Qi, Zhao, et al., Investigative Ophthalmology & Visual Science, 2014).
The inhibition of IRAK4 is also a suitable therapeutic approach for fibrotic disorders, for example hepatic fibrosis, myocarditis, primary biliary cirrhosis, cystic fibrosis (Zhao, Zhao, et al., Scand J Gastroenterol, 2011; Benias, Gopal, et al., Clin Res Hepatol Gastroenterol, 2012; Yang, L. and E. Seki, Front Physiol, 2012; Liu, Hu, et al., Biochim Biophys Acta., 2015).
By virtue of the key position that IRAK4 has in disorders mediated by TLR- and the IL-1R family, it is possible to treat chronic liver disorders, for example fatty liver hepatitis and especially non-alcoholic fatty liver disease (NAFLD) and/or non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH) in a preventative and/or therapeutic manner with IRAK4 inhibitors (Nozaki, Saibara, et al., Alcohol Clin Exp Res, 2004; Csak, T., A. Velayudham, et al., Am J Physiol Gastrointest Liver Physiol, 2011; Miura, Kodama, et al., Gastroenterology, 2010; Kamari, Shaish, et al., J Hepatol, 2011; Ye, Li, et al., Gut, 2012; Roh, Seki, J Gastroenterol Hepatol, 2013; Ceccarelli, S., V. Nobili, et al., World J Gastroenterol, 2014; Miura, Ohnishi, World J Gastroenterol, 2014; Stojsavljevic, Palcic, et al., World J Gastroenterol, 2014).
Because of the central role of IRAK4 in TLR-mediated processes, the inhibition of IRAK4 also enables the treatment and/or prevention of cardiovascular and neurological disorders, for example myocardial reperfusion damage, myocardial infarction, hypertension (Oyama, Blais, et al., Circulation, 2004; Timmers, Sluijter, et al., Circulation Research, 2008; Fang and Hu, Med Sci Monit, 2011; Bijani, International Reviews of Immunology, 2012; Bomfim, Dos Santos, et al., Clin Sci (Lond), 2012; Christia and Frangogiannis, European Journal of Clinical Investigation, 2013; Thompson and Webb, Clin Sci (Lond), 2013; Hernanz, Martínez-Revelles, et al., British Journal of Pharmacology, 2015; Frangogiannis, Curr Opin Cardiol, 2015; Bomfim, Echem, et al., Life Sciences, 2015), and also Alzheimer's disease, stroke, craniocerebral trauma, amyotrophic lateral sclerosis (ALS) and Parkinson's (Brough, Tyrrell, et al., Trends in Pharmacological Sciences, 2011; Carty and Bowie, Biochemical Pharmacology, 2011; Denes, Kitazawa, Cheng, et al., The Journal of Immunology, 2011; Lim, Kou, et al., The American Journal of Pathology, 2011; Béraud and Maguire-Zeiss, Parkinsonism & Related Disorders, 2012; Denes, Wilkinson, et al., Disease Models & Mechanisms, 2013; Noelker, Morel, et al., Sci. Rep., 2013; Wang, Wang, et al., Stroke, 2013; Xiang, Chao, et al., Rev Neurosci, 2015; Lee, Lee, et al., J Neuroinflammation, 2015).
Because of the involvement of TLR-mediated signals and IL-1 receptor family-mediated signals via IRAK4 in the case of pruritus and pain, including acute, chronic, inflammatory and neuropathic pain, there may be assumed to be a therapeutic effect in the indications mentioned through the inhibition of IRAK4. Examples of pain include

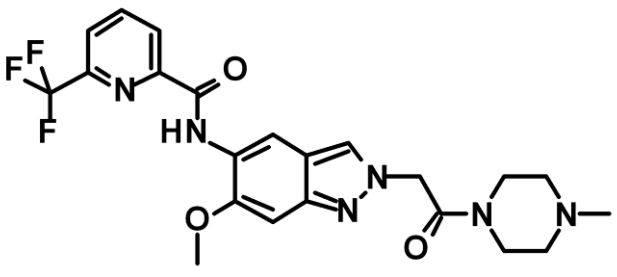
hyperalgesia, allodynia, premenstrual pain, endometriosis-associated pain, post-operative pain, interstitial cystitis, CRPS (complex regional pain syndrome), trigeminal neuralgia, prostatitis, pain caused by spinal cord injury, inflammation-induced pain, lower back pain, cancer pain, chemotherapy-associated pain, HIV treatment-induced neuropathy, burn-induced pain and chronic pain (Wolf, Livshits, et al., Brain, Behavior, and Immunity, 2008; Kim, Lee, et al., Toll-like Receptors: Roles in Infection and Neuropathology, 2009; del Rey, Apkarian, et al., Annals of the New York Academy of Sciences, 2012; Guerrero, Cunha, et al., European Journal of Pharmacology, 2012; Kwok, Hutchinson, et al., PLoS ONE, 2012; Nicotra, Loram, et al., Experimental Neurology, 2012; Chopra and Cooper, J Neuroimmune Pharmacol, 2013; David, Ratnayake, et al., Neurobiology of Disease, 2013; Han, Zhao, et al., Neuroscience, 2013; Liu and Ji, Pflugers Arch., 2013; Stokes, Cheung, et al., Journal of Neuroinflammation, 2013; Zhao, Zhang, et al., Neuroscience, 2013; Liu, Zhang, et al., Cell Research, 2014; Park, Stokes, et al., Cancer Chemother Pharmacol, 2014; Van der Watt, Wilkinson, et al., BMC Infect Dis, 2014; Won, K. A., M. J. Kim, et al., J Pain, 2014; Min, Ahmad, et al., Photochem Photobiol., 2015; Schrepf, Bradley, et al., Brain Behav Immun, 2015; Wong, L., J. D. Done, et al., Prostate, 2015).
This also applies to some oncological disorders. Particular lymphomas, for example ABC-DLBCL (activated B-cell diffuse large-cell B-cell lymphoma), mantle cell lymphoma and Waldenström's disease, and also chronic lymphatic leukaemia, melanoma, pancreatic tumour and liver cell carcinoma, are characterized by mutations in MyD88 or changes in MyD88 activity which can be treated by an IRAK4 inhibitor (Ngo, Young, et al., Nature, 2011; Puente, Pinyol, et al., Nature, 2011; Ochi, Nguyen, et al., J Exp Med, 2012; Srivastava, Geng, et al., Cancer Research, 2012; Treon, Xu, et al., New England Journal of Medicine, 2012; Choi, Kim, et al., Human Pathology, 2013; (Liang, Chen, et al., Clinical Cancer Research, 2013). In addition, MyD88 plays an important role in ras-dependent tumours, and so IRAK4 inhibitors are also suitable for treatment thereof (Kfoury, A., K. L. Corf, et al., Journal of the National Cancer Institute, 2013). There can also be assumed to be a therapeutic effect in breast cancer, ovarian carcinoma, colorectal carcinoma, head and neck carcinoma, lung cancer, prostate cancer through the inhibition of IRAK4, since the indications mentioned are associated with the signalling pathway (Szczepanski, Czystowska, et al., Cancer Res, 2009; Zhang, He, et al., Mol Biol Rep, 2009; Wang, Qian, et al., Br J Cancer Kim, 2010; Jo, et al., World J Surg Oncol, 2012; Zhao, Zhang, et al.; Front Immunol, 2014; Chen, Zhao, et al., Int J Clin Exp Pathol, 2015).
Inflammatory disorders such as CAPS (cryopyrin-associated periodic syndromes) including FCAS (familial cold autoinflammatory syndrome), MWS (Muckle-Wells syndrome), NOMID (neonatal-onset multisystem inflammatory disease) and CONCA (chronic infantile, neurological, cutaneous, and articular) syndrome; FMF (familial mediterranean fever), HIDS (hyper-IgD syndrome), TRAPS (tumour necrosis factor receptor 1-associated periodic syndrom), juvenile idiopathic arthritis, adult-onset Still's disease, Adamantiades-Behçet's disease, rheumatoid arthritis, osteoarthritis, keratoconjunctivitis sicca, PAPA syndrome (pyogenic arthritis, Pyoderma gangraenosum and acne), Schnitzler's syndrome and Sjögren syndrome are treated by blocking the IL-1 signal pathway; therefore here, too, an IRAK4 inhibitor is suitable for treatment of the diseases mentioned (Narayanan, Corrales, et al., Cornea, 2008; Brenner, Ruzicka, et al., British Journal of Dermatology, 2009; Henderson and Goldbach-Mansky, Clinical Immunology, 2010; Dinarello, European Journal of Immunology, 2011; Gul, Tugal-Tutkun, et al., Ann Rheum Dis, 2012; Pettersson,

Annals of MedicinePetterson, 2012; Ruperto, Brunner, et al., New England Journal of Medicine, 2012; Nordström, Knight, et al., The Journal of Rheumatology, 2012; Vijmasi, Chen, et al., Mol Vis, 2013; Yamada, Arakaki, et al., Opinion on Therapeutic Targets, 2013; de Koning, Clin Transl Allergy, 2014). The ligand of IL-33R, IL-33, is involved particularly in the pathogenesis of acute kidney failure, and so the inhibition of IRAK4 for prophylaxis and/or treatment is a suitable therapeutic approach (Akcay, Nguyen, et al., Journal of the American Society of Nephrology, 2011). Components of the IL-1 receptor family are associated with myocardial infarction, different pulmonary disorders such as asthma, COPD, idiopathic interstitial pneumonia, allergic rhinitis, pulmonary fibrosis and acute respiratory distress syndrome (ARDS), and so prophylactic and/or therapeutic action is to be expected in the indications mentioned through the inhibition of IRAK4 (Kang, Homer, et al., The Journal of Immunology, 2007; Imaoka, Hoshino, et al., European Respiratory Journal, 2008; Couillin, Vasseur, et al., The Journal of Immunology, 2009; Abbate, Kontos, et al., The American Journal of Cardiology, 2010; Lloyd, Current Opinion in Immunology, 2010; Pauwels, Bracke, et al., European Respiratory Journal, 2011; Haenuki, Matsushita, et al., Journal of Allergy and Clinical Immunology, 2012; Yin, Li, et al., Clinical & Experimental Immunology, 2012; Abbate, Van Tassell, et al., The American Journal of Cardiology, 2013; Alexander-Brett, et al., The Journal of Clinical Investigation, 2013; Bunting, Shadie, et al., BioMed Research International, 2013; Byers, Alexander-Brett, et al., The Journal of Clinical Investigation, 2013; Kawayama, Okamoto, et al., J Interferon Cytokine Res, 2013; Martínez-González, Roca, et al., American Journal of Respiratory Cell and Molecular Biology, 2013; Nakanishi, Yamaguchi, et al., PLoS ONE, 2013; Qiu, Li, et al., Immunology, 2013; Li, Guabiraba, et al., Journal of Allergy and Clinical Immunology, 2014; Saluja, Ketelaar, et al., Molecular Immunology, 2014; Lugrin, Parapanov, et al., The Journal of Immunology, 2015).

The prior art discloses a multitude of IRAK4 inhibitors (see, for example, Annual Reports in Medicinal Chemistry (2014), 49, 117 – 133).
US8293923 and US20130274241 disclose IRAK4 inhibitors having a 3-substituted indazole structure. There is no description of 2-substituted indazoles.

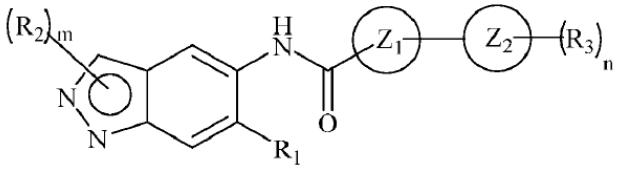
WO2013106254 and WO2011153588 disclose 2,3-disubstituted indazole derivatives.
WO2007091107 describes 2-substituted indazole derivatives for the treatment of Duchenne muscular dystrophy. The compounds disclosed do not have 6-hydroxyalkyl substitution.

WO2015091426 describes indazoles, such as Example 64, substituted at the 2 position by a carboxamide side chain.



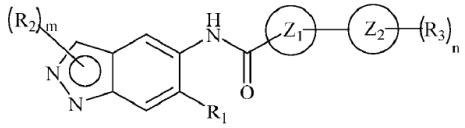
Example 64

WO2015104662 discloses 2-substituted indazoles of the following general formula:



in which R_2 is an alkyl or cycloalkyl group. There are explicit descriptions of 2-substituted indazoles having a methyl, 2-methoxyethyl and cyclopentyl group at the 2 position (Examples 1, 4 and 76). Also described by Example 117 is an indazole derivative having a hydroxyethyl substituent at the 1 position. However, no indazole derivatives having a 3-hydroxy-3-methylbutyl substituent at the 1 position or 2 position are described.
Indazoles having a hydroxyl-substituted alkyl group in the 2 position are encompassed generically by the general formula, but are not disclosed explicitly in WO2015104662. Indazoles having an alkyl group in the 2 position where the alkyl group is additionally substituted by a methylsulphonyl group are not encompassed by the general formula and the definitions of the R_2 substituents in WO2015104662.

In addition to the above-described substitution pattern on the indazole in 1 and 2 positions, WO2015104662 describes indazoles having substitution at the 6 position for which R_1 is defined as follows: alkyl, cyano, $-NR_aR_b$ or optionally substituted groups selected from cycloalkyl, aryl or heterocyclyl, where the substituents are independently alkyl, alkoxy, halogen, hydroxyl, hydroxyalkyl, amino, aminoalkyl, nitro, cyano, haloalkyl, haloalkoxy, $-OCOCH_2$-O-alkyl, $-OP(O)(O\text{-alkyl})_2$ or $-CH_2-OP(O)(O\text{-alkyl})_2$.
For imidazole compounds in which R_1 is an alkyl group, the effective filing date is 7 January 2015 (international filing date of WO2015104662). The Indian applications 146/CHE/2014 and 3018/CHE/2014 whose priority is claimed do not disclose any indazole compounds for which R_1 is an alkyl group.
Thus, indazole compounds of the following general formula:

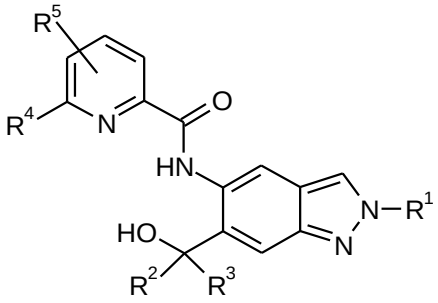


in which R_1 is an optionally substituted alkyl group are described for the first time on 7 January 2015 and hence after the priority date of the present application.
Examples of substituents at the 6 position described in WO2015104662 for R_1 are cyclopropyl, cyclohexyl, cyano, 3-fluorophenyl and saturated heterocyclic substituents. Indazoles having a hydroxyl-substituted alkyl group at position 6 are not described explicitly in WO2015104662.

The problem addressed by the present invention is that of providing novel compounds that act as inhibitors of interleukin-1 receptor associated kinase-4 (IRAK4).
The novel IRAK4 inhibitors are especially suitable for treatment and for prevention of proliferative, metabolic and inflammatory disorders characterized by an overreacting immune system. Particular mention should be made here of inflammatory skin disorders, cardiovascular disorders, lung disorders, eye disorders, neurological disorders, pain disorders and cancer.
In addition, the novel IRAK4 inhibitors are suitable for treatment and prevention

- of autoimmune and inflammatory disorders, especially rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, spondyloarthritis and gout,
- of metabolic disorders, especially hepatic disorders such as fatty liver, and
- of gynaecological disorders, especially of endometriosis and of endometriosis-associated pain and other endometriosis-associated symptoms such as dysmenorrhoea, dyspareunia, dysuria and dyschezia.

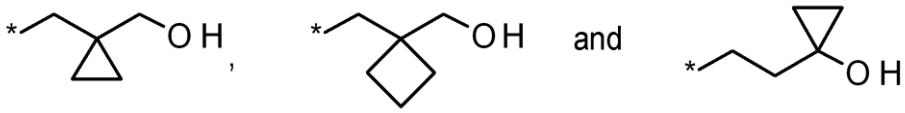
The present invention provides compounds of the general formula (I)



(I)

in which:

R^1 is C_1-C_6-alkyl, where the C_1-C_6-alkyl radical is unsubstituted or mono- or polysubstituted identically or differently by
halogen, hydroxyl, an unsubstituted or mono- or poly-halogen-substituted C_3-C_6-cycloalkyl, or an R^6, R^7SO_2, R^7SO or R^8O radical,
or a group selected from:



where * represents the bonding site of the group to the rest of the molecule;

R^2 and R^3 always have the same definition and are both either hydrogen or C_1-C_6-alkyl;

R^4 is halogen, cyano, an unsubstituted or a singly or multiply, identically or differently substituted C_1-C_6-alkyl or an unsubstituted or a singly or multiply, identically or differently substituted C_3-C_6-cycloalkyl, and the substituents are selected from the group of halogen and hydroxyl;

R^5 is hydrogen, halogen or an unsubstituted or mono- or poly-halogen-substituted C_1-C_6-alkyl;

R^6 is an unsubstituted or mono- or di-methyl-substituted monocyclic saturated heterocycle having 4 to 6 ring atoms, which contains a heteroatom or a heterogroup from the group of O, S, SO and SO_2;

R^7 is C_1-C_6-alkyl, where the C_1-C_6-alkyl radical is unsubstituted or mono- or polysubstituted identically or differently by halogen, hydroxyl or C_3-C_6-cycloalkyl,

or R^7 is C_3-C_6-cycloalkyl;

R^8 is C_1-C_6-alkyl, where the C_1-C_6-alkyl radical is unsubstituted or mono- or polysubstituted identically or differently by halogen;

and the diastereomers, enantiomers, salts, solvates or solvates of the salts thereof.

In the case of the synthesis intermediates and working examples of the invention described hereinafter, any compound specified in the form of a salt of the corresponding base or acid is generally a salt of unknown exact stoichiometric composition, as obtained by the respective preparation and/or purification process. Unless specified in more detail, additions to names and structural formulae, such as “hydrochloride”, “trifluoroacetate”, “sodium salt” or "x HCl", "x CF_3COOH", "x Na^+" should not therefore be understood in a stoichiometric sense in the case of such salts, but have merely descriptive character with regard to the salt-forming components present therein.
This applies correspondingly if synthesis intermediates or working examples or salts thereof were obtained in the form of solvates, for example hydrates, of unknown stoichiometric composition (if they are of a defined type) by the preparation and/or purification processes described.

Inventive compounds are the compounds of the formula (I) and the salts, solvates and solvates of the salts thereof, the compounds that are encompassed by formula (I) and are of the formulae mentioned below and the salts, solvates and solvates of the salts thereof and the compounds that are encompassed by the formula (I) and are mentioned below as embodiments and the salts, solvates and solvates of the salts thereof if the compounds that are encompassed by the formula (I) and are mentioned below are not already salts, solvates and solvates of the salts.
Preferred salts in the context of the present invention are physiologically acceptable salts of the inventive compounds. However, the invention also encompasses salts which themselves are unsuitable for pharmaceutical applications but which can be used, for example, for the isolation or purification of the inventive compounds.
Physiologically acceptable salts of the inventive compounds include acid addition salts of mineral acids, carboxylic acids and sulphonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.
Physiologically acceptable salts of the inventive compounds also include salts of conventional bases, by way of example and with preference alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having 1 to 16 carbon atoms, by way of example and with preference ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylenediamine and N-methylpiperidine.
Solvates in the context of the invention are described as those forms of the inventive compounds which form a complex in the solid or liquid state by coordination with

solvent molecules. Hydrates are a specific form of the solvates in which the coordination is with water.
The inventive compounds may, depending on their structure, exist in different stereoisomeric forms, i.e. in the form of configurational isomers or else, if appropriate, of conformational isomers (enantiomers and/or diastereomers, including those in the case of atropisomers). The present invention therefore encompasses the enantiomers and diastereomers, and the respective mixtures thereof. The stereoisomerically homogeneous constituents can be isolated from such mixtures of enantiomers and/or diastereomers in a known manner; chromatography processes are preferably used for this purpose, especially HPLC chromatography on an achiral or chiral phase.

If the inventive compounds can occur in tautomeric forms, the present invention encompasses all the tautomeric forms.

The present invention also encompasses all suitable isotopic variants of the inventive compounds. An isotopic variant of an inventive compound is understood here as meaning a compound in which at least one atom within the inventive compound has been exchanged for another atom of the same atomic number, but with a different atomic mass than the atomic mass which usually or predominantly occurs in nature. Examples of isotopes which can be incorporated into an inventive compound are those of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine, chlorine, bromine and iodine, such as 2H (deuterium), 3H (tritium), 13C, 14C, 15N, 17O, 18O, 32P, 33P, 33S, 34S, 35S, 36S, 18F, 36Cl, 82Br, 123I, 124I, 129I and 131I. Particular isotopic variants of an inventive compound, such as, in particular, those in which one or more radioactive isotopes have been incorporated, may be beneficial, for example, for the examination of the mechanism of action or of the active ingredient distribution in the body; because of the comparative ease of preparability and detectability, particularly compounds labelled with 3H or 14C isotopes are suitable for this purpose. In addition, the incorporation of isotopes, for example of deuterium, may lead to particular therapeutic benefits as a consequence of greater metabolic stability of the compound, for example an extension of the half-life in the body or a reduction in the active dose required; such modifications of the inventive compounds may therefore in some cases also constitute a preferred embodiment of the present invention. Isotopic variants of the inventive compounds can be prepared by the processes known to those skilled in the art, for example by the methods described further below and the procedures described in the working examples, by using corresponding isotopic modifications of the respective reagents and/or starting compounds.

The present invention further provides all the possible crystalline and polymorphous forms of the inventive compounds, where the polymorphs may be present either as single polymorphs or as a mixture of a plurality of polymorphs in all concentration ranges.
In the context of the present invention, unless specified otherwise, the substituents have the following meanings:

Alkyl in the context of the invention represents a straight-chain or branched alkyl radical having the particular number of carbon atoms specified. Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 1-methylpropyl, 2-methylpropyl,

tert-butyl, n-pentyl, 1-ethylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl and 2-ethylbutyl. Preference is given to methyl, ethyl, n-propyl, n-butyl, 2-methylbutyl, 3-methylbutyl and 2,2-dimethylpropyl.

Cycloalkyl in the context of the invention is a monocyclic saturated alkyl radical having the number of carbon atoms specified in each case. Preferred examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Alkoxy in the context of the invention represents a straight-chain or branched alkoxy radical having the particular number of carbon atoms specified. 1 to 6 carbon atoms are preferred. Examples include methoxy, ethoxy, n-propoxy, isopropoxy, 1-methylpropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy, isopentoxy, 1-ethylpropoxy, 1-methylbutoxy, 2-methylbutoxy, 3-methylbutoxy and n-hexoxy. Particular preference is given to a linear or branched alkoxy radical having 1 to 4 carbon atoms. Examples which may be mentioned as being preferred are methoxy, ethoxy, n-propoxy, 1-methylpropoxy, n-butoxy and isobutoxy.

Halogen in the context of the invention is fluorine, chlorine and bromine. Preference is given to fluorine.

Hydroxyl in the context of the invention is OH.

A monocyclic saturated heterocycle is a monocyclic saturated heterocycle which has 4 to 6 ring atoms and contains a heteroatom or a heterogroup from the group of O, S, SO and SO_2. A heterocycle having a heteroatom or a heterogroup from the group of O, SO and SO_2 is preferred. Examples include: oxetane, tetrahydrofuran, tetrahydro-2H-pyran-4-yl, 1,1-dioxidotetrahydro-2H-thiopyran-3-yl, 1,1-dioxidotetrahydro-2H-thiopyran-2-yl, 1,1-dioxidotetrahydro-2H-thiopyran-4-yl, 1,1-dioxidotetrahydrothiophen-3-yl, 1,1-dioxidotetrahydrothiophen-2-yl, 1,1-dioxidothietan-2-yl or 1,1-dioxidothietan-3-yl. Particular preference is given here to oxetane and tetrahydrofuran. Very particular preference is given to oxetan-3-yl.
A symbol * at a bond denotes the bonding site in the molecule.

When radicals in the inventive compounds are substituted, the radicals may be mono- or polysubstituted, unless specified otherwise. In the context of the present invention, all radicals which occur more than once are defined independently of one another. Substitution by one, two or three identical or different substituents is preferred.
A preferred embodiment of R^1 is a C_2-C_6-alkyl radical substituted by 1, 2 or 3 fluorine atoms. Particular preference is given to 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl and 4,4,4-trifluorobutyl. Very particular preference is given to a 4,4,4-trifluorobutyl radical.
A further preferred embodiment of R^1 is a C_2-C_6-alkyl radical substituted by one or two hydroxyl group(s) or one C_1-C_3-alkoxy or a tri-fluorine-substituted C_1-C_3-alkoxy.

Particular preference is given to a C_2-C_5-alkyl radical substituted by hydroxyl or C_1-C_3-alkoxy or trifluoromethoxy or 2,2,2-trifluoroethoxy. Very particular preference is given to 3-hydroxy-3-methylbutyl, 3-methoxypropyl, 3-hydroxypropyl, 3-trifluoromethoxypropyl, 2-methoxyethyl or 2-hydroxyethyl. Especially preferred is the 3-hydroxy-3-methylbutyl radical.

Further preferably, R^1 is a C_2-C_6-alkyl radical substituted by a C_1-C_6-alkyl-SO_2 group. A methyl-SO_2-substituted C_2-C_4-alkyl radical is particularly preferred. Especially preferred for R^1 are 2-(methylsulphonyl)ethyl or 3-(methylsulphonyl)propyl. From the latter group, 2-(methylsulphonyl)ethyl is particularly preferred.

Additionally preferably, R^1 is a C_1-C_3-alkyl radical substituted by oxetanyl, tetrahydrofuranyl, tetrahydro-2H-pyran-4-yl, 1,1-dioxidotetrahydro-2H-thiopyran-3-yl, 1,1-dioxidotetrahydro-2H-thiopyran-2-yl, 1,1-dioxidotetrahydro-2H-thiopyran-4-yl, 1,1-dioxidotetrahydrothiophen-3-yl, 1,1-dioxidotetrahydrothiophen-2-yl, 1,1-dioxidothietan-2-yl or 1,1-dioxidothietan-3-yl. Particular preference is given to a C_1-C_3-alkyl radical substituted by an oxetane group. Especially preferred for R^1 is an oxetan-3-ylmethyl group.

For R^2 and R^3, which always have the same definition, hydrogen or methyl are preferred. Methyl is particularly preferred.

In the case of R^4, preference is given to an unsubstituted or mono- or poly-halogen-substituted C_1-C_3-alkyl radical or a C_1-C_3-alkyl radical substituted by one hydroxyl group or a C_1-C_3-alkyl radical substituted by one hydroxyl group and three fluorine atoms.
For R^4, particular preference is given to the following radicals: methyl, ethyl, trifluoro-C_1-C_3-alkyl, difluoro-C_1-C_3-alkyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxypropan-2-yl and 2,2,2-trifluoro-1-hydroxyethyl. For R^4, particular preference is given to the methyl, trifluoromethyl and difluoromethyl radicals. Particular preference is given here to a trifluoromethyl radical.

A preferred embodiment of R^5 is hydrogen, fluorine, chlorine or C_1-C_3-alkyl. More preferably, R^5 is hydrogen, fluorine or methyl. Most preferably, R^5 is hydrogen or fluorine.

Particular preference is also given to compounds in which R^4 is methyl or trifluoromethyl and R^5 is fluorine. Very particular preference is given to compounds in which R^4 is methyl and R^5 is fluorine, where R^5 is in the ortho position to R^4.

For R^6, preferred embodiments include oxetanyl, tetrahydrofuranyl, tetrahydro-2H-pyran-4-yl, 1,1-dioxidotetrahydro-2H-thiopyran-3-yl, 1,1-dioxidotetrahydro-2H-thiopyran-2-yl, 1,1-dioxidotetrahydro-2H-thiopyran-4-yl, 1,1-dioxidotetrahydrothiophen-3-yl, 1,1-dioxidotetrahydrothiophen-2-yl, 1,1-dioxidothietan-2-yl or 1,1-dioxidothietan-3-yl. Particular preference is given here to oxetanyl. Very particular preference is given to oxetan-3-yl.

R^7 is exclusively connected to the functional groups –SO_2- and –SO-, i.e. is an R^7-substituted -SO_2- or SO group. In this connection, R^7 is preferably C_1-C_4-alkyl, where

the C_1-C_4-alkyl radical is unsubstituted or monosubstituted by hydroxyl or by cyclopropyl or substituted by three fluorine atoms. Additionally preferred for R^7 is a cyclopropyl radical. Particularly preferred for R^7 are methyl, ethyl or hydroxyethyl. Very particular preference is given to methyl for R^7.
This means that, in the case of a C_1-C_6-alkyl radical substituted by R^7SO_2- or R^7SO-, in the context of R^1, preference is given to a C_1-C_6-alkyl substituted by a C_1-C_6-alkyl-SO_2 or a C_1-C_6-alkyl-SO. For R^1, preference is given here especially to methylsulphonylethyl and methylsulphonylpropyl. Very particular preference is given here to methylsulphonylethyl.

For R^8, preference is given to an unsubstituted C_1-C_4-alkyl radical or a tri-fluorine-substituted C_1-C_4-alkyl radical. Particular preference is given to methyl, ethyl, trifluoromethyl or 2,2,2-trifluoroethyl. Very particular preference is given to methyl, trifluoromethyl or 2,2,2-trifluoroethyl.

Preference is given to compounds of the formula (I) in which

R^1 is C_1-C_6-alkyl, where the C_1-C_6-alkyl radical is unsubstituted or mono- or polysubstituted identically or differently by fluorine, hydroxyl or an R^6, R^7SO_2, R^7SO or R^8O radical;

R^2 and R^3 always have the same definition and are both either hydrogen or C_1-C_3-alkyl;

R^4 is halogen, cyano or C_1-C_3-alkyl, where the C_1-C_3-alkyl radical is unsubstituted or mono- or polysubstituted identically or differently by halogen or hydroxyl;

R^5 is hydrogen, fluorine, chlorine or C_1-C_3-alkyl;
R^6 is oxetanyl or tetrahydrofuranyl;
R^7 is C_1-C_4-alkyl, where the C_1-C_4-alkyl radical is unsubstituted or monosubstituted by hydroxyl or by cyclopropyl or substituted by three fluorine atoms;
R^8 is unsubstituted C_1-C_4-alkyl or tri-fluorine-substituted C_1-C_4-alkyl;

and the diastereomers, enantiomers, salts, solvates or solvates of the salts thereof.

Preference is additionally given to compounds of the formula (I) in which

R^1 is C_2-C_6-alkyl, where C_2-C_6-alkyl is unsubstituted, or
C_2-C_6-alkyl is mono-, di- or tri-fluorine-substituted or
C_2-C_6-alkyl is monosubstituted by hydroxyl, R^6, R^7SO_2, or R^8O,
or in which R^1 is an oxetanyl-substituted C_1-C_3-alkyl;

R^2 and R^3 always have the same definition and are both either hydrogen or methyl;

R^4 is an unsubstituted or mono- or poly-halogen-substituted C_1-C_3-alkyl radical or a C_1-C_3-alkyl radical substituted by one hydroxyl group or a C_1-C_3-alkyl radical substituted by one hydroxyl group and three fluorine atoms;

R^5 is hydrogen, fluorine or C_1-C_3-alkyl;

R^7 is C_1-C_3-alkyl;

R^8 is C_1-C_4-alkyl, where the C_1-C_4-alkyl radical is unsubstituted or mono-, di- or tri-fluorine-substituted;

and the diastereomers, enantiomers, salts, solvates or solvates of the salts thereof.

Particular preference is also given to compounds of the general formula (I) in which

R^1 is a C_2-C_5-alkyl radical substituted by hydroxyl or C_1-C_3-alkoxy or trifluoromethoxy or 2,2,2-trifluoroethoxy or trifluoromethyl or
is a methyl-SO_2-substituted C_2-C_4-alkyl radical or
is an oxetan-3-yl-substituted C_1-C_2-alkyl radical;

R^2 and R^3 always have the same definition and are both hydrogen or methyl;

R^4 is methyl, ethyl, trifluoro-C_1-C_3-alkyl, difluoro-C_1-C_3-alkyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxypropan-2-yl and 2,2,2-trifluoro-1-hydroxyethyl and

R^5 is hydrogen, fluorine or methyl;

and the diastereomers, enantiomers, salts, solvates or solvates of the salts thereof.

Very particular preference is given to compounds in which

R^1 is 4,4,4-trifluorobutyl, 3-hydroxy-3-methylbutyl, 3-hydroxybutyl, 3-methoxypropyl, 3-hydroxypropyl, 3-hydroxy-2-methylpropyl, 3-hydroxy-2,2-dimethylpropyl, 3-trifluoromethoxypropyl, 2-methoxyethyl, 2-hydroxyethyl, 2-(methylsulphonyl)ethyl or 3-(methylsulphonyl)propyl;

R^2 and R^3 are both methyl or hydrogen and

R^4 is difluoromethyl, trifluoromethyl or methyl and

R^5 is hydrogen or fluorine;

and the diastereomers, enantiomers, salts, solvates or solvates of the salts thereof.

Very particular preference is also given to compounds in which

R^1 is 3-hydroxy-3-methylbutyl, 3-hydroxybutyl, 3-hydroxy-2-methylpropyl, 3-hydroxy-2,2-dimethylpropyl, 3-(methylsulphonyl)propyl or 2-(methylsulphonyl)ethyl;

R^2 and R^3 are both methyl;

R^4 is difluoromethyl or trifluoromethyl; and

R^5 is hydrogen;

and the diastereomers, enantiomers, salts, solvates or solvates of the salts thereof.

Particular preference is additionally also given to compounds in which

R^1 is 3-hydroxy-3-methylbutyl, 3-hydroxybutyl, 3-hydroxy-2-methylpropyl, 3-hydroxy-2,2-dimethylpropyl, 3-(methylsulphonyl)propyl or 2-(methylsulphonyl)ethyl;

R^2 and R^3 are both methyl;

R^4 is methyl and

R^5 is fluorine, where R^5 is in the ortho position to R^4;

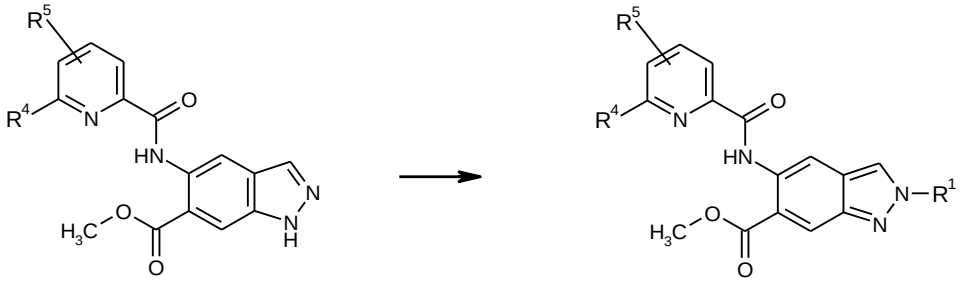
and the diastereomers, enantiomers, salts, solvates or solvates of the salts thereof.

The present invention especially provides the following compounds:

1) N-[6-(2-Hydroxypropan-2-yl)-2-(2-methoxyethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
2) N-[6-(Hydroxymethyl)-2-(2-methoxyethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
3) N-[6-(2-Hydroxypropan-2-yl)-2-(3-methoxypropyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
4) N-[6-(Hydroxymethyl)-2-(3-methoxypropyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
5) N-[2-(2-Hydroxyethyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
6) N-[6-(2-Hydroxypropan-2-yl)-2-(3-hydroxypropyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
7) N-[2-(2-Hydroxyethyl)-6-(hydroxymethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
8) N-[6-(2-Hydroxypropan-2-yl)-2-(oxetan-3-ylmethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
9) N-[6-(Hydroxymethyl)-2-(oxetan-3-ylmethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
10) N-{6-(2-Hydroxypropan-2-yl)-2-[3-(methylsulphonyl)propyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
11) N-[2-(3-Hydroxy-3-methylbutyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
12) N-{6-(2-Hydroxypropan-2-yl)-2-[2-(methylsulphonyl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
13) 6-(Difluoromethyl)-N-[2-(3-hydroxy-3-methylbutyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]pyridine-2-carboxamide
14) 6-(Difluoromethyl)-N-{6-(2-hydroxypropan-2-yl)-2-[2-(methylsulphonyl)ethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
15) 6-(Difluoromethyl)-N-[6-(2-hydroxypropan-2-yl)-2-(3-hydroxypropyl)-2H-indazol-5-yl]pyridine-2-carboxamide
16) N-[6-(2-Hydroxypropan-2-yl)-2-(4,4,4-trifluorobutyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

17) N-{6-(2-Hydroxypropan-2-yl)-2-[3-(trifluoromethoxy)propyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
18) N-{6-(2-Hydroxypropan-2-yl)-2-[3-(2,2,2-trifluoroethoxy)propyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
19) 5-Fluoro-N-[2-(3-hydroxy-3-methylbutyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-methylpyridine-2-carboxamide
20) N-[2-(3-Hydroxy-3-methylbutyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-methylpyridine-2-carboxamide
21) 6-(2-Hydroxypropan-2-yl)-N-[6-(2-hydroxypropan-2-yl)-2-(4,4,4-trifluorobutyl)-2H-indazol-5-yl]pyridine-2-carboxamide
22) N-{2-[2-(1-Hydroxycyclopropyl)ethyl]-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide.

The invention further provides a process for preparing compounds of the general formula (III) from compounds of the general formula (II)



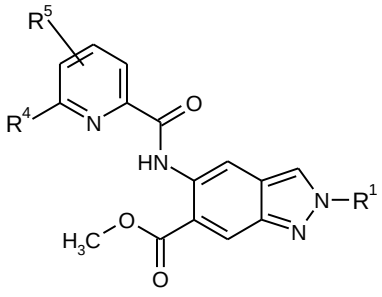
(II) (III)

in which

R^1 is 4,4,4-trifluorobutyl, 3-hydroxy-3-methylbutyl, 3-methoxypropyl, 3-hydroxypropyl, 3-hydroxy-2-methylpropyl, 3-hydroxy-2,2-dimethylpropyl, 3-trifluoromethoxypropyl, 2-methoxyethyl, 2-hydroxyethyl, 2-(methylsulphonyl)ethyl, 3-(methylsulphonyl)propyl or 2-(1-hydroxycyclopropyl)ethyl;
R^4 is difluoromethyl, trifluoromethyl or methyl; and
R^5 is hydrogen or fluorine;

by the reaction of (II) with appropriately substituted alkyl halides or alkyl 4-methylbenzenesulphonates in the presence of potassium carbonate.

The invention further provides compounds of the general formula (III)



(III)

in which

R^1 is 4,4,4-trifluorobutyl, 3-hydroxy-3-methylbutyl, 3-methoxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 3-hydroxy-2-methylpropyl, 3-hydroxy-2,2-

dimethylpropyl, 3-trifluoromethoxypropyl, 2-methoxyethyl, 2-hydroxyethyl, 2-(methylsulphonyl)ethyl, 3-(methylsulphonyl)propyl or 2-(1-hydroxycyclopropyl)ethyl;

R^4 is difluoromethyl, trifluoromethyl or methyl; and

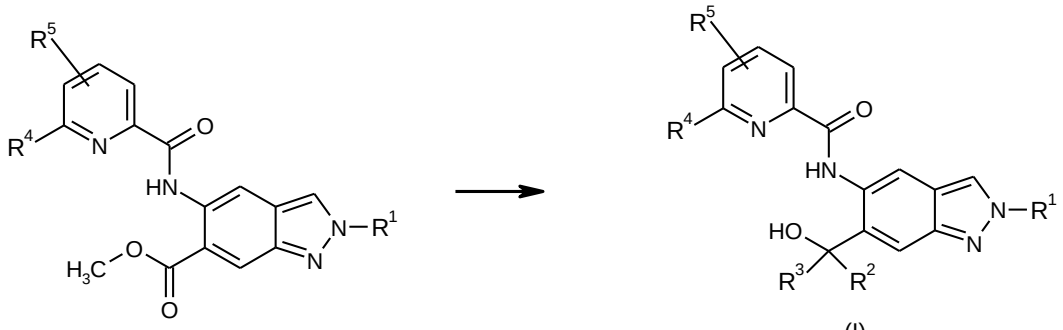
R^5 is hydrogen or fluorine;

and the diastereomers, enantiomers, salts, solvates or solvates of the salts thereof.

Preference is especially given to the following compounds of the general formula (III):
methyl 5-{[(5-fluoro-6-methylpyridin-2-yl)carbonyl]amino}-2-(3-hydroxy-3-methylbutyl)-2H-indazole-6-carboxylate and
methyl 2-(3-hydroxy-3-methylbutyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate.

The compounds of the general formula (III) are suitable for preparation of a portion of the compounds of the general formula (I).
Furthermore, the compounds of the general formula (III) are inhibitors of interleukin-1 receptor associated kinase-4 (IRAK4).

The invention further provides a process for preparing the inventive compounds of the general formula (I) from compounds of the formula (III)



(III) (I)

in which

R^1 is 4,4,4-trifluorobutyl, 3-hydroxy-3-methylbutyl, 3-hydroxybutyl, 3-methoxypropyl, 3-hydroxypropyl, 3-hydroxy-2-methylpropyl, 3-hydroxy-2,2-dimethylpropyl, 3-trifluoromethoxypropyl, 2-methoxyethyl, 2-hydroxyethyl, 3-(methylsulphonyl)propyl 2-(1-hydroxycyclopropyl)ethyl;

R^2 and R^3 are methyl;

R^4 is difluoromethyl, trifluoromethyl or methyl; and

R^5 is hydrogen or fluorine;

by a Grignard reaction with methylmagnesium bromide.
The inventive compounds act as inhibitors of IRAK4 kinase and have an unforeseeable useful pharmacological activity spectrum.
Thus, in addition to the subject matter mentioned above, the present invention also provides the use of the inventive compounds for treatment and/or prophylaxis of diseases in man and animals.
Treatment and/or prophylaxis of gynaecological disorders, inflammatory skin disorders, cardiovascular disorders, pulmonary disorders, eye disorders, autoimmune disorders, pain disorders, metabolic disorders, gout, hepatic disorders, metabolic syndrome, insulin resistance and cancers with the inventive IRAK4 inhibitors is

particularly preferred.
The inventive compounds are suitable for prophylaxis and/or treatment of various disorders and disease-related states, especially disorders mediated by TLR (except for TLR3) and/or the IL-1 receptor family and/or disorders whose pathology is mediated directly by IRAK4. IRAK4-associated disorders include multiple sclerosis, atherosclerosis, myocardial infarction, Alzheimer's disease, virus-induced myocarditis, gout, Vogt-Koyanagi-Harada syndrome, lupus erythematosus, psoriasis, spondyloarthritis and arthritis.
The inventive compounds can also be used for prophylaxis and/or treatment of disorders mediated by MyD88 and TLR (except for TLR3). This includes multiple sclerosis, rheumatoid arthritis, spondyloarthritis (especially psoriatic spondyloarthritis and Bekhterev's disease), metabolic syndrome including insulin resistance, diabetes mellitus, osteoarthritis, Sjögren syndrome, giant cell arteritis, sepsis, poly- and dermatomyositis, skin disorders such as psoriasis, atopic dermatitis, alopecia areata, acne inversa and acne vulgaris, pulmonary disorders such as pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), acute lung injury (ALI), interstitial lung disease (ILD), sarcoidosis and pulmonary hypertension.
Because of the mechanism of action of the inventive compounds, they are suitable for prophylaxis and/or treatment of the TLR-mediated disorders Behçet's disease, gout, endometriosis and endometriosis-associated pain and other endometriosis-associated symptoms such as dysmenorrhoea, dyspareunia, dysuria and dyschezia. In addition, the inventive compounds are suitable for prophylaxis and/or treatment in the case of transplant rejection, lupus erythematosus, adult-onset Still's disease and chronic inflammatory bowel disorders such as ulcerative colitis and Crohn's disease.
In addition to the disorders already listed, the use of the inventive compounds is also suitable for treatment and/or prevention of the following disorders: eye disorders such as keratitis, allergic conjunctivitis, keratoconjunctivitis sicca, macular degeneration and uveitis; cardiovascular disorders such as atherosclerosis, myocardial reperfusion damage, myocardial infarction, hypertension and neurological disorders such as Alzheimer's disease, stroke and Parkinson's.
The mechanism of action of the inventive compounds also enables the prophylaxis and/or treatment of hepatic disorders mediated by TLR and the IL-1 receptor family, especially NAFLD, NASH, ASH, liver fibrosis and liver cirrhosis.
The prophylaxis and/or treatment of pruritus and pain, especially of acute, chronic, inflammatory and neuropathic pain, is also provided by the inventive compounds.
Because of the mechanism of action of the inventive compounds, they are suitable for prophylaxis and/or treatment of oncological disorders such as lymphoma, chronic lymphatic leukaemia, melanoma and liver cell carcinoma, breast cancer, prostate cancer and Ras-dependent tumours.
Moreover, the inventive compounds are suitable for the treatment and/or prevention of disorders mediated via the IL-1 receptor family. These disorders include CAPS (cryopyrin-associated periodic syndromes) including FCAS (familial cold autoinflammatory syndrome), MWS (Muckle-Wells syndrome), NOMID (neonatal-onset multisystem inflammatory disease) and CONCA (chronic infantile, neurological, cutaneous, and articular) syndrome, FMF (familial mediterranean fever), HIDS (hyper-IgD syndrome), TRAPS (tumour necrosis factor receptor 1-associated periodic syndrome), juvenile idiopathic arthritis, adult-onset Still's disease, Adamantiades-Behçet's disease, rheumatoid arthritis, psoriasis, arthritis, Bekhterev's disease,

osteoarthritis, keratoconjunctivitis sicca und Sjögren syndrome, multiple sclerosis, lupus erythematosus, alopecia areata, type 1 diabetes mellitus, type 2 diabetes mellitus and the sequelae of myocardial infarction. Pulmonary disorders such as asthma, COPD, idiopathic interstitial pneumonia and ARDS, gynaecological disorders such as endometriosis and endometriosis-associated pain and other endometriosis-associated symptoms such as dysmenorrhoea, dyspareunia, dysuria and dyschezia, chronic-inflammatory bowel disorders such as Crohn's disease and ulcerative colitis are associated with dysregulation of the IL-1 receptor family and are suitable for therapeutic and/or prophylactic use of the inventive compounds.
The inventive compounds can also be used for treatment and/or prevention of IL-1 receptor family-mediated neurological disorders such as stroke, Alzheimer's, craniocerebral trauma, and dermatological disorders such as psoriasis, atopic dermatitis, acne inversa, alopecia areata and allergic contact dermatitis.

In addition, the inventive compounds are suitable for the treatment and/or prophylaxis of pain disorders, especially of acute, chronic, inflammatory and neuropathic pain. This preferably includes hyperalgesia, allodynia, pain from arthritis (such as osteoarthritis, rheumatoid arthritis and spondyloarthritis), premenstrual pain, endometriosis-associated pain, post-operative pain, pain from interstitial cystitis, CRPS (complex regional pain syndrome), trigeminal neuralgia, pain from prostatitis, pain caused by spinal cord injuries, inflammation-induced pain, lower back pain, cancer pain, chemotherapy-associated pain, HIV treatment-induced neuropathy, burn-induced pain and chronic pain.

The present invention further also provides a method for treatment and/or prevention of disorders, especially the disorders mentioned above, using an effective amount of at least one of the inventive compounds.
In the context of the present invention, the term "treatment" or "treating" includes inhibition, retardation, checking, alleviating, attenuating, restricting, reducing, suppressing, repelling or healing of a disease, a condition, a disorder, an injury or a health problem, or the development, the course or the progression of such states and/or the symptoms of such states. The term "therapy" is understood here to be synonymous with the term "treatment".
The terms "prevention", "prophylaxis" and "preclusion" are used synonymously in the context of the present invention and refer to the avoidance or reduction of the risk of contracting, experiencing, suffering from or having a disease, a condition, a disorder, an injury or a health problem, or a development or advancement of such states and/or the symptoms of such states.
The treatment or prevention of a disease, a condition, a disorder, an injury or a health problem may be partial or complete.
The inventive compounds can be used alone or, if required, in combination with other active ingredients. The present invention further provides medicaments containing at least one of the inventive compounds and one or more further active ingredients, especially for treatment and/or prevention of the abovementioned disorders. Preferred examples of active ingredients suitable for combinations include:
General mention may be made of active ingredients such as antibacterial (e.g. penicillins, vancomycin, ciprofloxacin), antiviral (e.g. aciclovir, oseltamivir) and antimycotic (e.g. naftifin, nystatin) substances and gamma globulins, immunomodulatory and immunosuppressive compounds such as cyclosporin,

Methotrexat®, TNF antagonists (e.g. Humira®,, Etanercept, Infliximab), IL-1 inhibitors (e.g. Anakinra, Canakinumab, Rilonacept), phosphodiesterase inhibitors (e.g. Apremilast), Jak/STAT in general (e.g. Tofacitinib, Baricitinib, GLPG0634), leflunomid, cyclophosphamide, rituximab, belimumab, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids (e.g. prednisone, prednisolone, methylprednisolone, hydrocortisone, betamethasone), cyclophosphamide, azathioprine and sulfasalazine; paracetamol, non-steroidal anti-inflammatory substances (NSAIDS) (aspirin, ibuprofen, naproxen, etodolac, celecoxib, colchicine).
The following should be mentioned for tumour therapy: immunotherapy (e.g. aldesleukin, alemtuzumab, basiliximab, catumaxomab, celmoleukin, denileukin diftitox, eculizumab, edrecolomab, gemtuzumab, ibritumomab tiuxetan, imiquimod, interferon-alpha, interferon beta, interferon-gamma, ipilimumab, lenalidomid, lenograstim, mifamurtid, ofatumumab, oprelvekin, picibanil, plerixafor, polysaccharide-K, sargramostim, sipuleucel-T, tasonermin, teceleukin, tocilizumab), antiproliferative substances, for example but not exclusively amsacrin, arglabin, arsenic trioxide, asparaginase, bleomycin, busulfan, dactinomycin, docetaxel, epirubicin, peplomycin, trastuzumab, rituximab, obinutuzumab, ofatumumab, tositumomab, aromatase inhibitors (e.g. exemestan, fadrozol, formestan, letrozol, anastrozol, vorozol), antioestrogens (e.g. chlormadinon, fulvestrant, mepitiostan, tamoxifen, toremifen), oestrogens (e.g. oestradiol, polyoestradiol phosphate, raloxifen), gestagens (e.g. medroxyprogesteron, megestrol), topoisomerase I inhibitors (e.g. irinotecan, topotecan), topoisomerase II inhibitors (e.g. amrubicin, daunorubicin, elliptiniumacetat, etoposid, idarubicin, mitoxantron, teniposid), microtubuli-active substances (e.g. cabazitaxel, eribulin, paclitaxel, vinblastin, vincristin, vindesin, vinorelbin), telomerase inhibitors (e.g. imetelstat), alkylating substances and histone deacetylase inhibitors (e.g. bendamustin, carmustin, chlormethin, dacarbazin, estramustin, ifosfamid, lomustin, mitobronitol, mitolactol, nimustin prednimustin, procarbazin, ranimustin, streptozotocin, temozolomid, thiotepa, treosulfan, trofosfamid, vorinostat, romidepsin, panobinostat); substances which affect cell differentation processes, such as abarelix, aminoglutethimid, bexaroten, MMP inhibitors (peptide mimetics, non-peptide mimetics and tetracyclines, for example marimastat, BAY 12-9566, BMS-275291, clodronate, prinomastat, doxycycline), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus, zotarolimus), antimetabolites (e.g. clofarabin, doxifluridin, methotrexate, 5-fluorouracil, cladribin, cytarabin, fludarabin, mercaptopurin, methotrexate, pemetrexed, raltitrexed, tegafur, tioguanin), platinum compounds (e.g. carboplatin, cisplatin, cisplatinum, eptaplatin, lobaplatin, miriplatin, nedaplatin, oxaliplatin); antiangiogenic compounds (e.g. bevacizumab), antiandrogenic compounds (e.g. bevacizumab, enzalutamid, flutamid, nilutamid, bicalutamid, cyproteron, cyproteron acetate), proteasome inhibitors (e.g. bortezomib, carfilzomib, oprozomib, ONYX0914), gonadoliberin agonists and antagonists (e.g. abarelix, buserelin, deslorelin, ganirelix, goserelin, histrelin, triptorelin, degarelix, leuprorelin), methionine aminopeptidase inhibitors (e.g. bengamide derivatives, TNP-470, PPI-2458), heparanase inhibitors (e.g. SST0001, PI-88); inhibitors against genetically modified Ras protein (e.g. farnesyl transferase inhibitors such as lonafarnib, tipifarnib), HSP90 inhibitors (e.g. geldamycin derivatives such as 17-allylaminogeldanamycin, 17–demethoxygeldanamycin (17AAG), 17-DMAG, retaspimycin hydrochloride, IPI-493, AUY922, BIIB028, STA-9090, KW-2478), kinesin spindle protein inhibitors (e.g. SB715992, SB743921, pentamidine/chlorpromazine), MEK (mitogen-activated protein kinase kinase)

inhibitors (e.g. trametinib, BAY 86-9766 (refametinib), AZD6244), kinase inhibitors (e.g.: sorafenib, regorafenib, lapatinib, Sutent, dasatinib, cetuximab, BMS-908662, GSK2118436, AMG 706, erlotinib, gefitinib, imatinib, nilotinib, pazopanib, roniciclib, sunitinib, vandetanib, vemurafenib), hedgehog signal inhibitors (e.g. cyclopamin, vismodegib), BTK (Bruton's tyrosine kinase) inhibitor (e.g. ibrutinib), JAK/pan-JAK (janus kinase) inhibitor (e.g. SB-1578, baricitinib, tofacitinib, pacritinib, momelotinib, ruxolitinib, VX-509, AZD-1480, TG-101348), PI3K inhibitor (e.g. BAY 1082439, BAY 80-6946 (copanlisib), ATU-027, SF-1126, DS-7423, GSK-2126458, buparlisib, PF-4691502, BYL-719, XL-147, XL-765, idelalisib), SYK (spleen tyrosine kinase) inhibitor (e.g. fostamatinib, Excellair, PRT-062607), p53 gene therapy, bisphosphonates (e.g. etridonat, clodronat, tiludronat, pamidronat, alendronic acid, ibandronat, risedronat, zoledronat). For combination, the following active ingredients should also be mentioned by way of example but not exclusively: rituximab, cyclophosphamide, doxorubicin, doxorubicin in combination with oestrone, vincristine, chlorambucil, fludarabin, dexamethasone, cladribin, prednisone, 131I-chTNT, abirateron, aclarubicin, alitretinoin, bisantren, calcium folinate, calcium levofolinate, capecitabin, carmofur, clodronic acid, romiplostim, crisantaspase, darbepoetin alfa, decitabin, denosumab, dibrospidium chloride, eltrombopag, endostatin, epitiostanol, epoetin alfa, filgrastim, fotemustin, gallium nitrate, gemcitabin, glutoxim, histamine dihydrochloride, hydroxycarbamide, improsulfan, ixabepilon, lanreotid, lentinan, levamisol, lisurid, lonidamin, masoprocol, methyltestosterone, methoxsalen, methyl aminolevulinate, miltefosin, mitoguazon, mitomycin, mitotan, nelarabin, nimotuzumab, nitracrin, omeprazol, palifermin, panitumumab, pegaspargase, PEG epoetin beta (methoxy-PEG epoetin beta), pegfilgrastim, peg interferon alfa-2b, pentazocin, pentostatin, perfosfamid, pirarubicin, plicamycin, poliglusam, porfimer-sodium, pralatrexate, quinagolid, razoxan, sizofiran, sobuzoxan, sodium glycididazole, tamibaroten, the combination of tegafur and gimeracil and oteracil, testosterone, tetrofosmin, thalidomide, thymalfasin, trabectedin, tretinoin, trilostan, tryptophan, ubenimex, vapreotid, yttrium-90 glass microbeads, zinostatin, zinostatin stimalamer.

Also suitable for tumour therapy is a combination of a non-drug therapy such as chemotherapy (e.g. azacitidine, belotecan, enocitabine, melphalan, valrubicin, vinflunin, zorubicin), radiotherapy (e.g. I-125 seeds, palladium-103 seed, radium-223 chloride) or phototherapy (e.g. temoporfin, talaporfin) which is accompanied by a drug treatment with the inventive IRAK4 inhibitors or which, after the non-drug tumour therapy such as chemotherapy, radiotherapy or phototherapy has ended, are supplemented by a drug treatment with the inventive IRAK4 inhibitors.
In addition to those mentioned above, the inventive IRAK4 inhibitors can also be combined with the following active ingredients:
active ingredients for Alzheimer's therapy, for example acetylcholinesterase inhibitors (e.g. donepezil, rivastigmine, galantamin, tacrine), NMDA (N-methyl-D-aspartate) receptor antagonists (e.g. memantine); L-DOPA/carbidopa (L-3,4-dihydroxyphenylalanine), COMT (catechol-O-methyltransferase) inhibitors (e.g. entacapon), dopamine agonists (e.g. ropinrol, pramipexol, bromocriptin), MAO-B (monoaminooxidase-B) inhibitors (e.g. selegilin), anticholinergics (e.g. trihexyphenidyl) and NMDA antagonists (e.g. amantadin) for treatment of Parkinson's; beta-interferon (IFN-beta) (e.g. IFN beta-1b, IFN beta-1a Avonex® and Betaferon®), glatiramer acetate, immunoglobulins, natalizumab, fingolimod and

immunosuppressants such as mitoxantrone, azathioprine and cyclophosphamide for treatment of multiple sclerosis; substances for treatment of pulmonary disorders, for example beta-2-sympathomimetics (e.g. salbutamol), anticholinergics (e.g. glycopyrronium), methylxanthines (e.g. theophylline), leukotriene receptor antagonists (e.g. montelukast), PDE-4 (phosphodiesterase type 4) inhibitors (e.g. roflumilast), methotrexate, IgE antibodies, azathioprine and cyclophosphamide, cortisol-containing preparations; substances for treatment of osteoarthritis such as non-steroidal anti-inflammatory substances (NSAIDs). In addition to the two therapies mentioned, methotrexate and biologics for B-cell and T-cell therapy (e.g. rituximab, abatacept) should be mentioned for rheumatoid disorders, for example rheumatoid arthritis, spondyloarthritis and juvenile idiopathic arthritis. Neurotrophic substances such as acetylcholinesterase inhibitors (e.g. donepezil), MAO (monoaminooxidase) inhibitors (e.g. selegiline), interferons und anticonvulsives (e.g. gabapentin); active ingredients for treatment of cardiovascular disorders such as beta-blockers (e.g. metoprolol), ACE inhibitors (e.g. benazepril), angiotensin receptor blockers (e.g. losartan, valsartan), diuretics (e.g. hydrochlorothiazide), calcium channel blockers (e.g. nifedipine), statins (e.g. simvastatin, fluvastatin); anti-diabetic drugs, for example metformin, glinides (e.g. nateglinide), DPP-4 (dipeptidyl peptidase-4) inhibitors (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin), SGLT2 (sodium/glucose cotransporter 2) inhibitors/ gliflozin (e.g. dapagliflozin, empagliflozin), incretin mimetics (hormone glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptid 1 (GLP-1) analogues/agonists) (e.g. exenatide, liraglutide, lixisenatide), α-glucosidase inhibitors (e.g. acarbose, miglitol, voglibiose) and sulphonylureas (e.g. glibenclamide, tolbutamide), insulin sensitizers (e.g. pioglitazone) and insulin therapy (e.g. NPH insulin, insulin lispro), substances for treatment of hypoglycaemia for treatment of diabetes and metabolic syndrome. Lipid-lowering drugs, for example fibrates (e.g. bezafibrate, etofibrate, fenofibrate, gemfibrozil), nicotinic acid derivatives (e.g. nicotinic acid/laropiprant), ezetimib, statins (e.g. simvastatin, fluvastatin), anion exchangers (e.g. colestyramine, colestipol, colesevelam). Active ingredients such as mesalazine, sulfasalazine, azathioprine, 6-mercaptopurine or methotrexate, probiotic bacteria (Mutaflor, VSL#3®, Lactobacillus GG, Lactobacillus plantarum, L. acidophilus, L. casei, Bifidobacterium infantis 35624, Enterococcus fecium SF68, Bifidobacterium longum, Escherichia coli Nissle 1917), antibiotics, for example ciprofloxacin and metronidazole, anti-diarrhoea drugs, for example loperamide, or laxatives (bisacodyl) for treatment of chronic-inflammatory bowel disorders. Immunosuppressants such as glucocorticoids and non-steroidale anti-inflammatory substances (NSAIDs), cortisone, chloroquin, cyclosporine, azathioprine, belimumab, rituximab, cyclophosphamide for treatment of lupus erythematosus. By way of example but not exclusively, calcineurin inhibitors (e.g. tacrolimus and ciclosporin), cell division inhibitors (e.g. azathioprine, mycophenolate mofetil, mycophenolic acid, everolimus or sirolimus), rapamycin, basiliximab, daclizumab, anti-CD3 antibodies, anti-T-lymphocyte globulin/anti-lymphocyte globulin for organ transplants. Vitamin D3 analogues, for example calcipotriol, tacalcitol or calcitriol, salicylic acid, urea, ciclosporine, methotrexate, efalizumab for dermatological disorders.

Mention should also be made of medicaments comprising at least one of the inventive compounds and one or more further active ingredients, especially EP4 inhibitors (prostaglandin E2 receptor 4 inhibitors), P2X3 inhibitors (P2X purinoceptor 3), PTGES inhibitors (prostaglandin E synthase inhibitors) or AKR1C3 inhibitors (aldo-

keto reductase family 1 member C3 inhibitors), for treatment and/or prevention of the aforementioned disorders.

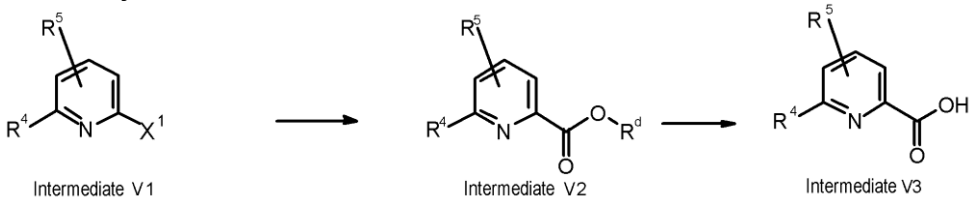
The inventive compounds can act systemically and/or locally. For this purpose, they can be administered in a suitable manner, for example by the oral, parenteral, pulmonal, nasal, sublingual, lingual, buccal, rectal, dermal, transdermal or conjunctival route, via the ear or as an implant or stent.
The inventive compounds can be administered in administration forms suitable for these administration routes.
Suitable administration forms for oral administration are those which work according to the prior art and release the inventive compounds rapidly and/or in a modified manner and which contain the inventive compounds in crystalline and/or amorphous and/or dissolved form, for example tablets (uncoated or coated tablets, for example with gastric juice-resistant or retarded-dissolution or insoluble coatings which control the release of the inventive compound), tablets or films/oblates which disintegrate rapidly in the oral cavity, films/lyophilizates, capsules (for example hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.
Parenteral administration can be accomplished with avoidance of a resorption step (for example by an intravenous, intraarterial, intracardiac, intraspinal or intralumbar route) or with inclusion of a resorption (for example by an intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal route). Administration forms suitable for parenteral administration include preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilizates or sterile powders.
For the other administration routes, suitable examples are inhalable medicament forms (including powder inhalers, nebulizers), nasal drops, solutions or sprays, tablets, films/oblates or capsules for lingual, sublingual or buccal administration, suppositories, ear or eye preparations, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (e.g. patches), milk, pastes, foams, sprinkling powders, implants or stents.
Preference is given to oral or parenteral administration, especially oral administration.
The inventive compounds can be converted to the administration forms mentioned. This can be accomplished in a manner known per se by mixing with inert, nontoxic, pharmaceutically suitable excipients. These excipients include carriers (for example microcrystalline cellulose, lactose, mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersing or wetting agents (for example sodium dodecylsulphate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (e.g. antioxidants, for example ascorbic acid), colorants (e.g. inorganic pigments, for example iron oxides) and flavour and/or odour correctants.
The present invention further provides medicaments which comprise at least one inventive compound, typically together with one or more inert, nontoxic, pharmaceutically suitable excipients, and the use thereof for the aforementioned purposes.
In general, it has been found to be advantageous in the case of parenteral administration to administer amounts of about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg, of body weight to achieve effective results. In the case of oral administration the dosage is about 0.01 to 100 mg/kg, preferably about 0.01 to 20 mg/kg and most preferably 0.1 to 10 mg/kg of body weight.

It may nevertheless be necessary in some cases to deviate from the stated amounts, specifically as a function of the body weight, route of administration, individual response to the active ingredient, nature of the preparation and time or interval over which administration takes place. Thus in some cases it may be sufficient to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of administration of greater amounts, it may be advisable to divide them into several individual doses over the day.
The working examples which follow illustrate the invention. The invention is not restricted to the examples.
Unless stated otherwise, the percentages in the tests and examples which follow are percentages by weight; parts are parts by weight. Solvent ratios, dilution ratios and concentration data for the liquid/liquid solutions are based in each case on volume.

Preparation of the inventive compounds

The preparation of the inventive compounds is illustrated by the synthesis schemes which follow.

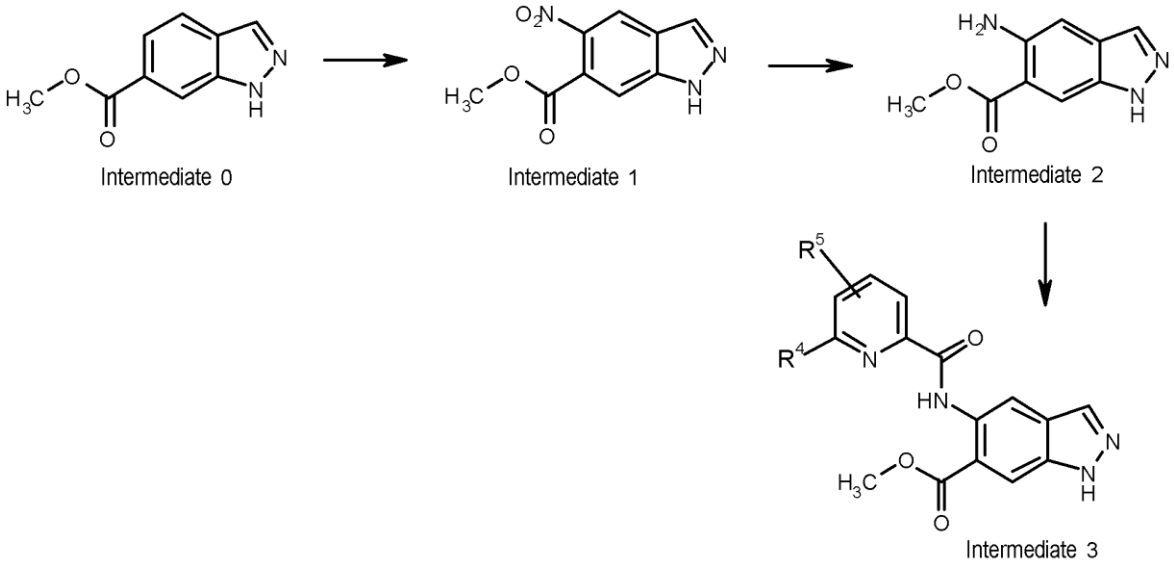
Starting materials used for synthesis of the inventive compounds are carboxylic acids (Intermediate V3), which are commercially available or can be prepared by routes known from the literature or analogously to routes known from the literature (see, for example, European Journal of Organic Chemistry 2003, 8, 1559 – 1568, Chemical and Pharmaceutical Bulletin, 1990, 38, 9, 2446 – 2458, Synthetic Communications 2012, 42, 658 – 666, Tetrahedron, 2004, 60, 51, 11869 - 11874) (see, for example, Synthesis Scheme 1). Some carboxylic acids V3 can be prepared proceeding from carboxylic esters (Intermediate V2) by hydrolysis (cf., for example, the reaction of ethyl 6-(hydroxymethyl)pyridine-2-carboxylate with aqueous sodium hydroxide solution in methanol, WO200411328) or – in the case of a *tert*-butyl ester – by reaction with an acid, for example hydrogen chloride or trifluoroacetic acid (cf., for example, Dalton Transactions, 2014, 43, 19, 7176 – 7190). The carboxylic acids V3 can also be used in the form of their alkali metal salts. The Intermediates V2 can optionally also be prepared from the Intermediates V1 which bear a chlorine, bromine or iodine as substituent X^1 by reaction in a carbon monoxide atmosphere, optionally under elevated pressure, in the presence of a phosphine ligand, for example 1,3-bis(diphenylphosphino)propane, a palladium compound, for example palladium(II) acetate, and a base, for example triethylamine, with addition of ethanol or methanol in a solvent, for example dimethyl sulphoxide (for preparation methods see, for example, WO2012112743, WO 2005082866, Chemical Communications (Cambridge, England), 2003, 15, 1948 – 1949, WO200661715). The Intermediates V1 are either commercially available or can be prepared by routes known from the literature. Illustrative preparation methods are detailed in WO 2012061926, European Journal of Organic Chemistry, 2002, 2, 327 – 330, Synthesis, 2004, 10, 1619 – 1624, Journal of the American Chemical Society, 2013, 135, 32, 12122 – 12134, Bioorganic and Medicinal Chemistry Letters, 2014, 24, 16, 4039 – 4043, US2007185058, WO2009117421.



Synthesis Scheme 1

X^1 is chlorine, bromine or iodine.
R^d is methyl, ethyl, benzyl or *tert*-butyl.
R^4, R^5 are each as defined in the general formula (I).

Methyl 5-amino-1H-indazole-6-carboxylate (Intermediate 2) can be obtained proceeding from methyl 1H-indazole-6-carboxylate (Intermediate 0) according to Synthesis Scheme 2 by nitration and reduction of the nitro group of Intermediate 1 with hydrogen in the presence of palladium on charcoal analogously to WO 2008/001883. For preparation of the Intermediates 3 proceeding from Intermediate 2, it is possible to use various coupling reagents known from the literature (Amino Acids, Peptides and Proteins in Organic Chemistry, Vol.3 – Building Blocks, Catalysis and Coupling Chemistry, Andrew B. Hughes, Wiley, Chapter 12 - Peptide-Coupling Reagents, 407-442; Chem. Soc. Rev., 2009, 38, 606). For example, it is possible to use 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in combination with 1-hydroxy-1H-benzotriazole hydrate (HOBt, WO2012107475; Bioorg. Med. Chem. Lett., 2008 , 18, 2093), (1H-benzotriazol-1-yloxy)(dimethylamino)-N,N-dimethylmethaniminium tetrafluoroborate (TBTU, CAS 125700-67-6), (dimethylamino)-N,N-dimethyl(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methanaminium hexafluorophosphate (HATU, CAS 148893-10-1), propanephosphonic anhydride (as solution in ethyl acetate or DMF, CAS68957-94-8) or di-1H-imidazol-1-ylmethanone (CDI) as coupling reagents, with addition of a base such as triethylamine or N-ethyl-N-isopropylpropan-2-amine in each case to the reaction mixture. Preference is given to the use of TBTU and N-ethyl-N-isopropylpropan-2-amine in THF.



Synthesis Scheme 2

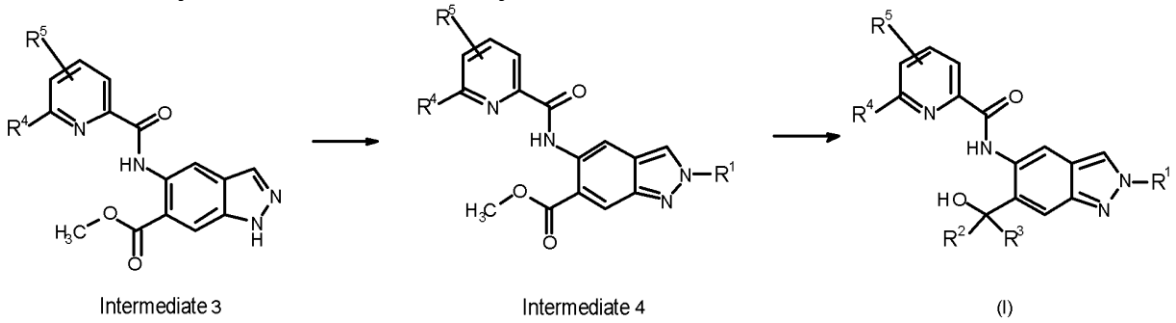
The substituents R^4, R^5 are each as defined in the general formula (I).

Proceeding from the Intermediates 3, it is possible to prepare 2-substituted indazole derivatives (Intermediate 4) (see synthesis scheme 3). Useful reactions for this purpose include those with optionally substituted alkyl chlorides, alkyl bromides, alkyl iodides or alkyl 4-methylbenzenesulphonates. The alkyl halides or alkyl 4-methylbenzenesulphonates used are commercially available or can be prepared analogously to routes known from literature (for the preparation of alkyl 4-

methylbenzenesulphonates, one example is the reaction of an appropriate alcohol with 4-methylbenzenesulphonyl chloride in the presence of triethylamine or pyridine; see, for example, Bioorganic and Medicinal Chemistry, 2006, 14, 12 4277 – 4294). Optionally, in the case of use of alkyl chlorides or alkyl bromides, it is also possible to add an alkali metal iodide such as potassium iodide or sodium iodide. Bases used may, for example, be potassium carbonate, caesium carbonate or sodium hydride. In the case of reactive alkyl halides, it is also possible in some cases to use N-cyclohexyl-N-methylcyclohexanamine. Useful solvents include, for example, 1-methylpyrrolidin-2-one, DMF, DMSO or THF. Optionally, the alkyl halides or alkyl 4-methylbenzenesulphonates used may have functional groups which have optionally been protected with a protecting group beforehand (see also P. G. M. Wuts, T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, Fourth Edition, ISBN: 9780471697541). If, for example, alkyl halides or alkyl 4-methylbenzenesulphonates having one or more hydroxyl groups are used, these hydroxyl groups may optionally be protected by a *tert*-butyl(dimethyl)silyl group or a similar silicon-containing protecting group familiar to those skilled in the art. Alternatively, the hydroxyl groups may also be protected by the tetrahydro-2H-pyran (THP) group or by the acetyl or benzoyl group. The protecting groups used can then be detached subsequently to the synthesis of Intermediate 4, or else after the synthesis of (I). If, for example, a *tert*-butyl(dimethylsilyl) group is used as protecting group, it can be detached using tetrabutylammonium fluoride in a solvent such as THF, for example. A THP protecting group can be detached, for example, using 4-methylbenzenesulphonic acid (optionally in monohydrate form). Acetyl groups or benzoyl groups can be detached by treatment with aqueous sodium hydroxide solution.

Optionally, the alkyl halides or alkyl 4-methylbenzenesulphonates used may contain functional groups which can be converted by oxidation or reduction reactions known to those skilled in the art (see, for example, *Science of Synthesis*, Georg Thieme Verlag). If, for example, the functional group is a sulphide group, this can be oxidized by methods known in the literature to a sulphoxide or sulphone group. In the case of a sulphoxide group, this can likewise be oxidized to a sulphone group. For these oxidation steps, it is possible to use, for example, 3-chloroperbenzoic acid (CAS 937-14-4) (in this regard, see also, for example, US201094000 for the oxidation of a 2-(methylsulphanyl)ethyl-1H-pyrazole derivative to a 2-(methylsulphinyl)ethyl-1H-pyrazole derivative and the oxidation of a further 2-(methylsulphanyl)ethyl-1H-pyrazole derivative to a 2-(methylsulphonyl)ethyl-1H-pyrazole derivative). If the alkyl halides or tosylates used contain a keto group, this can be reduced by reduction methods known to those skilled in the art to an alcohol group (see, for example, Chemische Berichte, 1980, 113, 1907 – 1920 for the use of sodium borohydride). These oxidation or reduction steps can be effected subsequently to the synthesis of Intermediate 4, or else after the synthesis of the inventive compounds of the general formula (I). Alternatively, Intermediate 4 can be prepared via Mitsunobu reaction (see, for example, K. C. K. Swamy et. al. Chem. Rev. 2009, 109, 2551 – 2651) of Intermediate 3 with optionally substituted alkyl alcohols. It is possible to utilize various phosphines such as triphenylphosphine, tributylphosphine or 1,2-diphenylphosphinoethane in combination with diisopropyl azodicarboxylate (CAS 2446-83-5) or further diazene derivatives mentioned in the literature (K. C. K. Swamy et. al. Chem. Rev. 2009, 109, 2551 – 2651). Preference is given to the use of triphenylphosphine and diisopropyl azodicarboxylate. If the alkyl alcohol bears a

functional group it is possible – as in the case of the abovementioned reactions with alkyl halides – for known protecting group strategies (further pointers can be found in P. G. M. Wuts, T. W. Greene, Greene's Protective Groups in Organic Synthesis, Fourth Edition, ISBN: 9780471697541) and – as in the case of the abovementioned reactions with alkyl halides – for oxidation or reduction steps to be effected correspondingly to the synthesis of Intermediate 4, or else after the synthesis of the inventive compounds of the general formula (I). Proceeding from Intermediate 4, inventive compounds of the general formula (I) where R^2 and R^3 are defined as C_1-C_6-alkyl (where R^2 and R^3 have the same definition) may be obtained by a Grignard reaction (cf., for example, the reaction of a methyl 1H-indazole-6-carboxylate derivative with methylmagnesium bromide in EP 2489663). For the Grignard reaction, it is possible to use alkylmagnesium halides. Particular preference is given to methylmagnesium chloride or methylmagnesium bromide in THF or diethyl ether, or else in mixtures of THF and diethyl ether. Alternatively, proceeding from Intermediate 4, inventive compounds of the general formula (I) where R^2 and R^3 are defined as C_1-C_6-alkyl (where R^2 and R^3 have the same definition) may be obtained by a reaction with an alkyllithium reagent (cf., for example, the reaction of a methyl 2-amino-4-chloro-1-methyl-1H-benzimidazole-7-carboxylate derivative with isopropyllithium or tert-butyllithium in WO2006116412). Proceeding from Intermediate 4, it is possible to prepare inventive compounds of the general formula (I) where R^2 and R^3 are defined as H by reduction with lithium aluminium hydride in THF, lithium borohydride in THF or sodium borohydride in THF, optionally with addition of methanol, or mixtures of lithium borohydride and sodium borohydride.



Synthesis Scheme 3

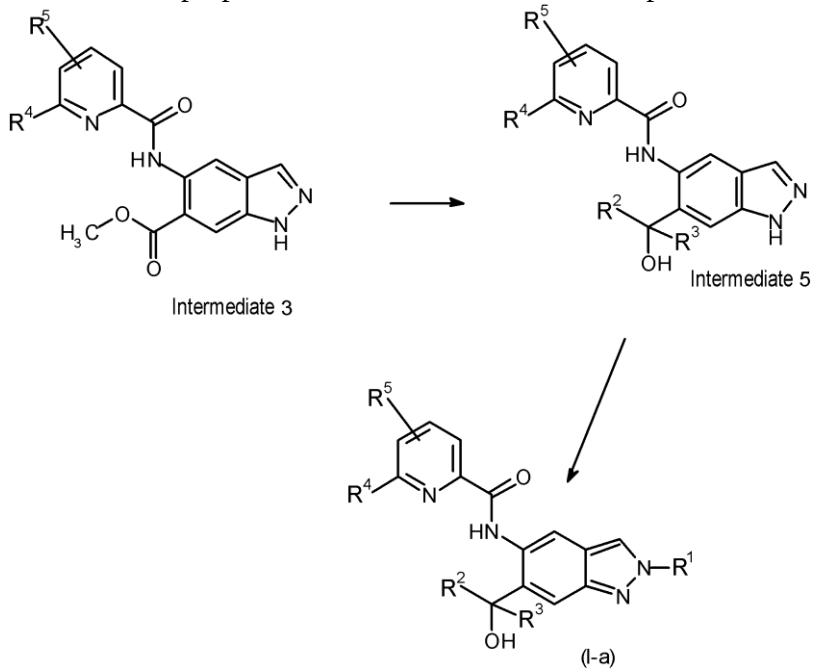
The substituents R^1, R^2, R^3, R^4, R^5 are each as defined in the general formula (I).

Proceeding from Intermediate 3, Intermediate 5 where R^2 and R^3 are defined as C_1-C_6-alkyl (where R^2 and R^3 have the same definition) may be obtained by a Grignard reaction (cf., for example, Synthesis Scheme 4). For this purpose, it is possible to use suitable alkylmagnesium halides, for example methylmagnesium chloride or methylmagnesium bromide in THF or in diethyl ether or else in mixtures of THF and diethyl ether.

Proceeding from Intermediate 5, it is then possible to prepare a portion (I-a) of the inventive compounds (I) where R^2 and R^3 are defined as C_1-C_6-alkyl (where R^2 and R^3 have the same definition). For this purpose, analogously to Synthesis Scheme 3 (preparation of Intermediate 3), useful reactions are those of Intermediate 5 with optionally substituted alkyl chlorides, alkyl bromides, alkyl iodides or alkyl 4-methylbenzenesulphonates. It is possible to use protecting group strategies analogously to those described in Synthesis Scheme 3.

Alternatively, for preparation of a portion (I-a) of the inventive compounds (I) where

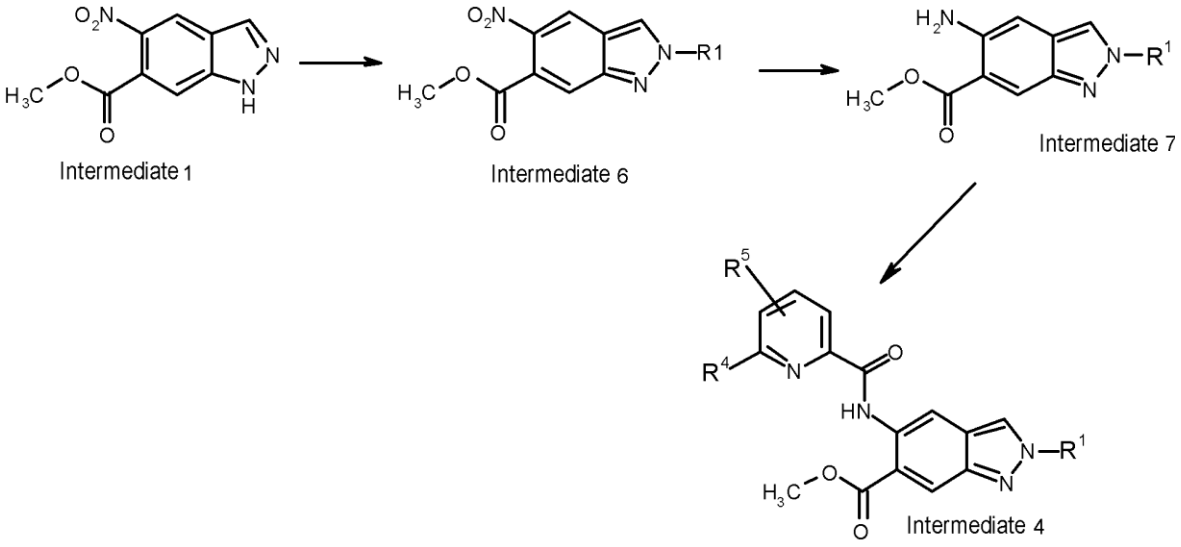
R^2 and R^3 are defined as C_1-C_6-alkyl (where R^2 and R^3 have the same definition), it is possible to use the Mitsunobu reaction of Intermediate 5 with optionally substituted alkyl alcohols (analogously to Synthesis Scheme 3).
If R^1 in the compounds of the formula (I-a) includes a suitable functional group, it is optionally possible subsequently, in analogy to Synthesis Scheme 3, to use oxidation or reduction reactions for preparation of further inventive compounds.



Synthesis Scheme 4

The substituents R^1, R^4, R^5 are each as defined in the general formula (I). R^2 and R^3 always have the same definition and are both C_1-C_6-alkyl.

Proceeding from Intermediate 1, it is possible to prepare Intermediate 4 in an alternative manner (see Synthesis Scheme 5). First of all, Intermediate 1 is converted to Intermediate 6 by methods as in Synthesis Scheme 3 (preparation of Intermediate 4 from Intermediate 3).
Intermediate 6 can then be converted to Intermediate 7 by reduction of the nitro group. For example, the nitro group can be reduced with palladium on carbon under a hydrogen atmosphere (cf., for example, WO2013174744 for the reduction of 6-isopropoxy-5-nitro-1H-indazole to 6-isopropoxy-1H-indazol-5-amine) or by the use of iron and ammonium chloride in water and ethanol (see, for example, also Journal of the Chemical Society, 1955, 2412-2419), or by the use of tin(II) chloride (CAS 7772-99-8). The use of iron and ammonium chloride in water and ethanol is preferred. The preparation of Intermediate 4 from Intermediate 7 can be effected analogously to Synthesis Scheme 2 (preparation of Intermediate 3 from Intermediate 2).
As described for Synthesis Scheme 3, it is optionally possible to use protecting group strategies in the case of Synthesis Scheme 5 as well. Optionally, it is additionally possible, proceeding from Intermediate 6 or Intermediate 7, as described for Synthesis Scheme 3, to conduct oxidation or reduction reactions known to those skilled in the art (cf., for example *Science of Synthesis*, Georg Thieme Verlag).



Synthesis Scheme 5

The substituents R^1, R^4, R^5 are each as defined in the general formula (I).

Synthesis of the example compounds

Abbreviations and elucidations

DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulphoxide
THF	tetrahydrofuran
RT	room temperature
HPLC	high-performance liquid chromatography
h	hour(s)
HCOOH	formic acid
MeCN	acetonitrile
min	minute(s)
UPLC	ultrahigh-performance liquid chromatography
DAD	diode array detector
ELSD	evaporating light scattering detector
ESI	electrospray ionization
SQD	single quadrupole detector
CPG	core-pulled precision glass
NH_3	ammonia

The term *sodium chloride solution* always means a saturated aqueous sodium chloride solution.

The chemical names of the intermediates and examples were generated using the ACD / LABS (Batch Version 12.01.) software.

Methods

In some cases, the inventive compounds and precursors and/or intermediates thereof were analysed by LC-MS.

Method A1: UPLC (MeCN-HCOOH):

Instrument: Waters Acquity UPLC-MS SQD 3001; column: Acquity UPLC BEH C18 1.7 50 x 2.1 mm; eluent A: water + 0.1% by vol. of formic acid (99%), eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow rate 0.8 ml/min; temperature: 60°C; injection: 2 µl; DAD scan: 210-400 nm; MS ESI+, ESI-, scan range 160-1000 m/z; ELSD.

Method A2: UPLC (MeCN-NH_3):
Instrument: Waters Acquity UPLC-MS SQD 3001; column: Acquity UPLC BEH C18 1.7 50 x 2.1 mm; eluent A: water + 0.2% by vol. of ammonia (32%), eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow rate 0.8 ml/min; temperature: 60°C; injection: 2 µl; DAD scan: 210-400 nm; MS ESI+, ESI-, scan range 160-1000 m/z; ELSD.

Method A3: (LC-MS)
Instrument: Agilent 1290 Infinity LC; column: Acquity UPLC BEH C18 1.7 50 x 2.1 mm; eluent A: water + 0.05% by vol. of formic acid, eluent B: acetonitrile + 0.05% by vol. of formic acid; gradient: 0-1.7 min 2-90% B, 1.7-2.0 min 90% B; flow rate 1.2 ml/min; temperature: 60°C; injection: 2 µl; DAD scan: 190-390 nm; MS: Agilent TOF 6230.

Method A4: (LC-MS)
Instrument: Waters Acquity; column: Kinetex (Phenomenex), 50 x 2 mm; eluent A: water + 0.05% by vol. of formic acid, eluent B: acetonitrile + 0.05% by vol. of formic acid; gradient: 0-1.9 min 1-99% B, 1.9-2.1 min 99% B; flow rate 1.5 ml/min; temperature: 60°C; injection: 0.5 µl; DAD scan: 200-400 nm.

In some cases, the inventive compounds and the precursors and/or intermediates thereof were purified by the following illustrative preparative HPLC methods:

Method P1: system: Waters Autopurification system: Pump 2545, Sample Manager 2767, CFO, DAD 2996, ELSD 2424, SQD; column: XBridge C18 5 µm 100 x 30 mm; eluent A: water + 0.1% by vol. of formic acid, eluent B: acetonitrile; gradient: 0-8 min 10-100% B, 8-10 min 100% B; flow: 50 ml/min; temperature: room temperature; solution: max. 250 mg / max. 2.5 ml DMSO or DMF; injection: 1 x 2.5 ml; detection: DAD scan range 210–400 nm; MS ESI+, ESI-, scan range 160-1000 m/z.
Method P2: system: Waters Autopurification system: Pump 254, Sample Manager 2767, CFO, DAD 2996, ELSD 2424, SQD 3100; column: XBridge C18 5 µm 10 x 30 mm; eluent A: water + 0.2% by vol. of ammonia (32%), eluent B: methanol; gradient: 0-8 min 30-70% B; flow: 50 ml/min; temperature: room temperature; detection: DAD scan range 210–400 nm; MS ESI+, ESI-, scan range 160-1000 m/z; ELSD.

Method P3: system: Labomatic, pump: HD-5000, fraction collector: LABOCOL Vario-4000, UV detector: Knauer UVD 2.1S; column: XBridge C18 5 µm 100x30 mm; eluent A: water + 0.2% by vol. of ammonia (25%), eluent B: acetonitrile; gradient: 0-1 min 15% B, 1-6.3 min 15-55% B, 6.3-6.4 min 55-100% B, 6.4-7.4 min 100% B; flow: 60 ml/min; temperature: room temperature; solution: max. 250 mg / 2 ml DMSO; injection: 2 x 2 ml; detection: UV 218 nm; Software: SCPA PrepCon5.

Method P4: system: Labomatic, pump: HD-5000, fraction collector: LABOCOL

Vario-4000, UV detector: Knauer UVD 2.1S; column: Chromatorex RP C18 10 µm 125 x 30 mm; eluent A: water + 0.1% by vol. of formic acid, eluent B: acetonitrile; gradient: 0-15 min 65 – 100% B; flow: 60 ml/min; temperature: room temperature; solution: max. 250 mg / 2 ml DMSO; injection: 2 x 2 ml; detection: UV 254 nm; Software: SCPA PrepCon5.

Method P5: system: Sepiatec: Prep SFC100, column: Chiralpak IA 5 µm 250x20 mm; eluent A: carbon dioxide, eluent B: ethanol; gradient: isocratic 20% B; flow: 80 ml/min; temperature: 40°C; solution: max. 250 mg / 2 ml DMSO; injection: 5 x 0.4 mL; detection: UV 254 nm.

Method P6: system: Agilent: Prep 1200, 2 x prep pump, DLA, MWD, Gilson: Liquid Handler 215; column: Chiralcel OJ-H 5 µm 250 x 20 mm; eluent A: hexane, eluent B: ethanol; gradient: isocratic 30% B; flow: 25 ml/min; temperature: 25°C; solution: 187 mg / 8 ml ethanol/methanol; injection: 8 x 1.0 ml; detection: UV 280 nm.

Method P7: system: Labomatic, pump: HD-5000, fraction collector: LABOCOL Vario-4000, UV detector: Knauer UVD 2.1S; column: XBridge C18 5 µm 100 x 30 mm; eluent A: water + 0.1% by vol. of formic acid, eluent B: acetonitrile; gradient: 0-3 min: 65% B isocratic, 3-13 min: 65-100% B; flow: 60 ml/min; temperature: room temperature; solution: max. 250 mg / 2 ml DMSO; injection: 2 x 2 ml; detection: UV 254 nm.

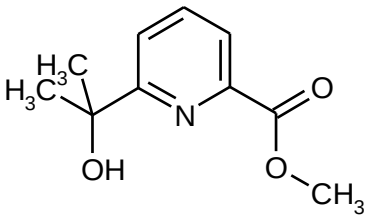
Method P8: system: Agilent: Prep 1200, 2 x prep pump, DLA, MWD, Gilson: Liquid Handler 215; column: Chiralpak IF 5 µm 250 x 20 mm; eluent A: ethanol, eluent B: methanol; gradient: isocratic 50% B; flow: 25 ml/min; temperature: 25°C; solution: 600 mg / 7 ml N,N-dimethylformamide; injection: 10 x 0.7 ml; detection: UV 254 nm.

In some cases, substance mixtures were purified by column chromatography on silica gel.

For preparation of some of the inventive compounds and the precursors and/or intermediates thereof, a column chromatography purification ("flash chromatography") was conducted on silica gel using Isolera® devices from Biotage. This was done using cartridges from Biotage, for example the "SNAP Cartridge, KP_SIL" cartridge of different size and "Interchim Puriflash Silica HP 15UM flash column" cartridges from Interchim of different size.

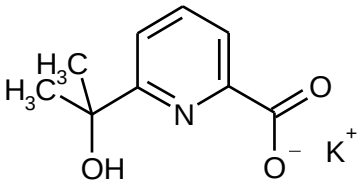
Starting materials

Intermediate V2-1
Methyl 6-(2-hydroxypropan-2-yl)pyridine-2-carboxylate



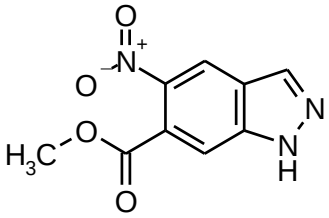
2.00 g (9.26 mmol) of 2-(6-bromopyridin-2-yl)propan-2-ol (CAS 638218-78-7) were dissolved in 20 ml of methanol and 20 ml of DMSO. Subsequently, 250 mg of 1,3-bis(diphenylphosphino)propane, 130 mg of palladium(II) acetate and 3 ml of triethylamine were added. The reaction mixture was purged three times with carbon monoxide at room temperature and stirred under a 13 bar carbon monoxide atmosphere for 30 min. The carbon monoxide atmosphere was removed by applying a vacuum and the mixture was stirred under a 14 bar carbon monoxide atmosphere at 100°C for 24 h. The autoclave was decompressed, water was added to the reaction mixture, and the reaction mixture was extracted three times with ethyl acetate, washed with saturated aqueous sodium hydrogencarbonate solution and sodium chloride solution, filtered through a hydrophobic filter and concentrated. This gave 1.60 g of a crude product.
UPLC-MS (Method A1): R_t = 0.76 min (UV detector: TIC), mass found 195.00.

Intermediate V3-1
Potassium 6-(2-hydroxypropan-2-yl)pyridine-2-carboxylate



1.60 g of the crude product of Intermediate 0-1 were initially charged in 15 ml of methanol, 0.74 g of potassium hydroxide was added and the mixture was stirred at 50°C for 16.5 h. After concentration, this gave 2.1 g of a residue which was used without further purification.
UPLC-MS (Method A1): R_t = 0.47 min (UV detector: TIC), mass found 181.00.

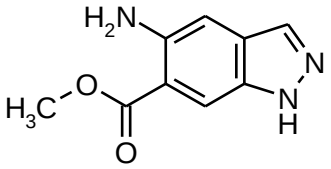
Intermediate 1-1
Methyl 5-nitro-1H-indazole-6-carboxylate



4.60 g (26.1 mmol) of methyl 1H-indazole-6-carboxylate (CAS No: 170487-40-8) were dissolved in 120 ml of sulphuric acid (96%) and cooled to -15°C in a three-neck flask having a CPG stirrer, dropping funnel and internal thermometer. Over a period of 15 min, the nitrating acid (10 ml of 96% sulphuric acid in 5 ml of 65% nitric acid), which had been prepared and cooled beforehand, was added dropwise to this solution. After the dropwise addition had ended, the mixture was stirred for a further 1 h (internal temperature at -13°C). The reaction mixture was added to ice, and the

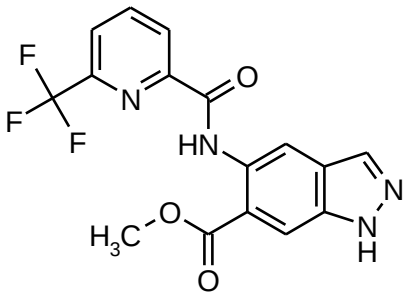
precipitate was filtered off with suction, washed with water and dried in a drying cabinet at 50°C under reduced pressure. 5.49 g of the title compound were obtained.
UPLC-MS (Method A2): R_t = 0.75 min
MS (ESIpos): m/z = 222$(M+H)^+$
^{1}H NMR (400 MHz, DMSO-d6): δ [ppm] = 3.87 (s, 3 H), 7.96 (s, 1 H), 8.44 (s, 1 H), 8.70 (s, 1 H), 13.98 (br. s., 1 H).

Intermediate 2-1
Methyl 5-amino-1H-indazole-6-carboxylate



4.40 g (19.8 mmol) of methyl 5-nitro-1H-indazole-6-carboxylate (Intermediate 1-1) were dissolved in 236 ml of methanol and hydrogenated with 1.06 g (0.99 mmol) of palladium on activated carbon under standard hydrogen pressure at 25°C for 3 h. The reaction mixture was filtered through Celite, the filter was washed with methanol, and the filtrate was concentrated. 3.53 g of the title compound were obtained.
^{1}H NMR (300 MHz, DMSO-d6): δ [ppm] = 3.85 (s, 3 H) 6.01 (s, 2 H) 6.98 (s, 1 H) 7.79 - 7.91 (m, 1 H) 7.99 (s, 1 H) 12.84 (br. s., 1 H).

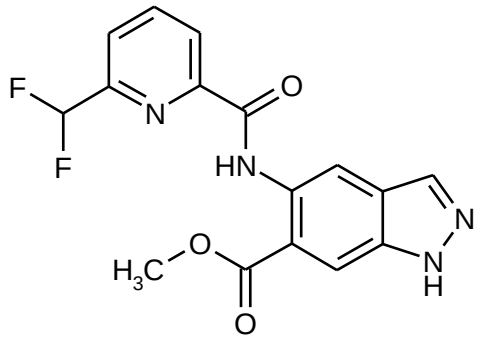
Intermediate 3-1
Methyl 5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate



4.95 g (25.9 mmol) of 6-(trifluoromethyl)pyridine-2-carboxylic acid were initially charged in 45 ml of THF. 9.07 g (28.2 mmol) of O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate and 4.92 ml (28.2 mmol) of N-ethyl-N-isopropylpropan-2-amine were added and the mixture was stirred at 25°C for 30 min. Subsequently, 4.50 g (23.5 mmol) of methyl 5-amino-1H-indazole-6-carboxylate (Intermediate 2-1) were added and the mixture was stirred at 25°C for 24 h. The reaction mixture was filtered with suction through a membrane filter and the solids were washed with THF and with water, and dried in a drying cabinet overnight. 7.60 g of the title compound were obtained.
UPLC-MS (Method A2): R_t = 1.16 min
MS (ESIpos): m/z = 365 $(M+H)^+$
^{1}H NMR (400 MHz, DMSO-d6): δ [ppm] = 3.97 (s, 3 H), 8.13 - 8.27 (m, 2 H), 8.30 (s, 1 H), 8.33 - 8.45 (m, 1 H), 8.45 - 8.51 (m, 1 H), 9.15 (s, 1 H), 12.57 (s, 1 H), 13.44 (s, 1 H).

Intermediate 3-2

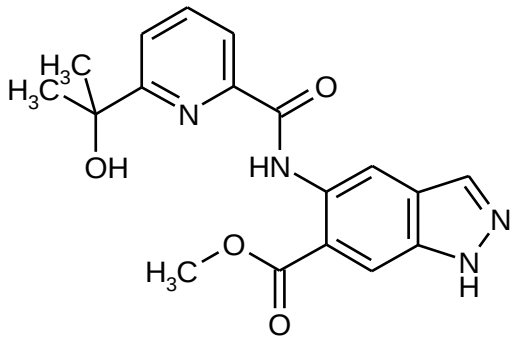
Methyl 5-({[6-(difluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate



2.85 g (23.5 mmol) of 6-(difluoromethyl)pyridine-2-carboxylic acid were initially charged in 30 ml of THF. 6.05 g (18.8 mmol) of O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate and 3.3 ml of N-ethyl-N-isopropylpropan-2-amine were added and the mixture was stirred at room temperature for 10 minutes. Subsequently, 3.00 g (15.7 mmol) of methyl 5-amino-1H-indazole-6-carboxylate were added and the mixture was stirred at room temperature overnight. The reaction mixture was admixed with water, and the precipitate was filtered off with suction and washed repeatedly with water and dichloromethane. This gave 1.53 g (27% of theory) of the title compound. The phases of the filtrate were separated, the organic phase was concentrated, admixed with a little dichloromethane and suspended in an ultrasound bath, and the precipitate was filtered off with suction. This gave a further 1.03 g of the title compound.
1H-NMR (first product fraction, 300MHz, DMSO-d6): δ [ppm]= 3.99 (s, 3H), 7.09 (t, 1H), 8.00 (d, 1H), 8.21 - 8.40 (m, 4H), 9.14 (s, 1H), 12.53 (s, 1H), 13.44 (s, 1H).

Intermediate 3-3

Methyl 5-({[6-(2-hydroxypropan-2-yl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate

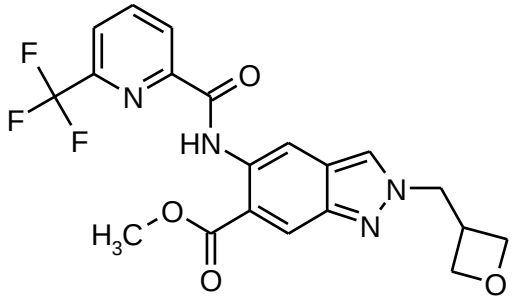


2.10 g of potassium 6-(2-hydroxypropan-2-yl)pyridine-2-carboxylate (Intermediate V3-1) were initially charged in 15 ml of THF. 3.69 g (11.5 mmol) of O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate and 2.00 ml of N-ethyl-N-isopropylpropan-2-amine were added and the mixture was stirred at room temperature for 15 min. Subsequently, 1.83 g (9.58 mmol) of methyl 5-amino-1H-indazole-6-carboxylate (Intermediate 2-1) were added and the mixture was stirred at room temperature for 19 h. The mixture was admixed with water and ethyl acetate, the undissolved solids were filtered off, the phases of the filtrate were separated, and the aqueous phase was extracted twice with ethyl acetate, washed with sodium chloride solution, filtered through a hydrophobic filter, concentrated and purified by column

chromatography on silica gel (hexane/ethyl acetate). After the solvents had been removed, 1.56 g of the title compound were obtained as a yellow foam.
UPLC-MS (Method A1): R_t = 1.00 min (UV detector: TIC Smooth), mass found 354.00.
1H-NMR (500MHz,DMSO-d6): δ [ppm] = 1.63 (s, 6H), 3.97 (s, 3H), 5.37(s ,1H), 7.90 - 7.95 (m, 1H), 8.03-8.07 (m, 2H), 8.23(s, 1H),8.29 (s, 1H), 9.19 (s, 1H), 12.79 (s, 1H), 13.41 (br.s., 1H).

Intermediate 4-1

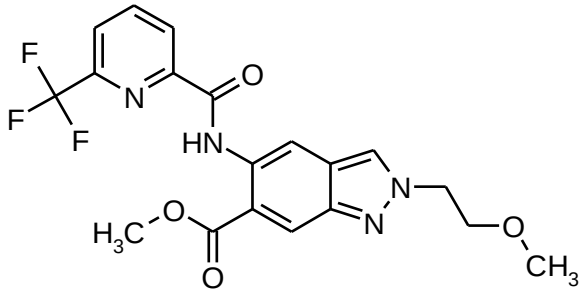
Methyl 2-(oxetan-3-ylmethyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate



1.00 g (2.66 mmol) of methyl 5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate (Intermediate 3-1) was dissolved in 10 ml of DMF and, after addition of 1.10 g (7.99 mmol) of potassium carbonate and 221 mg (1.33 mmol) of potassium iodide, the mixture was stirred at 25°C for 30 min. 603 mg (3.99 mmol) of 3-bromomethyloxetane were added, and the mixture was stirred at 25°C for 24 h. The reaction mixture was partitioned between water and ethyl acetate. The mixture was extracted twice with ethyl acetate, and the combined organic phases were filtered through a hydrophobic filter and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate). 260 mg of the title compound were obtained.
UPLC-MS (Method A2): R_t = 1.24 min
MS (ESIpos): m/z = 435$(M+H)^+$
^{1}H NMR (400 MHz, DMSO-d6): δ [ppm] = 3.49 - 3.64 (m, 1 H), 3.95 (s, 3 H), 4.49 (t, 2 H), 4.68 (dd, 2 H), 4.81 (d, 2 H), 8.20 (dd, 1 H), 8.35 - 8.41 (m, 1 H), 8.43 - 8.49 (m, 2 H), 8.55 - 8.58 (m, 1 H), 9.06 (s, 1 H), 12.53 (s, 1 H).

Intermediate 4-2

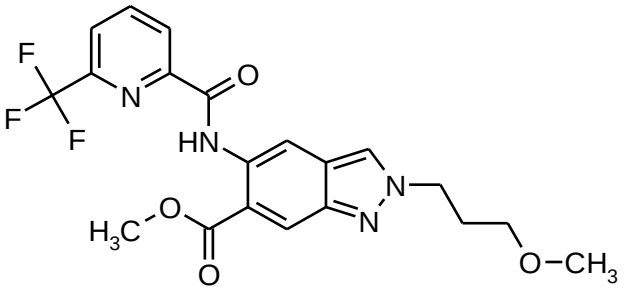
Methyl 2-(2-methoxyethyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate



1.00 g (2.75 mmol) of methyl 5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate (Intermediate 3-1) was dissolved in 5 ml of DMF, and 387

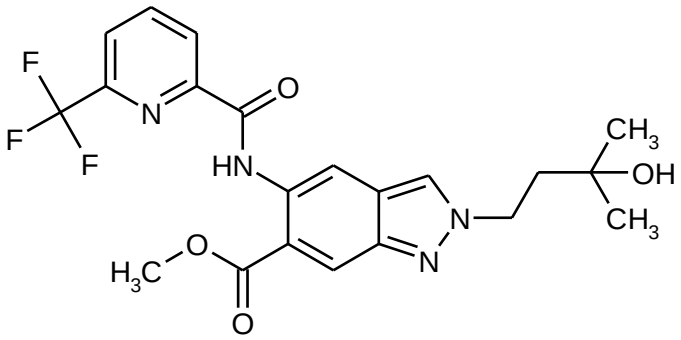
µl (4.12 mmol) of 2-bromoethyl methyl ether, 1.14 g (8.23 mmol) of potassium carbonate and 228 mg (1.37 mmol) of potassium iodide were added while stirring. The reaction mixture was stirred at 25°C for 24 h, diluted with water and extracted twice with ethyl acetate. The combined organic phases were filtered through a hydrophobic filter and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate). 12 mg of the title compound were obtained.
UPLC-MS (Method A1): R_t = 1.24 min
MS (ESIpos): m/z = 423 $(M+H)^+$
^{1}H NMR (400 MHz, DMSO-d6): δ [ppm] = 3.24 (s, 3 H), 3.86 (t, 2 H), 3.96 (s, 3 H), 4.65 (t, 2 H), 8.21 (dd, 1 H), 8.35 - 8.42 (m, 1 H), 8.43 - 8.51 (m, 2 H), 8.52 (d, 1 H), 9.06 (s, 1 H), 12.53 (s, 1 H).

Intermediate 4-3
Methyl 2-(3-methoxypropyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate



1.00 g (2.75 mmol) of methyl 5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate (Intermediate 3-1) was dissolved in 5 ml of DMF, and 460 µl (4.12 mmol) of 1-bromo-3-methoxypropane, 1.14 g (8.23 mmol) of potassium carbonate and 228 mg (1.37 mmol) of potassium iodide were added while stirring. The reaction mixture was stirred at 25°C for 72 h, diluted with water and extracted twice with ethyl acetate. The combined organic phases were filtered through a hydrophobic filter and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate). 28 mg of the title compound were obtained.
UPLC-MS (Method A1): R_t = 1.29 min
MS (ESIpos): m/z = 437 $(M+H)^+$
^{1}H NMR (400 MHz, DMSO-d6): δ [ppm] = 2.17 (quin, 2 H), 3.24 (s, 3 H), 3.33 - 3.36 (m, 2 H), 3.96 (s, 3 H), 4.53 (t, 2 H), 8.21 (dd, 1 H), 8.35 - 8.42 (m, 1 H), 8.45 - 8.49 (m, 2 H), 8.54 (d, 1 H), 9.06 (s, 1 H), 12.54 (s, 1 H).

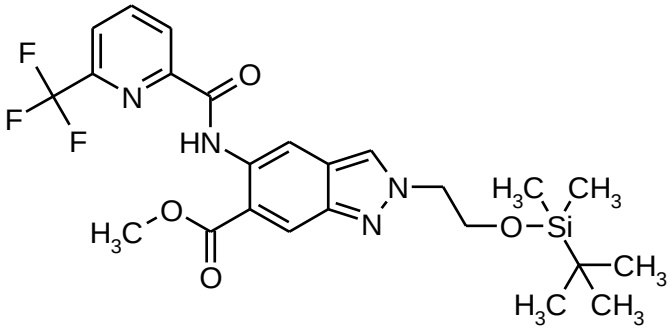
Intermediate 4-4
Methyl 2-(3-hydroxy-3-methylbutyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate
Preparation Method 1



930 mg (2.55 mmol) of methyl 5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate (Intermediate 3-1), 1.06 g of potassium carbonate and 212 mg of potassium iodide were initially charged in 9 ml of DMF and the mixture was stirred for 15 min. Then 0.62 ml of 4-bromo-2-methylbutan-2-ol was added and the mixture was stirred at 60°C for 16 h. The mixture was admixed with water and extracted twice with ethyl acetate, and the extract was washed three times with saturated sodium chloride solution, filtered and concentrated. Column chromatography purification on silica gel (hexane/ethyl acetate) gave 424 mg of the title compound.
UPLC-MS (Method A2): R_t = 1.21 min (UV detector: TIC), mass found 450.00.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.16 (s, 6 H) 2.02 - 2.11 (m, 2 H) 3.96 (s, 3 H) 4.51 - 4.60 (m, 3 H) 8.20 (dd, *J*=7.83, 1.01 Hz, 1 H) 8.39 (s, 1 H) 8.45 (s, 2 H) 8.55 (d, *J*=0.76 Hz, 1 H) 9.05 (s, 1 H) 12.52 (s, 1 H)

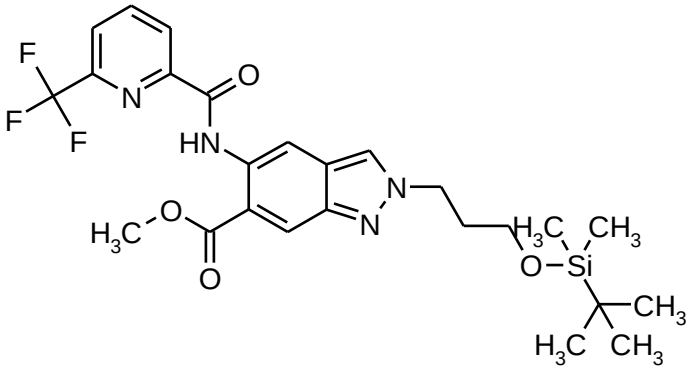
Preparation Method 2
1.95 g (7.03 mmol) of methyl 5-amino-2-(3-hydroxy-3-methylbutyl)-2H-indazole-6-carboxylate (Intermediate 7-1) were initially charged in 30 ml of THF. 1.48 g (7.73 mmol) of 6-(trifluoromethyl)pyridine-2-carboxylic acid, 2.71 g (8.44 mmol) of O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate and 1.47 ml (8.44 mmol) of N-ethyl-N-isopropylpropan-2-amine were added and the mixture was stirred at 25°C for 20.5 h. Water was added, the mixture was extracted three times with ethyl acetate and the extracts were washed with sodium chloride solution, filtered through a hydrophobic filter and concentrated. The residue was separated by column chromatography on silica gel (hexane/ethyl acetate gradient). 2.79 g of the title compound were obtained.
UPLC-MS (Method A1): R_t = 1.23 min (UV detector: TIC), mass found 450.00.

Intermediate 4-5
Methyl 2-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate



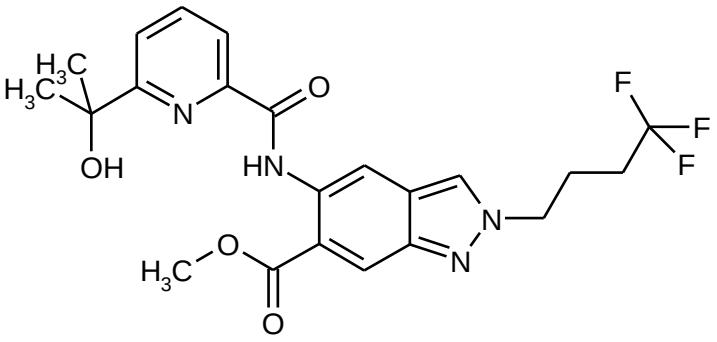
1.00 g (2.66 mmol, 97%) of methyl 5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate (Intermediate 3-1) was initially charged in 50 ml of DMF, 1.10 g (7.99 mmol) of potassium carbonate and 221 mg (1.33 mmol) of potassium iodide were added while stirring, and the mixture was stirred at 25°C for 30 min. Subsequently, 857 µl (3.99 mmol) of (2-bromoethoxy)(tert-butyl)dimethylsilane were added and the mixture was stirred at 25°C for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phases were filtered through a hydrophobic filter and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate). 400 mg of the title compound were obtained.
UPLC-MS (Method A1): R_t = 1.58 min
MS (ESIpos): m/z = 523$(M+H)^+$
^{1}H NMR (300 MHz, DMSO-d6): δ [ppm] = -0.18 - -0.13 (m, 6 H), 0.74 (s, 9 H), 3.96 (s, 3 H), 4.08 (t, 2 H), 4.57 (t, 2 H), 8.15 - 8.25 (m, 1 H), 8.32 - 8.43 (m, 1 H), 8.43 - 8.52 (m, 3 H), 9.07 (s, 1 H), 12.53 (s, 1 H).

Intermediate 4-6
Methyl 2-(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate



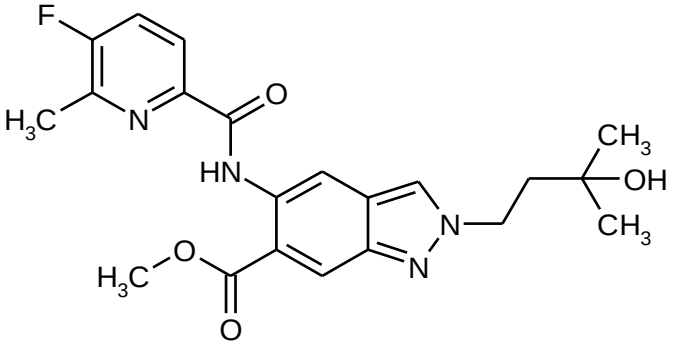
Analogously to Intermediate 4-5, 1.00 g (2.75 mmol) of methyl 5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate (Intermediate 3-1) was dissolved in 10 ml of DMF, 1.14 g (8.24 mmol) of potassium carbonate and 228 mg (1.37 mmol) of potassium iodide were added while stirring, and the mixture was stirred at 25°C for 30 min. Subsequently, 1.04 g (4.12 mmol) of (3-bromopropoxy)(tert-butyl)dimethylsilane were added and the mixture was stirred at 25°C for 24 h. The reaction mixture was filtered and the filtercake was washed with ethyl acetate. The reaction mixture was partitioned between water and ethyl acetate and the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were filtered through a hydrophobic filter and concentrated. Purification of the residue by preparative HPLC gave 428 mg of the title compound.
UPLC-MS (Method A1): R_t = 1.63 min
MS (ESIpos): m/z = 537$(M+H)^+$
^{1}H NMR (400 MHz, DMSO-d6): δ [ppm] = -0.02 - 0.06 (m, 6 H), 0.87 (s, 9 H), 2.14 (quin, 2 H), 3.62 (t, 2 H), 3.96 (s, 3 H), 4.54 (t, 2 H), 8.20 (d, 1 H), 8.35 - 8.42 (m, 1 H), 8.43 - 8.48 (m, 3 H), 8.49 - 8.53 (m, 1 H), 9.06 (s, 1 H).

Intermediate 4-7
Methyl 5-({[6-(2-hydroxypropan-2-yl)pyridin-2-yl]carbonyl}amino)-2-(4,4,4-trifluorobutyl)-2H-indazole-6-carboxylate



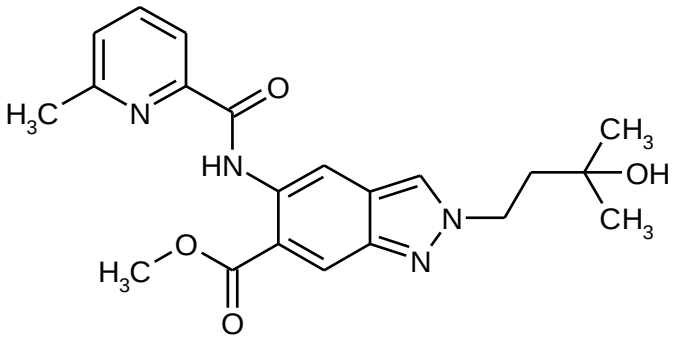
300 mg (0.80 mmol) of methyl 5-({[6-(2-hydroxypropan-2-yl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate (Intermediate 3-3) were initially charged in 4.5 ml of DMF. 287 mg (1.21 mmol) of 1,1,1-trifluoro-4-iodobutane and 333 mg of potassium carbonate were added and the mixture was stirred at 100°C for 23 h. Water was added, and the mixture was extracted three times with ethyl acetate. The mixture was concentrated and the product was purified by preparative HPLC. This gave 72 mg of the title compound.
UPLC-MS (Method A1): R_t = 1.26 min (UV detector: TIC), mass found 464.17.

Intermediate 4-8
Methyl 5-{[(5-fluoro-6-methylpyridin-2-yl)carbonyl]amino}-2-(3-hydroxy-3-methylbutyl)-2H-indazole-6-carboxylate



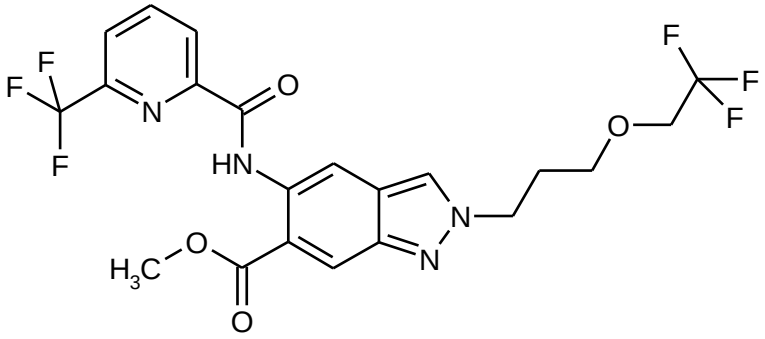
195 mg (0.46 mmol) of methyl 5-amino-2-(3-hydroxy-3-methylbutyl)-2H-indazole-6-carboxylate (Intermediate 7-1) were reacted with 78 mg (0.50 mmol) of 5-fluoro-6-methylpyridine-2-carboxylic acid analogous to Intermediate 4-4 (Preparation Method 2) within 19.5 h. 228 mg of a crude product were obtained after analogous aqueous workup.
UPLC-MS (Method A1): R_t = 1.20 min (UV detector: TIC), mass found 414.00.

Intermediate 4-9
Methyl 2-(3-hydroxy-3-methylbutyl)-5-{[(6-methylpyridin-2-yl)carbonyl]amino}-2H-indazole-6-carboxylate



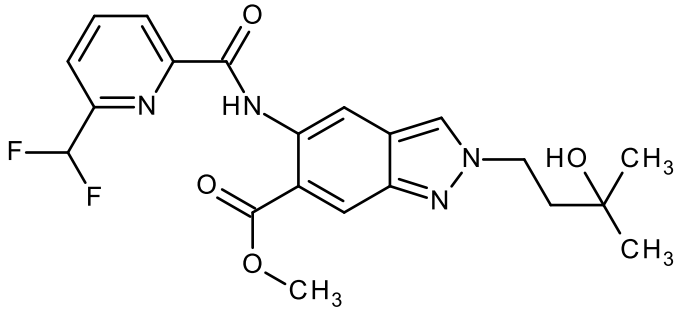
195 mg (0.45 mmol) of methyl 5-amino-2-(3-hydroxy-3-methylbutyl)-2H-indazole-6-carboxylate (Intermediate 7-1) were reacted with 70 mg (0.50 mmol) of 6-methylpyridine-2-carboxylic acid analogously to preparation of Intermediate 4-4 (Preparation Method 2) within 19.5 h. 278 mg of the title compound as crude product were obtained after analogous aqueous workup.
UPLC-MS (Method A1): R_t = 1.14 min (UV detector: TIC), mass found 396.00.

Intermediate 4-10
Methyl 2-[3-(2,2,2-trifluoroethoxy)propyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate



A mixture of 250 mg (0.58 mmol) of methyl 5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate (Intermediate 3-1), 193 mg (0.88 mmol) of 3-bromopropyl 2,2,2-trifluoroethyl ether, 242 mg of potassium carbonate and 145 mg of potassium iodide in 3 ml of DMF was stirred at 100°C for 20 h. Water was added, the mixture was extracted with ethyl acetate and the extract was washed with sodium chloride solution and concentrated. Purification by preparative HPLC gave 52 mg of the title compound.
UPLC-MS (Method A1): R_t = 1.39 min (UV detector: TIC), mass found 504.12.

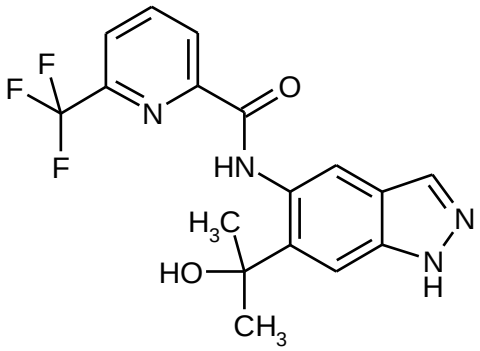
Intermediate 4-11
Methyl 5-({[6-(difluoromethyl)pyridin-2-yl]carbonyl}amino)-2-(3-hydroxy-3-methylbutyl)-2H-indazole-6-carboxylate



2.00 g of methyl 5-amino-2-(3-hydroxy-3-methylbutyl)-2H-indazole-6-carboxylate (Intermediate 7-1) were initially charged in 40 ml of THF. 1.50 g of 6-(difluoromethyl)pyridine-2-carboxylic acid, 2.78 g of *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU, CAS Number 125700-67-6) and 1.5 ml of N-ethyl-N-isopropylpropan-2-amine were added and the mixture was stirred at RT for 24 h. Water was added, the mixture was extracted three times with ethyl acetate, and the combined organic phases were washed with sodium chloride solution and filtered through a hydrophobic filter. The mixture was concentrated and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate). This gave 3.05 g of the title compound as a yellow solid.
UPLC-MS (Method A1): Rt = 1.15 min (UV detector TIC), mass found 432.00.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.17 (s, 6H), 2.04 - 2.11 (m, 2H), 3.99 (s, 3H), 4.52 - 4.60 (m, 3H), 7.10 (t, 1H), 8.00 (dd, 1H), 8.28 - 8.38 (m, 2H), 8.44 – 8.47 (m, 1H), 8.56 (d, 1H), 9.05 (s, 1H), 12.49 (s, 1H).

Intermediate 5-1

N-[6-(2-Hydroxypropan-2-yl)-1H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

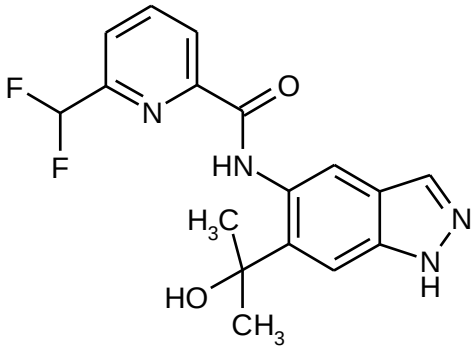


To a solution, cooled in an ice-water cooling bath, of 1.50 g (4.12 mmol) of methyl 5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate (Intermediate 3-1) in 20 ml of THF were cautiously added 6.9 ml (5 equivalents) of a 3M methylmagnesium bromide solution in diethyl ether. The mixture was stirred while cooling with an ice bath for 1 h and at room temperature for 19.5 h. Another 2 equivalents of methylmagnesium bromide solution were added and the mixture was stirred at room temperature for a further 24 h. Saturated aqueous ammonium chloride solution was added and the mixture was stirred and extracted three times with ethyl acetate. The combined organic phases were washed with sodium chloride solution, filtered through a hydrophobic filter and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate). 763 mg of the title

compound were obtained.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.63 (s, 6H), 5.99 (s, 1H), 7.49 (s, 1H), 8.06 (s, 1H), 8.14 - 8.19 (m, 1H), 8.37 (t, 1H), 8.46 (d, 1H), 8.78 (s, 1H), 12.32 (s, 1H), 12.97 (s, 1H).

Intermediate 5-2

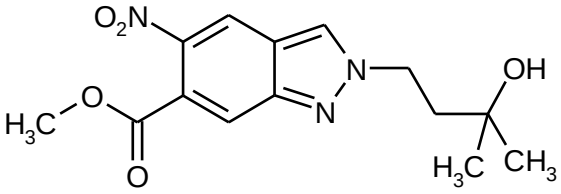
6-(Difluoromethyl)-N-[6-(2-hydroxypropan-2-yl)-1H-indazol-5-yl]pyridine-2-carboxamide



Analogously to the preparation of Intermediate 5-1, 2.40 g (6.93 mmol) of methyl 5-({[6-(difluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate (Intermediate 3-2) in 10 ml of THF were reacted with three portions of 3M methylmagnesium bromide solution in diethyl ether (6.9 ml, then stirring at room temperature for 45 min; 11.6 ml, then stirring at room temperature for 2 h; 6.9 ml, then stirring at room temperature for 2 h). After the workup as for Intermediate 5-1, 2.39 g of a crude product were obtained, which were used further without further purification.

Intermediate 6-1

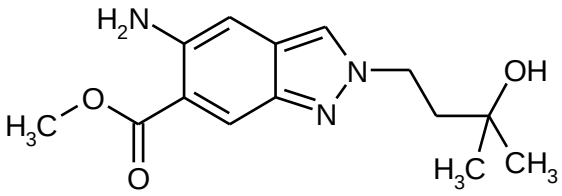
Methyl 2-(3-hydroxy-3-methylbutyl)-5-nitro-2H-indazole-6-carboxylate



5.00 g (22.6 mmol) of methyl 5-nitro-1H-indazole-6-carboxylate (Intermediate 1-1) were initially charged in 40 ml of DMF. 5.65 g (33.9 mmol) of 4-bromo-2-methylbutan-2-ol, 9.37 g (67.8 mmol) of potassium carbonate and 5.63 g (33.9 mmol) of potassium iodide were added and the mixture was stirred at 100°C for 20 h. Water was added, the mixture was extracted three times with ethyl acetate and the extracts were washed with sodium chloride solution, filtered through a hydrophobic filter and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate). The solids obtained were extracted by stirring with diethyl ether, filtered off with suction, washed with diethyl ether and dried. 2.49 g of the title compound were obtained.
UPLC-MS (Method A1): R_t = 0.93 min (UV detector: TIC), mass found 307.00.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.15 (s, 6H), 2.02 - 2.11 (m, 2H), 3.84 (s, 3H), 4.54 (s, 1H), 4.58 - 4.65 (m, 2H), 8.05 (s, 1H), 8.69 (s, 1H), 8.86 (s, 1H).

Intermediate 7-1

Methyl 5-amino-2-(3-hydroxy-3-methylbutyl)-2H-indazole-6-carboxylate

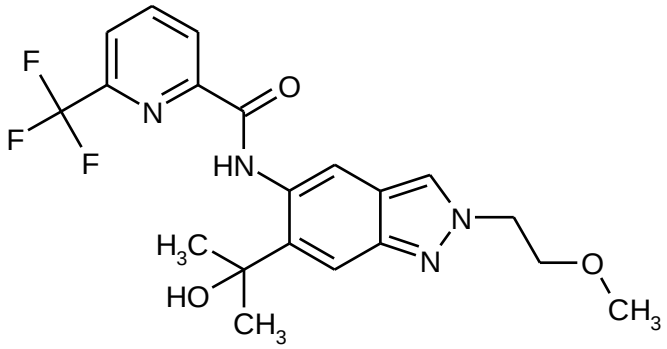


4.53 g of iron and 217 mg of ammonium chloride were added to 2.49 g (8.10 mmol) of methyl 2-(3-hydroxy-3-methylbutyl)-5-nitro-2H-indazole-6-carboxylate (Intermediate 6-1) in 30 ml of ethanol and 10 ml of water, and the mixture was stirred at 90°C for 21.5 h. The mixture was filtered through Celite and washed through with ethanol three times, and the filtrate was concentrated and the residue was admixed with water. Extraction was effected three times with ethyl acetate (to improve the phase separation, sodium chloride solution was added). The combined organic phases were washed with sodium chloride solution, filtered through a hydrophobic filter and concentrated. This gave 1.95 g (85% of theory) of the title compound.
UPLC-MS (Method A1): R_t = 0.67 min (UV detector: TIC), mass found 277.00.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.14 (s, 6H), 1.96 - 2.08 (m, 2H), 3.85 (s, 3H), 4.39 - 4.51 (m, 3H), 5.81 (s, 2H), 6.80 (s, 1H), 8.05 (s, 1H), 8.18 (s, 1H).

Working examples

Example 1

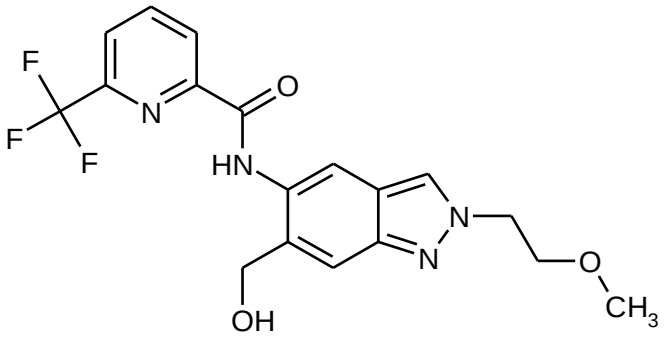
N-[6-(2-Hydroxypropan-2-yl)-2-(2-methoxyethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide



75 mg (0.18 mmol) of methyl 2-(2-methoxyethyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate (Intermediate 4-2) were dissolved in 500 µl of THF and admixed with 887 µl (0.89 mmol) of a 1 M methylmagnesium bromide solution in THF. The reaction mixture was stirred at 25°C for 60 min. Subsequently, 1 ml of a saturated aqueous ammonium chloride solution was added cautiously and the mixture was filtered. The aqueous phase was extracted twice with ethyl acetate, and the organic phases were combined, filtered through a hydrophobic filter and concentrated. The residue was dissolved in 3 ml of DMSO and purified by preparative HPLC. The product-containing fractions were freeze-dried. 20 mg of the title compound were obtained.
UPLC-MS (Method A1): R_t = 1.08 min
MS (ESIpos): m/z = 423 $(M+H)^+$
^{1}H NMR (300 MHz, DMSO-d6): δ [ppm] = 1.62 (s, 6 H), 3.22 (s, 3 H), 3.82 (t, 2 H), 4.55 (t, 2 H), 5.96 (s, 1 H), 7.57 (s, 1 H), 8.16 (d1 H), 8.29 - 8.42 (m, 2 H), 8.42 - 8.50 (m, 1 H), 8.71 (s, 1 H), 12.36 (s, 1 H)

Example 2

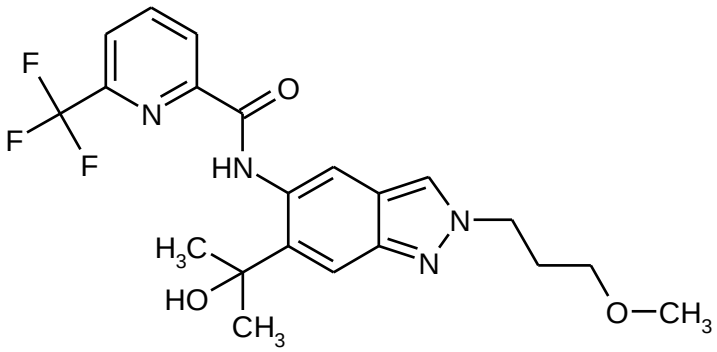
N-[6-(Hydroxymethyl)-2-(2-methoxyethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide



13 mg (0.36 mmol) of lithium aluminium hydride were suspended in 1 ml of THF and the mixture was cooled to 0°C. 75 mg (0.17 mmol) of methyl 2-(2-methoxyethyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate (Intermediate 4-2) dissolved in 500 µl of THF were added dropwise and the mixture was stirred at 25°C for 60 min. The mixture was diluted with water and extracted twice with ethyl acetate, and the combined organic phases were washed with sodium chloride solution, filtered through a hydrophobic filter, concentrated and dried under reduced pressure. This gave 13 mg of the title compound.
UPLC-MS (Method A2): R_t = 0.99 min
MS (ESIpos): m/z = 394 $(M+H)^+$
^{1}H NMR (400 MHz, DMSO-d6): δ [ppm] = 3.23 (s, 3 H), 3.83 (t, 2 H), 4.56 (t, 2 H), 4.69 (d, 2 H), 5.77 (t, 1 H), 7.57 (s, 1 H), 8.19 (d, 1 H), 8.33 - 8.41 (m, 2 H), 8.43 - 8.47 (m, 1 H), 8.51 (s, 1 H), 11.20 (s, 1 H)

Example 3

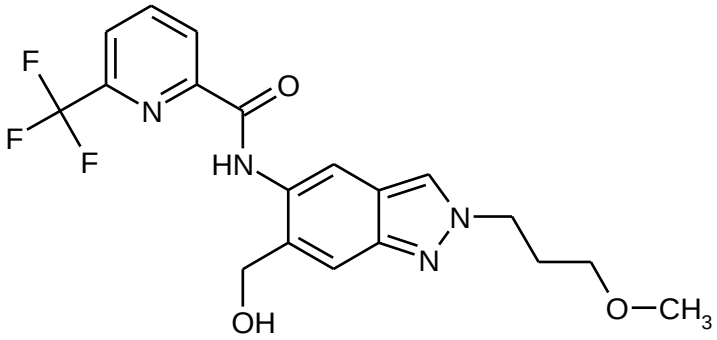
N-[6-(2-Hydroxypropan-2-yl)-2-(3-methoxypropyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide



75 mg (0.17 mmol) of methyl 2-(3-methoxypropyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate (Intermediate 4-3) were dissolved in 500 µl of THF and admixed with 859 µl (0.86 mmol) of a 1 M methylmagnesium bromide solution in THF. The reaction mixture was stirred at 25°C for 60 min. Subsequently, 1 ml of a saturated ammonium chloride solution was added cautiously and the mixture was filtered. The aqueous phase was extracted twice with ethyl acetate, and the organic phases were combined, filtered through a hydrophobic filter and concentrated. The residue was dissolved in 3 ml of DMSO and purified by preparative HPLC. The product-containing fractions were freeze-dried. 25 mg of the title compound were obtained.
UPLC-MS (Method A1): R_t = 1.13 min

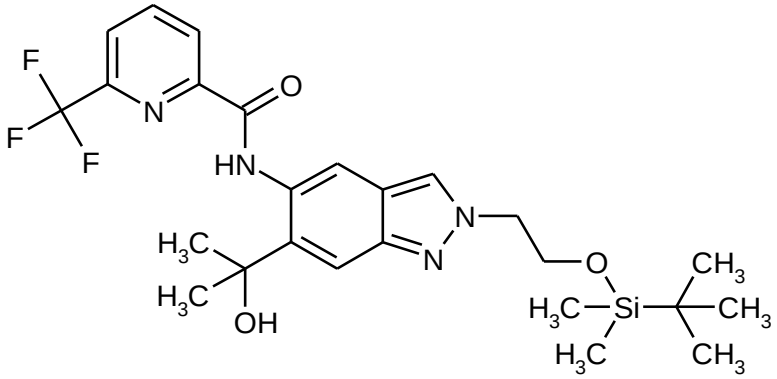
MS (ESIpos): m/z = 437 $(M+H)^+$
^{1}H NMR (400 MHz, DMSO-d6): δ [ppm] = 1.62 (s, 6 H), 2.14 (quin, 2 H), 3.23 (s, 3 H), 3.26 - 3.32 (m, 2 H), 4.44 (t, 2 H), 5.95 (s, 1 H), 7.58 (s, 1 H), 8.16 (d, 1 H), 8.31 - 8.40 (m, 2 H), 8.43 - 8.48 (m, 1 H), 8.72 (s, 1 H), 12.36 (s, 1 H).

Example 4
N-[6-(Hydroxymethyl)-2-(3-methoxypropyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide



13 mg of lithium aluminium hydride were suspended in THF and the mixture was cooled to 0°C. 75 mg (0.17 mmol) of methyl 2-(3-methoxypropyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate (Intermediate 4-3) in THF were added dropwise and the mixture was allowed to come to room temperature within 30 min. The mixture was diluted with water and filtered, the residue was washed with ethyl acetate and the filtrate was extracted with ethyl acetate. The combined ethyl acetate phases were washed with sodium chloride solution, filtered through a hydrophobic filter and concentrated. The residue was purified by preparative HPLC.
^{1}H NMR (300 MHz, DMSO-d_6): δ [ppm] = 2.14 (quin, 2 H), 3.23 (s, 3 H), 3.29 (t, 2 H), 4.45 (t, 2 H), 4.68 (d, 2 H), 5.77 (t, 1 H), 7.58 (s, 1 H), 8.18 (d, 1 H), 8.32 - 8.48 (m, 3 H), 8.51 (s, 1 H), 11.21 (s, 1 H).

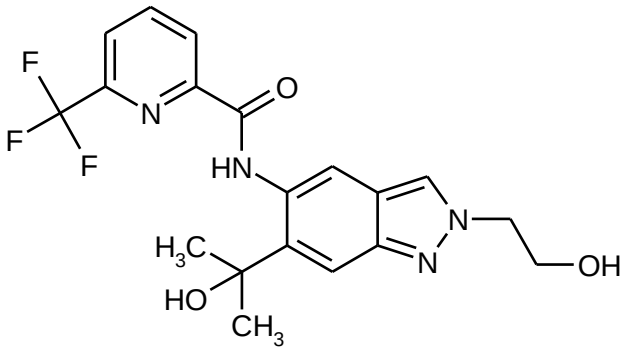
Example 5
N-[2-(2-Hydroxyethyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
Stage A:
Preparation of N-[2-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide



100 mg (0.19 mmol) of methyl 2-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate

(Intermediate 4-5) were dissolved in 1 ml of THF and admixed with 669 µl (0.67 mmol) of a 1 M methylmagnesium bromide solution in THF. The reaction mixture was stirred at 25°C for 60 min. Another 287 µl (0.29 mmol) of a 1 M methylmagnesium bromide solution in THF were added and the mixture was stirred at 25°C for 3 h. Subsequently, 20 ml of a saturated ammonium chloride solution were added cautiously and the mixture was filtered. The aqueous phase was extracted twice with ethyl acetate, and the organic phases were combined, dried over magnesium sulphate, filtered, concentrated and dried under reduced pressure. This gave 50 mg of N-[2-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide.
UPLC-MS (Method A2): R_t = 1.51 min
MS (ESIpos): m/z = 523$(M+H)^+$
^{1}H NMR (300 MHz, DMSO-d6): δ [ppm] = -0.17 - -0.09 (m, 6 H), 0.78 (s, 9 H), 1.62 (s, 6 H), 4.04 (t, 2 H), 4.47 (t, 2 H), 5.98 (s, 1 H), 7.57 (s, 1 H), 8.16 (d, 1 H), 8.29 (s, 1 H), 8.37 (t, 1 H), 8.45 (d, 1 H), 8.73 (s, 1 H), 12.38 (s, 1 H).

Stage B:



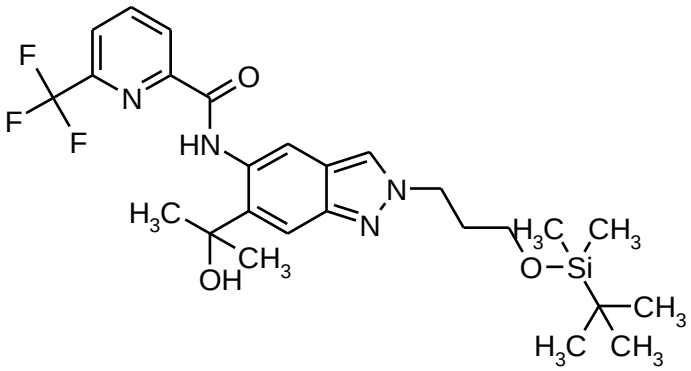
50 mg (96 µmol) of N-[2-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-6-(hydroxymethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide were dissolved in 1.0 ml of THF and admixed with 144 µl (0.14 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF. The reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with water and extracted twice with ethyl acetate, and the combined organic phases were washed with saturated sodium chloride solution, filtered through a hydrophobic filter and concentrated. This gave 36 mg of N-[2-(2-hydroxyethyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Example 5).
^{1}H-NMR (400MHz, DMSO-d_6): d [ppm] = 1.62 (s, 6H), 3.86 (q, 2H), 4.43 (t, 2H), 4.95 (t, 1H), 5.94 (s, 1H), 7.57 (s, 1H), 8.16 (dd, 1H), 8.30 (s, 1H), 8.37 (t, 1H), 8.45 (d, 1H), 8.72 (s, 1H), 12.36 (s, 1H).
UPLC-MS (Method A2): R_t = 0.97 min (UV detector: TIC), mass found 408.00.

Example 6

N-[6-(2-Hydroxypropan-2-yl)-2-(3-hydroxypropyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

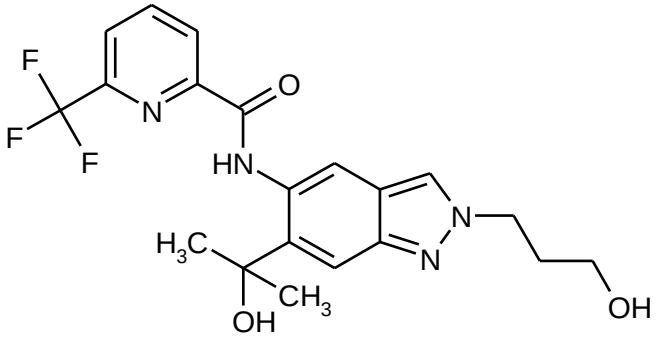
Stage A:

Preparation of N-[2-(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide



50 mg (0.09 mmol) of methyl 2-(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate (Intermediate 4-6) were dissolved in 500 µl of THF and admixed with 326 µl (0.33 mmol) of a 1 M methylmagnesium bromide solution in THF. The reaction mixture was stirred at 25°C for 60 min. Subsequently, 20 ml of a saturated ammonium chloride solution were added cautiously and the mixture was extracted twice with ethyl acetate. The combined organic phases were filtered through a hydrophobic filter, concentrated and dried under reduced pressure. The residue was purified by preparative HPLC. 40 mg of N-[2-(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide were obtained.
UPLC-MS (Method A1): R_t = 1.58 min
MS (ESIpos): m/z = 537$(M+H)^+$
^{1}H NMR (300 MHz, DMSO-d6): δ [ppm] = 0.02 - 0.05 (m, 6 H), 0.84 - 0.91 (m, 9 H), 1.62 (s, 6 H), 2.02 - 2.18 (m, 2 H), 3.55 - 3.62 (m, 2 H), 4.45 (t, 2 H), 5.96 (s, 1 H), 7.57 (s, 1 H), 8.16 (d, 1 H), 8.31 (s, 1 H), 8.33 - 8.42 (m, 1 H), 8.45 (d, 1 H), 8.72 (s, 1 H), 12.37 (s, 1 H).

Stage B:



37 mg (0.07 mmol) of N-[2-(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide were dissolved in 500 µl of THF and admixed with 207 µl (0.21 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF. The reaction mixture was stirred at 25°C for 2 h. The mixture was diluted with water and extracted twice with ethyl acetate, and the combined organic phases were washed with saturated sodium chloride solution, filtered and concentrated. After purification by preparative HPLC, 10 mg of N-[6-(2-hydroxypropan-2-yl)-2-(3-hydroxypropyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Example 6, contained secondary component) were obtained.
UPLC-MS (Method A2): R_t = 1.00 min

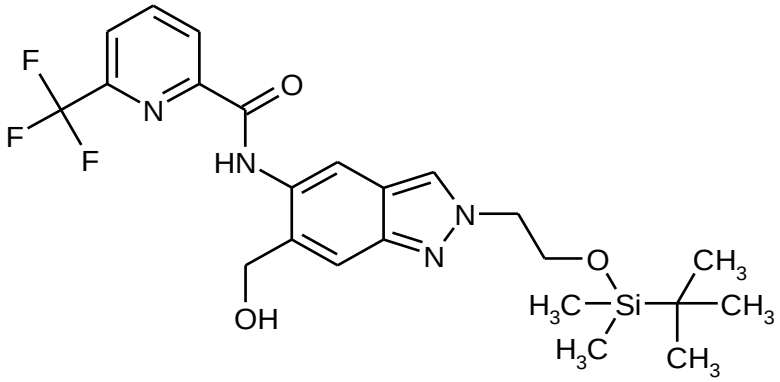
MS (ESIpos): m/z = 423 $(M+H)^+$
^{1}H NMR selected signals (400 MHz, DMSO-d6): δ [ppm] = 1.61 (s), 2.00 - 2.12 (m), 3.38 (t, 2 H), 4.44 (t, 2 H), 4.62 (br. s., 1 H), 5.93 (br. s., 1 H), 7.55 (s, 1 H), 8.13 (d, 1 H), 8.27 - 8.38 (m, 2 H), 8.43 (d, 1 H), 8.71 (s, 1 H), 12.30 (br. s., 1 H).

Example 7

N-[2-(2-Hydroxyethyl)-6-(hydroxymethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

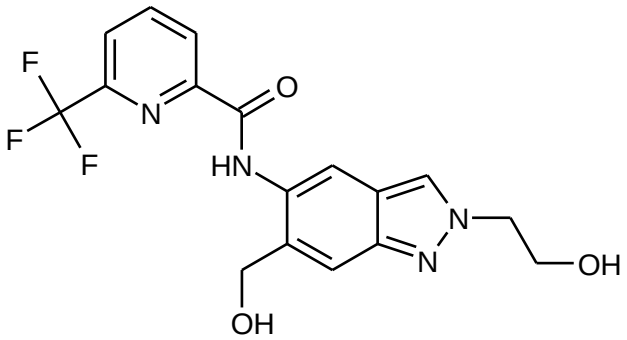
Stage A:

N-[2-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-6-(hydroxymethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide



100 mg (0.19 mmol) of methyl 2-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate (Intermediate 4-5) were dissolved in 1 ml of THF and admixed with 191 µl (0.38 mmol) of a 2 M lithium borohydride solution. The mixture was left to stir at 25°C for 24 h. 14 mg (0.38 mmol) of sodium borohydride and 500 µl of methanol were added, and the mixture was stirred at 25°C for 4 h. Another 14 mg (0.38 mmol) of sodium borohydride were added, and the mixture was stirred at 25°C for 24 h. Water was added cautiously to the reaction mixture and the organic phase was removed. The mixture was then extracted twice with ethyl acetate, and the combined organic phases were washed with saturated sodium chloride solution, filtered through a hydrophobic filter and concentrated. The residue was taken up in 2 ml of DMSO and purified by preparative HPLC. This gave 30 mg of N-[2-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-6-(hydroxymethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide.
UPLC-MS (Method A2): R_t = 1.44 min
MS (ESIpos): m/z = 495$(M+H)^+$
^{1}H NMR (300 MHz, DMSO-d6): δ [ppm] = -0.16 - -0.12 (m, 6 H), 0.75 - 0.79 (m, 9 H), 4.05 (t, 2 H), 4.48 (t, 2 H), 4.69 (d, 2 H), 5.75 - 5.77 (m, 1 H), 7.57 (s, 1 H), 8.18 (dd, 1 H), 8.30 - 8.33 (m, 1 H), 8.38 (t, 1 H), 8.45 (d, 1 H), 8.51 (s, 1 H), 11.20 (s, 1 H).

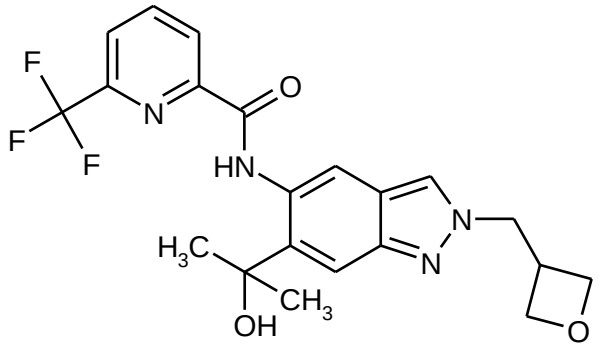
Stage B:



33 mg (0.07 mmol) of N-[2-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-6-(hydroxymethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide were dissolved in 1 ml of THF and admixed with 100 µl (0.10 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF. The reaction mixture was stirred at 25°C for 1 h. The mixture was diluted with water and extracted twice with ethyl acetate, and the combined organic phases were washed with saturated sodium chloride solution, filtered through a hydrophobic filter, concentrated and dried under reduced pressure. 25 mg of N-[2-(2-hydroxyethyl)-6-(hydroxymethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Example 7) were obtained.
UPLC-MS (Method A2): R_t = 0.87 min
MS (ESIpos): m/z = 381 $(M+H)^+$
^{1}H NMR (300 MHz, DMSO-d6): δ [ppm] = 3.87 (q, 2 H), 4.44 (t, 2 H), 4.69 (d, 2 H), 4.98 (t, 1 H), 5.70 - 5.81 (m, 1 H), 7.57 (s, 1 H), 8.11 - 8.23 (m, 1 H), 8.31 - 8.42 (m, 2 H), 8.43 - 8.49 (m, 1 H), 8.51 (s, 1 H), 11.20 (s, 1 H).

Example 8

N-[6-(2-Hydroxypropan-2-yl)-2-(oxetan-3-ylmethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

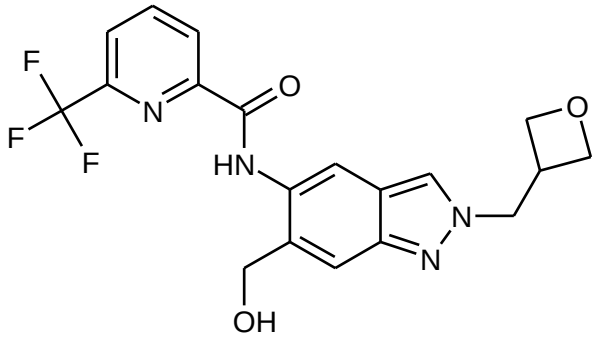


50 mg (0.12 mmol) of methyl 2-(oxetan-3-ylmethyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate (Intermediate 4-1) were dissolved in 500 µl of THF and admixed with 576 µl (0.58 mmol) of a 1 M methylmagnesium bromide solution in THF. The reaction mixture was stirred at 25°C for 60 min. Subsequently, 20 ml of a saturated aqueous ammonium chloride solution were added cautiously and the mixture was concentrated. The aqueous phase was extracted twice with ethyl acetate, and the organic phases were combined, dried over magnesium sulphate, filtered and concentrated. The residue was dissolved in 2.0 ml of DMSO and purified by preparative HPLC. The product-containing fractions were freeze-dried. 30 mg of the title compound were obtained.
UPLC-MS (Method A2): R_t = 1.03 min
MS (ESIpos): m/z = 435 $(M+H)^+$

^{1}H NMR (400 MHz, DMSO-d6): δ [ppm] = 1.62 (s, 6 H), 3.45 - 3.61 (m, 1 H), 4.48 (t, 2 H), 4.66 (dd, 2 H), 4.72 (d, 2 H), 5.94 (s, 1 H), 7.57 (s, 1 H), 8.16 (d, 1 H), 8.33 - 8.42 (m, 2 H), 8.42 - 8.47 (m, 1 H), 8.72 (s, 1 H), 12.36 (s, 1 H).

Example 9

N-[6-(Hydroxymethyl)-2-(oxetan-3-ylmethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide



75 mg (0.17 mmol) of methyl 2-(oxetan-3-ylmethyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate (Intermediate 4-1) were dissolved in 1 ml of a mixture of THF/methanol (1:1), and 8 mg (0.21 mmol) of sodium borohydride were added. The mixture was left to stir at 25°C for 60 min. The reaction mixture was concentrated, and the residue was admixed with water. The suspension was stirred vigorously for 15 min, and the solids were filtered off with suction, washed twice with water and twice with diethyl ether, and dried under reduced pressure. 48 mg of the title compound were obtained.

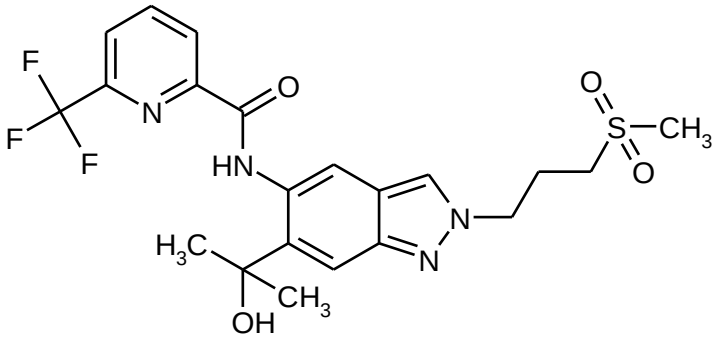
UPLC-MS (Method A2): R_t = 0.94 min

MS (ESIpos): m/z = 407 $(M+H)^+$

^{1}H NMR (300 MHz, DMSO-d6): δ [ppm] = 3.55 (s, 1 H), 4.48 (t, 2 H), 4.61 - 4.77 (m, 6 H), 7.57 (s, 1 H), 8.18 (dd, 1 H), 8.33 - 8.49 (m, 3 H), 8.51 (s, 1 H), 11.21 (s, 1 H).

Example 10

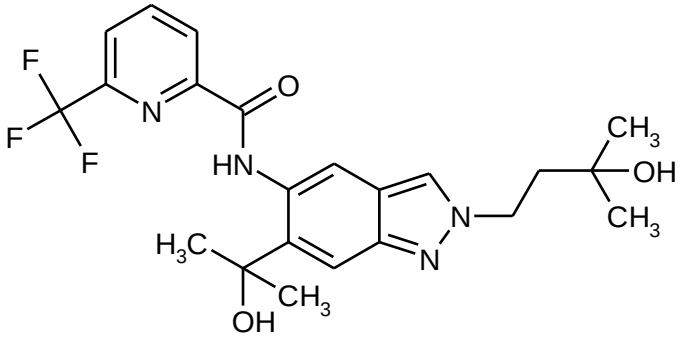
N-{6-(2-Hydroxypropan-2-yl)-2-[3-(methylsulphonyl)propyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide



A mixture of 500 mg (1.32 mmol) of N-[6-(2-hydroxypropan-2-yl)-1H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate 5-1), 569 mg of potassium carbonate and 114 mg of potassium iodide in 5.0 ml of DMF was stirred at room temperature for 15 min. 414 mg of 1-bromo-3-(methylsulphonyl)propane were added and the mixture was stirred at room temperature overnight. Water was added, the mixture was twice extracted with ethyl acetate and the extracts were washed with sodium chloride solution and concentrated. The residue was purified by column

chromatography (dichloromethane/methanol gradient). Extracting the product fraction by stirring with diethyl ether gave 59 mg of the title compound.
UPLC-MS (Method A2): R_t = 1.02 min
MS (ESIpos): m/z = 485 (M+H)+
^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.63 (s, 6H), 2.26 - 2.42 (m, 2H), 2.99 (s, 3H), 3.06 - 3.16 (m, 2H), 4.55 (t, 2H), 5.96 (s, 1H), 7.60 (s, 1H), 8.16 (d, 1H), 8.33 - 8.48 (m, 3H), 8.73 (s, 1H), 12.37 (s, 1H).

Example 11
N-[2-(3-Hydroxy-3-methylbutyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide



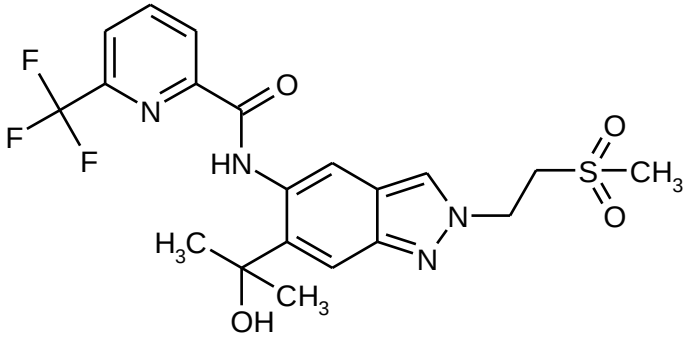
Preparation Method 1
705 mg (1.57 mmol) of methyl 2-(3-hydroxy-3-methylbutyl)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate (Intermediate 4-4) were initially charged in 10 ml of THF and cooled in an ice-water cooling bath. 2.6 ml (5.0 equivalents) of 3M methylmagnesium bromide solution (in diethyl ether) were added and the mixture was left to stir while cooling with an ice bath for 1 h and at room temperature for 4.5 h. Another 1 equivalent of the methylmagnesium bromide solution was added and the mixture was left to stir at room temperature for 20.5 h. Another 1 equivalent again of the methylmagnesium bromide solution was added and the mixture was left to stir at room temperature for 22 h. The reaction mixture was admixed with saturated aqueous ammonium chloride solution, stirred and extracted three times with ethyl acetate. The combined organic phases were washed with sodium chloride solution, filtered through a hydrophobic filter and concentrated. This gave 790 mg of a residue which was purified by means of preparative HPLC. This gave 234 mg of the title compound and 164 mg of a product fraction which was extracted by stirring with diethyl ether. After filtration with suction followed by drying, a further 146 mg of the title compound were obtained.
UPLC-MS (Method A1): R_t = 1.10 min (UV detector: TIC), mass found 450.00.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.14 (s, 6H), 1.61 (s, 6H), 1.99 - 2.08 (m, 2H), 4.42 - 4.55 (m, 3H), 5.93 (s, 1H), 7.56 (s, 1H), 8.15 (dd, 1H), 8.32 - 8.39 (m, 2H), 8.41 - 8.47 (m, 1H), 8.70 (s, 1H), 12.34 (s, 1H).

Preparation Method 2
A mixture of 500 mg (1.37 mmol) of N-[6-(2-hydroxypropan-2-yl)-1H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate 5-1), 569 mg of potassium carbonate and 114 mg of potassium iodide in 5 ml of DMF was stirred at room temperature for 15 min. 344 mg (1.5 equivalents) of 4-bromo-2-methylbutan-2-ol were added and the mixture was heated to 100°C for 2 h. Another 0.5 equivalent of 4-

bromo-2-methylbutan-2-ol was added and the mixture was stirred at room temperature for 16 h. The mixture was admixed with water and extracted twice with ethyl acetate, and the combined organic phases were washed with saturated sodium chloride solution and filtered through a hydrophobic filter and concentrated. The residue was purified by column chromatography purification on silica gel (hexane/ethyl acetate). This gave 100 mg of a product fraction which was extracted by stirring with diethyl ether. After drying, 60 mg of the title compound were obtained.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.14 (s, 6 H), 1.61 (s, 6H), 1.99 - 2.07 (m, 2 H), 4.43 - 4.52 (m, 3 H) 5.94 (s, 1 H) 7.57 (s, 1 H) 8.15 (dd, 1H) 8.33 - 8.40 (m, 2 H), 8.42 - 8.48 (m, 1 H), 8.71 (s, 1 H), 12.35 (s, 1 H)

Example 12

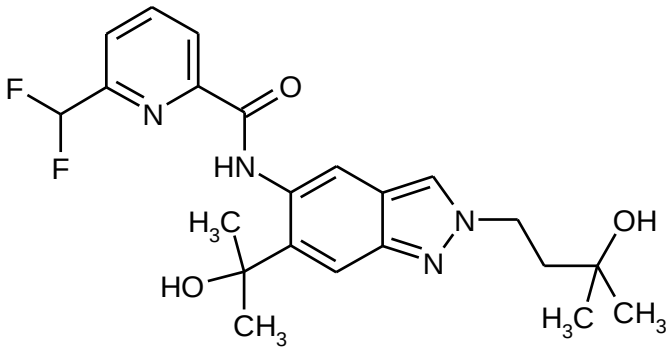
N-{6-(2-Hydroxypropan-2-yl)-2-[2-(methylsulphonyl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide



160 mg (0.44 mmol) of N-[6-(2-hydroxypropan-2-yl)-1H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate 5-1) were suspended together with 182 mg of potassium carbonate and 36 mg of potassium iodide in 1.0 ml of DMF, and the mixture was stirred at room temperature for 15 min. Then 123 mg of 2-bromoethyl methyl sulphone (0.66 mmol) were added and the mixture was stirred at room temperature overnight. Water was added, the mixture was extracted twice with ethyl acetate and the extracts were washed with saturated aqueous sodium chloride solution, filtered through a hydrophobic filter and concentrated. Purification of the residue by preparative HPLC gave 20 mg of the title compound.
UPLC (Method A2): R_t = 1.01 min;
MS (ESIpos): m/z = 471 (M+H)+
^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm]= 1.63 (s, 6 H), 2.90 (s, 3 H), 3.85 (t, 2 H), 4.86 (t, 2 H), 5.97 (s, 1 H), 7.59 (s, 1 H), 8.13 - 8.19 (m, 1 H), 8.37 (s, 1 H), 8.41 - 8.48 (m, 2 H), 8.74 (s, 1 H), 12.37 (s, 1 H).

Example 13

6-(Difluoromethyl)-N-[2-(3-hydroxy-3-methylbutyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]pyridine-2-carboxamide



Preparation Method 1

A mixture of 250 mg of 6-(difluoromethyl)-N-[6-(2-hydroxypropan-2-yl)-1H-indazol-5-yl]pyridine-2-carboxamide (crude product of Intermediate 5-2), 144 mg of potassium iodide and 239 mg of potassium carbonate in 2.5 ml of DMF was stirred at room temperature for 15 min. 145 mg (0.87 mmol) of 4-bromo-2-methylbutan-2-ol were added, the mixture was stirred at 110°C for 3 h, another 96 mg of 4-bromo-2-methylbutan-2-ol were added and the mixture was stirred at 110°C for 4 h. Water was added, the mixture was extracted twice with ethyl acetate and the extract was washed with semisaturated aqueous sodium chloride solution, filtered through a hydrophobic filter and concentrated. Purification was effected by column chromatography on silica gel (hexane/ethyl acetate). 61 mg of the title compound were obtained.

UPLC-MS (Method A1): R_t = 1.00 min (UV detector: TIC), mass found 432.00.

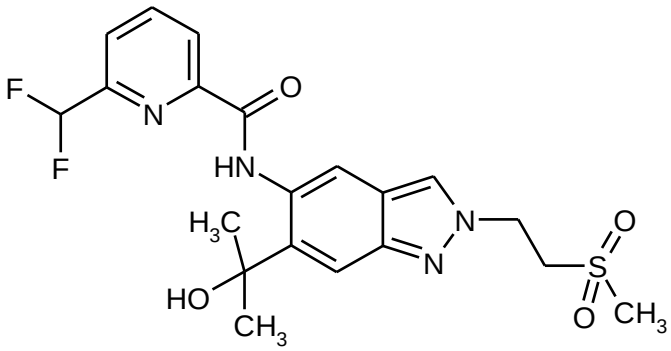
^{1}H-NMR (300MHz, DMSO-d_6): δ [ppm]= 1.14 (s, 6H), 1.63 (s, 6H), 1.97 - 2.08 (m, 2H), 4.41 - 4.55 (m, 3H), 5.99 (s, 1H), 7.03 (t, 1H), 7.56 (s, 1H), 7.94 – 8.00 (m, 1H), 8.24 - 8.38 (m, 3H), 8.71 (s, 1H), 12.49 (s, 1H).

Preparation Method 2

Analogously to the preparation of Example 11 (Preparation Method 1), 3.00 g of methyl 5-({[6-(difluoromethyl)pyridin-2-yl]carbonyl}amino)-2-(3-hydroxy-3-methylbutyl)-2H-indazole-6-carboxylate (Intermediate 4-11) were reacted with 3M methylmagnesium bromide solution (in diethyl ether). After purification of the crude product by extractive stirring with diethyl ether followed by preparative HPLC, 1.37 g of the title compound were obtained.

Example 14

6-(Difluoromethyl)-N-{6-(2-hydroxypropan-2-yl)-2-[2-(methylsulphonyl)ethyl]-2H-indazol-5-yl}pyridine-2-carboxamide



A mixture of 250 mg of 6-(difluoromethyl)-N-[6-(2-hydroxypropan-2-yl)-1H-indazol-5-yl]pyridine-2-carboxamide (crude product of Intermediate 5-2), 144 mg of potassium iodide and 239 mg of potassium carbonate in 2.5 ml of DMF was stirred at room

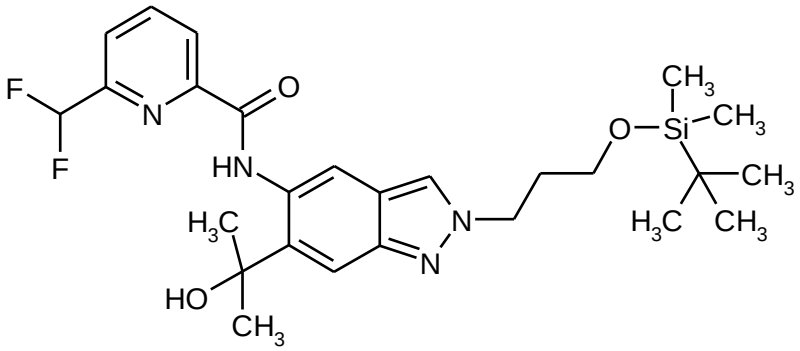
temperature for 15 min. 162 mg of 2-bromoethyl methyl sulphone (0.87 mmol) were added and the mixture was stirred at 110°C for 3 h. Water was added, the mixture was extracted twice with ethyl acetate and the extract was washed with semisaturated aqueous sodium chloride solution, filtered through a hydrophobic filter and concentrated. The residue was purified by preparative HPLC and the product fractions were additionally purified by column chromatography purification on silica gel (hexane/ethyl acetate). 40 mg of the title compound were obtained.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.65 (s, 6H), 2.90 (s, 3H), 3.85 (t, 2H), 4.85 (t, 2H), 6.03 (s, 1H), 7.04 (t, 1H), 7.59 (s, 1H), 7.98 (d, 1H), 8.25 - 8.36 (m, 2H), 8.43 (s, 1H), 8.75 (s, 1H), 12.52 (s, 1H).

Example 15

6-(Difluoromethyl)-N-[6-(2-hydroxypropan-2-yl)-2-(3-hydroxypropyl)-2H-indazol-5-yl]pyridine-2-carboxamide

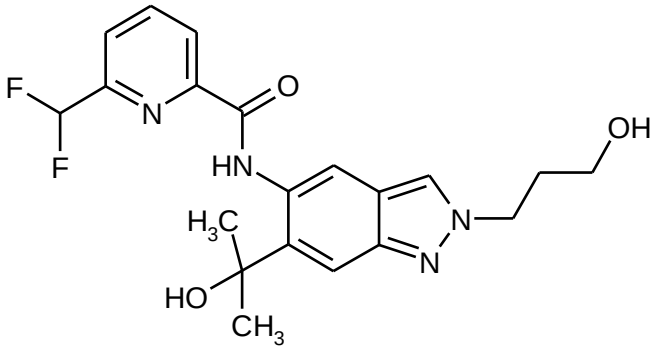
Stage A:

Preparation of N-[2-(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-(difluoromethyl)pyridine-2-carboxamide



A mixture of 250 mg of 6-(difluoromethyl)-N-[6-(2-hydroxypropan-2-yl)-1H-indazol-5-yl]pyridine-2-carboxamide (Intermediate 5-2), 48 mg of potassium iodide and 239 mg of potassium carbonate in 2.5 ml of DMF was stirred at room temperature for 15 min. 219 mg (0.87 mmol, 1.5 equivalents) of (3-bromopropoxy)(tert-butyl)dimethylsilane were added and the mixture was stirred at 110°C for 3 h. Another 1 equivalent of (3-bromopropoxy)(tert-butyl)dimethylsilane was added and the mixture was stirred at 100°C for 4 h. Water was added, the mixture was extracted with ethyl acetate and the extract was washed with aqueous sodium chloride solution, filtered through a hydrophobic filter and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate). 92 mg of the title compound were obtained.

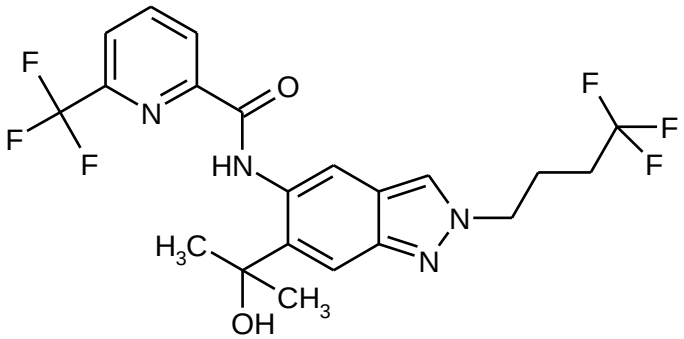
Stage B:



Analogously to the preparation of Example 6, Stage B, 92 mg of N-[2-(3-{[tert-butyl(dimethyl)silyl]oxy}propyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-(difluoromethyl)pyridine-2-carboxamide were reacted with 0.53 ml of a 1 M solution of tetrabutylammonium fluoride in THF within 1 h. Aqueous workup as in Example 6 and purification by preparative HPLC gave 46 mg of the title compound.
UPLC-MS (Method A1): R_t = 0.92 min (UV detector: TIC), mass found 404.00.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.64 (s, 6H), 2.05 (quin, 2H), 3.35 - 3.46 (m, 2H), 4.45 (t, 2H), 4.64 (t, 1H), 5.99 (s, 1H), 7.04 (t, 1H), 7.57 (s, 1H), 7.95 – 7.99 (m, 1H), 8.25 - 8.36 (m, 3H), 8.73 (s, 1H), 12.50 (s, 1H).

Example 16

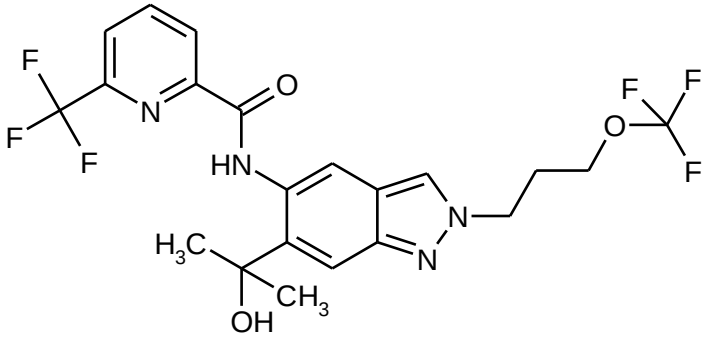
N-[6-(2-Hydroxypropan-2-yl)-2-(4,4,4-trifluorobutyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide



A mixture of 210 mg (0.58 mmol) of N-[6-(2-hydroxypropan-2-yl)-1H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate 5-1) in 3 ml of DMF was admixed with 0.11 ml (0.87 mmol) of 1,1,1-trifluoro-4-iodobutane and 239 mg of potassium carbonate, and the mixture was stirred at 80°C for 6 h. After addition of water, the mixture was extracted three times with ethyl acetate, and the combined organic phases were washed with saturated sodium chloride solution, filtered through a hydrophobic filter and concentrated. The crude product was purified by preparative HPLC. 19 mg of the title compound were obtained.
UPLC-MS (Method A1): R_t = 1.27 min (UV detector: TIC), mass found 474.15.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.62 (s, 6H), 2.10 - 2.33 (m), 4.49 (t, 2H), 5.94 (s, 1H), 7.59 (s, 1H), 8.13 - 8.18 (m, 1H), 8.32 - 8.41 (m, 2H), 8.41 - 8.47 (m, 1H), 8.72 (s, 1H), 12.35 (s, 1H).

Example 17

N-{6-(2-Hydroxypropan-2-yl)-2-[3-(trifluoromethoxy)propyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

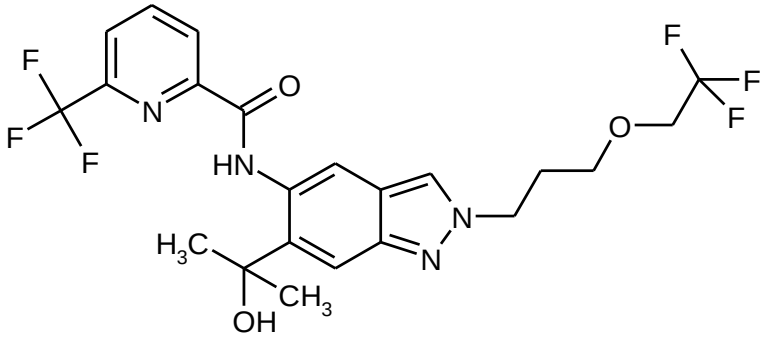


150 mg (0.33 mmol) of N-[6-(2-hydroxypropan-2-yl)-1H-indazol-5-yl]-6-

(trifluoromethyl)pyridine-2-carboxamide (Intermediate 5-1) were initially charged in 2 ml of THF. 58 mg (0.40 mmol) of 3-(trifluoromethoxy)propan-1-ol, 131 mg of triphenylphosphine and 71 µl of diisopropyl azodicarboxylate (DIAD, CAS 2446-83-5) were added and the mixture was stirred at room temperature for 19 h. 0.83 ml of sodium hydroxide solution (2M) was added and the mixture was stirred at 40°C for 5 h. The mixture was diluted with water and extracted three times with ethyl acetate, and the combined organic phases were concentrated and purified by preparative HPLC. 16 mg of the title compound were obtained as a crude product.
UPLC-MS (Method A2): R_t = 1.26 min (UV detector: TIC), mass found 490.14.
^{1}H-NMR (400MHz, DMSO-d_6, selected signals): δ [ppm]= 1.61 (s, 6H), 1.84 (d, 1H), 2.32 (quint., 2H), 4.08 (t, 2H), 4.51 (t, 2H), 7.58 (s, 1H), 8.15 (d, 1H), 8.31 – 8.39 (m, 2H), 8.44 (d, 1H), 8.72 (s, 1H), 12.35 (s, 1H).

Example 18

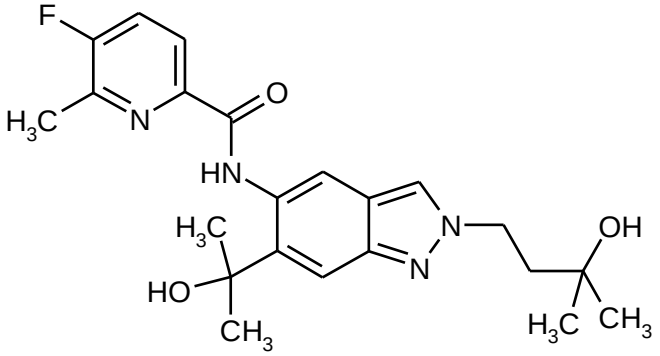
N-{6-(2-Hydroxypropan-2-yl)-2-[3-(2,2,2-trifluoroethoxy)propyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide



Analogously to the preparation of Example 11 (Preparation Method 1), 52 mg (0.10 mmol) of methyl 2-[3-(2,2,2-trifluoroethoxy)propyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate (Intermediate 4-10) in 3 ml of THF were reacted with 2 × 171 µl of 3M magnesium bromide solution in diethyl ether. Purification by preparative HPLC gave 12 mg of the title compound.
UPLC-MS (Method A1): R_t = 1.25 min (UV detector: TIC), mass found 504.16.
^{1}H-NMR (500 MHz, DMSO-d_6): δ [ppm] = 1.63 (s, 6H), 2.20(quin, 2H), 3.58(t, 2H),4.05(q, 2H), 4.47(t, 2H),5.94(s, 1H), 7.58 (s, 1H), 8.15 (dd, 1H), 8.32 (s, 1H), 8.36 (t, 1H), 8.45(d, 1H), 8.73 (s, 1H), 12.36 (s,1H).

Example 19

5-Fluoro-N-[2-(3-hydroxy-3-methylbutyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-methylpyridine-2-carboxamide

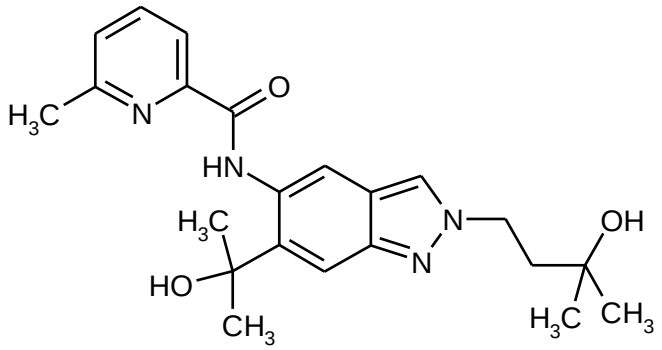


228 mg (0.31 mmol) of methyl 5-{[(5-fluoro-6-methylpyridin-2-yl)carbonyl]amino}-

2-(3-hydroxy-3-methylbutyl)-2H-indazole-6-carboxylate (Intermediate 4-8) were initially charged in 4.5 ml of THF and cooled with an ice cooling bath. 0.63 ml of 3M methylmagnesium bromide solution (in diethyl ether) was added and the mixture was left to stir while cooling with an ice bath for 2 h and at room temperature for 21 h. The reaction mixture was admixed with saturated aqueous ammonium chloride solution and extracted three times with ethyl acetate. The combined organic phases were concentrated. The residue was purified by preparative HPLC. 82 mg of the title compound were obtained.
UPLC-MS (Method A2): R_t = 1.03 min (UV detector: TIC), mass found 414.21.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.13 (s, 6H), 1.63 (s, 6H), 1.99 - 2.05 (m, 2H), 2.55 - 2.59 (m, 3H), 4.42 - 4.50 (m, 3H), 5.95 (s, 1H), 7.54 (s, 1H), 7.83 (t, 1H), 8.05 (dd, 1H), 8.31 (s, 1H), 8.68 (s, 1H), 12.33 (s, 1H).

Example 20

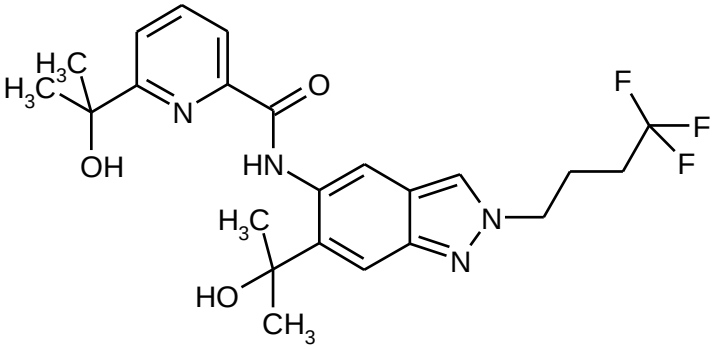
N-[2-(3-Hydroxy-3-methylbutyl)-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl]-6-methylpyridine-2-carboxamide



278 mg (0.48 mmol) of methyl 2-(3-hydroxy-3-methylbutyl)-5-{[(6-methylpyridin-2-yl)carbonyl]amino}-2H-indazole-6-carboxylate (Intermediate 4-9) were initially charged in 5.0 ml of THF and cooled with an ice cooling bath. 0.97 ml of 3M methylmagnesium bromide solution (in diethyl ether) was added and the mixture was left to stir while cooling with an ice bath for 2 h and at room temperature for 20.5 h. Another 0.48 ml of 3M methylmagnesium bromide solution was added and the mixture was left to stir at room temperature for 67 h. The mixture was admixed with saturated aqueous ammonium chloride solution and extracted three times with ethyl acetate, and the extracts were washed with sodium chloride solution, filtered through a hydrophobic filter and concentrated. The residue was purified by preparative HPLC. 111 mg of the title compound were obtained.
UPLC-MS (Method A2): R_t = 0.97 min (UV detector: TIC), mass found 396.22.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.15 (s, 6H), 1.64 (s, 6H), 2.00 - 2.08 (m, 2H), 2.61 (s, 3H), 4.41 - 4.59 (m, 3H), 5.92 (s, 1H), 7.50 (dd, 1H), 7.56 (s, 1H), 7.90 - 7.99 (m, 2H), 8.33 (s, 1H), 8.70 (s, 1H), 12.39 (s, 1H).

Example 21

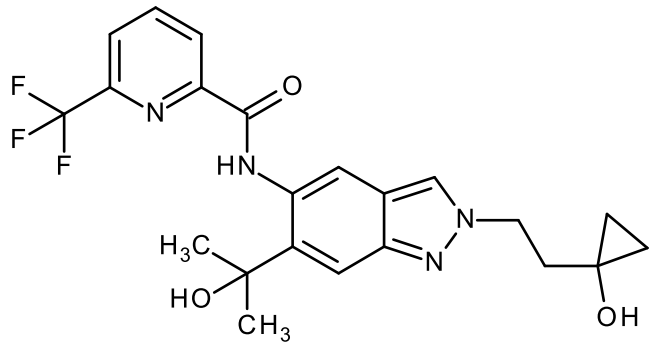
6-(2-Hydroxypropan-2-yl)-N-[6-(2-hydroxypropan-2-yl)-2-(4,4,4-trifluorobutyl)-2H-indazol-5-yl]pyridine-2-carboxamide



A solution of 72 mg (0.16 mmol) of methyl 5-({[6-(2-hydroxypropan-2-yl)pyridin-2-yl]carbonyl}amino)-2-(4,4,4-trifluorobutyl)-2H-indazole-6-carboxylate (Intermediate 4-7) in 10 ml of THF was cooled in an ice/water cooling bath. 0.26 ml of 3M methylmagnesium bromide solution in diethyl ether was added and the mixture was stirred for 2 h and then at room temperature for 20 h. Another 1 equivalent of the 3M methylmagnesium bromide solution was added and the mixture was stirred at room temperature for 24 h. Saturated aqueous ammonium chloride solution was added, the mixture was three times extracted with ethyl acetate and the extracts were washed with sodium chloride solution and concentrated. Preparative HPLC gave 22 mg (31% of theory) of the title compound.
UPLC-MS (Method A2): R_t = 1.15 min (UV detector: TIC), mass found 464.20.
^{1}H-NMR (400MHz, DMSO-d_6): δ [ppm]= 1.56 (s, 6H), 1.64 (s, 6H), 2.07 - 2.34 (m, 4H), 4.49 (t, 2H), 5.32 (s, 1H), 6.05 (s, 1H), 7.60 (s, 1H), 7.87 (dd, 1H), 7.99 - 8.05 (m, 2H), 8.35 (s, 1H), 8.79 (s, 1H), 12.45 (s, 1H).

Example 22

N-{2-[2-(1-Hydroxycyclopropyl)ethyl]-6-(2-hydroxypropan-2-yl)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide



250 mg (0.69 mmol) of N-[6-(2-hydroxypropan-2-yl)-1H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate 5-1) were initially charged in 5 ml of DMSO. 159 mg (0.96 mmol) of 1-(2-bromoethyl)cyclopropanol, 285 mg of potassium carbonate and 171 mg of potassium iodide were added and the mixture was stirred at 100°C for 5 h. Water was added and the mixture was extracted three times with ethyl acetate. The combined organic phases were washed with sodium chloride solution, filtered through a hydrophobic filter and concentrated. The residue was purified by preparative HPLC (column: Waters XBridge C18 5µ 100x30mm, eluent A: water + 0.1% by volume of formic acid (99%), eluent B: acetonitrile). Freeze-drying gave 45 mg of the title compound.

^{1}H-NMR (500MHz, DMSO-d_6): δ [ppm]= 0.18 - 0.22 (m, 2H), 0.48 - 0.52 (m, 2H), 1.62 (s, 6H), 2.08 (t, 2H), 4.54 - 4.60 (m, 2H), 5.36 (s, 1H), 5.96 (s, 1H), 7.57 (s, 1H), 8.16 (dd, 1H), 8.34 - 8.39 (m, 2H), 8.45 (d, 1H), 8.72 (s, 1H), 12.36 (s, 1H).

Assessment of physiological efficacy

IRAK4 kinase assay

The IRAK4-inhibitory activity of the inventive substances was measured in the IRAK4 TR-FRET assay (TR-FRET = Time Resolved Fluorescence Resonance Energy Transfer) described hereinafter.

Recombinant fusion protein from N-terminal GST (glutathione S-transferase) and human IRAK4, expressed in baculovirus-infected insect cells (Hi5, BTI-TN-5B1-4, cell line purchased from Invitrogen, catalogue No. B855-02) and purified via affinity chromatography, was used as enzyme. The substrate used for the kinase reaction was the biotinylated peptide biotin-Ahx-KKARFSRFAGSSPSQASFAEPG (C-terminus in amide form) which can be purchased, for example, from Biosyntan GmbH (Berlin-Buch).

For the assay, 11 different concentrations in the range from 20 µM to 0.073 nM were prepared from a 2 mM solution of the test substance in DMSO. 50 nl of the respective solution were pipetted into a black low-volume 384-well microtitre plate (Greiner Bio-One, Frickenhausen, Germany), 2 µl of a solution of IRAK4 in assay buffer [50 mM HEPES pH 7.5, 5 mM MgCl2, 1.0 mM dithiothreitol, 30 µM activated sodium orthovanadate, 0.1% (w/v) of bovine gamma-globulin (BGG) 0.04% (v/v) nonidet-P40 (Sigma)] were added and the mixture was incubated for 15 min to allow prebinding of the substances to the enzyme prior to the kinase reaction. The kinase reaction was then started by addition of 3 µl of a solution of adenosine triphosphate (ATP, 1.67 mM = final concentration in 5 µl of assay volume: 1 mM) and peptide substrate (0.83 µM = final concentration in 5 µl assay volume: 0.5 µM) in assay buffer, and the resulting mixture was incubated at 22°C for the reaction time of 45 min. The concentration of the IRAK4 was adjusted to the respective activity of the enzyme and set such that the assay was carried out in the linear range. Typical concentrations were in the order of about 0.2 nM. The reaction was stopped by addition of 5 µl of a solution of TR-FRET detection reagents [0.1 µM streptavidin-XL665 (Cisbio Bioassays; France, catalogue No. 610SAXLG)] and 1.5 nM anti-phosphoserine antibody [Merck Millipore, "STK Antibody", catalogue No. 35-002] and 0.6 nM LANCE EU-W1024-labelled anti-mouse-IgG antibody (Perkin-Elmer, product No. AD0077; alternatively, it is possible to use a terbium cryptate-labelled anti-mouse-IgG antibody from Cisbio Bioassays) in aqueous EDTA solution (100 mM EDTA, 0.4 % [w/v] bovine serum albumin [BSA] in 25 mM HEPES pH 7.5).

The resulting mixture was incubated at 22°C for 1 h to allow formation of a complex of the biotinylated phosphorylated substrate and the detection reagents. The amount of the phosphorylated substrate was then evaluated by measuring the resonance energy transfer from europium chelate-labelled anti-mouse-IgG antibody to streptavidin-XL665. To this end, the fluorescence emissions at 620 nm and 665 nm were measured after excitation at 350 nm in a TR-FRET measuring instrument, for example a Rubystar (BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio of the emissions at 665 nm and 622 nm was taken as a measure of the amount of phosphorylated substrate. The data were normalized (enzyme reaction

without test substance = 0% inhibition; all other assay components but no enzyme = 100% inhibition). Typically, the test substances were tested on the same microtitre plates at 11 different concentrations in the range from 20 µM to 0.073 nM (20 µM, 5.7 µM, 1.6 µM, 0.47 µM, 0.13 µM, 38 nM, 11 nM, 3.1 nM, 0.89 nM, 0.25 nM and 0.073 nM). The dilution series were prepared prior to the assay (2 mM to 7.3 nM in 100% DMSO) by serial dilutions. The IC_{50} values were calculated by a 4-parameter fit.

Table 1: IC_{50} values of the example compounds in the IRAK4 kinase assay

Example	IC_{50} [nM]
1	30.6
2	135.6
3	7.2
4	52.7
5	264.5
6	35.7
7	867.3
8	15.0
9	103.8
10	18.5
11	3.4
12	10.7
13	1.3
14	10.8
15	12.3
16	21.5
17	36.0
18	47.5
19	8.9
20	13.3
21	117.2
22	3.7

The inhibitory activity of the inventive substances of the general formula (III) with respect to IRAK4 was likewise measured in the IRAK4 TR-FRET assay described above. The following are mentioned by way of example: the compound Intermediate 4-2 with an IC_{50} = 21.7 nM, Intermediate 4-3 with an IC_{50} = 13.0 nM and Intermediate 4-4 with an IC_{50} = 6.2 nM.

TNF-α secretion in THP-1 cells

With the aid of this test, it is possible to test substances for their ability to inhibit secretion of TNF-α (tumour necrosis factor alpha) in THP-1 cells (human monocytic acute leukaemia cell line). TNF-α is a cytokine involved in inflammatory processes. In this test, TNF-α secretion is triggered by incubation with bacterial lipopolysaccharide (LPS).

THP-1 cells were kept in continuous suspension cell culture [RPMI 1460 medium with L-Glutamax (Gibco, Cat. No. 61870-044) supplemented with foetal calf serum (FCS) 10% (Invitrogen, Cat. No. 10082-147), 1% penicillin/streptomycin (Gibco BRL, Cat. No. 15140-114)] and should not exceed a cell concentration of $1x10^6$ cells/ml. The assay is carried out in cell culture medium (RPMI 1460 medium with L-Glutamax supplemented with FCS 10%).
In each case 2-2.5 µl of the cell suspension (corresponds to 4000 cells) per well were dispensed into a 384-well test plate (Greiner, Cat. No. 784076), in each of which 40-50 nl substance had been dissolved in 100% DMSO. This was done using 10 different concentrations in the range from 20 µM to 0.073 nM for each substance. The cells were incubated at room temperature for 15 min. 2-2.5 µl of 0.1 µg/ml LPS (Sigma, *Escherichia coli* 055:B5, Cat. No. L5418) dissolved in cell culture medium (final concentration 0.05 µg/ml) were then dispensed into each well. As neutral control, cells were treated with 0.05 µg/ml LPS and 1% DMSO and, as inhibitor control, with 1% DMSO only.
The plates were centrifuged at 80 g for 30 s and incubated at 37°C, 5% CO_2 and 95% atmospheric humidity for 17 h. The amount of TNF-α was determined using the TNF-alpha HTRF Detection Kit (Cisbio, Cat. No. 62TNFPEB/C). To this end, 2 µl of the detection solution in each case, consisting of anti-TNF-α-XL665 conjugate and anti-TNF-α-cryptate conjugate dissolved in the reconstitution buffer in accordance with the manufacturer's instructions, were added for the HTRF (Homogeneous Time-Resolved Fluorescence) test. After the addition, the mixture was incubated either at room temperature for 3 h or at 4°C overnight. The signals were then read at 620/665 nm using an HTRF-enabled measuring instrument such as the BMG PheraStar.

The activity of the substances is expressed as the ratio between neutral and inhibitor control in per cent. The IC_{50} values were calculated using a 4-parameter fit.

Table 2: IC_{50} values of the example compounds with respect to the secretion of TNF-α in THP-1 cells

Example	IC_{50} [µM]
1	1.0
2	15.1
3	0.7
4	5.6
5	5.4
6	0.9
7	16.4
8	1.0
9	6.5
10	1.0
11	0.2
12	0.3
13	0.1
14	0.2
15	0.2
16	0.2

Example	IC_{50} [µM]
17	0.5
18	0.3
19	0.1
20	0.2
21	1.8

***In vitro* LPS (lipopolysaccharide)-induced cytokine production in human PBMCs (peripheral blood mononuclear cells)**

The effect of the inventive compounds of the general formula (I) on induced cytokine production in human PBMCs was examined. Cytokine production was induced here by LPS, a TLR4 ligand, which leads to activation of the IRAK4-mediated signal path. The human PBMCs were obtained from anti-coagulated human whole blood. For this purpose, 15 ml of Ficoll-Paque (Biochrom, Cat. No. L6115) were initially charged in Leucosep tubes and 20 ml of human blood were added. After centrifugation of the blood at 800 g for 15 min at room temperature, the plasma including the platelets was removed and discarded. The PBMCs were transferred into centrifugation tubes and made up with PBS (phosphate-buffered saline) (Gibco, Cat. No. 14190). The cell suspension was centrifuged at room temperature at 250 g for 10 min and the supernatant was discarded. The PBMCs were resuspended in complete medium (RPMI 1640, without L-glutamine (PAA, Cat. No. E15-039), 10% FCS; 50 U/ml penicillin, 50 µg/ml streptomycin (PAA, Cat. No. P11-010) and 1% L-glutamine (Sigma, Cat. No. G7513)).
The assay was also carried out in complete medium. The PBMCs were sown in 96-well plates at a cell density of $2.5x10^5$ cells/well. The inventive compounds were subjected to serial dilution in a constant volume of 100% DMSO and used in the assay at 8 different concentrations in the range from 10 µM to 3 nM such that the final DMSO concentration was 0.4% DMSO. Prior to the actual stimulation, the cells were then pre-incubated therewith for 30 min. To induce cytokine secretion, the cells were stimulated with 0.1 µg/ml LPS (Sigma, *Escherichia coli* 0128:B12, Cat. No. L2887) for 24 hours. Cell viability was determined using the CellTiter-Glo luminescent assay (Promega, Cat. No. G7571 (G755/G756A)) in accordance with the manufacturer's instructions. The amount of secreted TNF-α in the cell culture supernatant was determined using the Human ProInflammatory 9-Plex Tissue Culture Kit (MSD, Cat. No. K15007B) in accordance with the instructions of the manufacturer. By way of example, Example Compound 11 and Example Compound 12 have activity ≤ 1 µM.

***In vitro* TLR-4/TLR-7-induced interleukin (IL)-23 secretion of human dendritic cells (DCs)**

The effect of the inventive compounds of the general formula (I) on the induced production of the pro-inflammatory cytokine IL-23 which plays an essential role for the generation of TH-17 cells was examined in human DCs. It is stated that TH-17 cells play a crucial role in the pathogenesis of disorders such as rheumatoid arthritis, psoriatic arthritis, Bekhterev's disease (ankylosing spondylitis) or else multiple sclerosis (Lubberts, Nat. Rev. Rheumatol., 2015; Marinoni et al., Auto. Immun.

Highlights, 2014; Isailovic et al., J. Autoimmun., 2015; Staschke et al., J Immunol., 2009). To detect the effect of the inventive compounds on IL-23 production, human primary monocytes (isolated from human PBMCs with the aid of magnetic separation [Miltenyi Biotech, Monocyte Isolation Kit, Cat. No. 130-091-153] with addition of growth factors (recombinant human GM-CSF [PeproTech, Cat. No. 300-03] and IL-4 [PeproTech, Cat. No. 200-04]) in complete medium (VLE (very low endotoxin) RPMI 1640 [Biochrom AG, Cat. No. FG1415], 10% Fetal Bovine Serum (FBS) [Gibco, Cat - No. 10493-106]; 50 µM β-mercaptoethanol (Gibco, Cat. No. 31350], 50 U/ml penicillin and streptomycin [Gibco, Cat. No. 15140-114]) were differentiated in culture over 6 days to give DCs. After the DCs had been harvested, they were resuspended in complete medium and sown in a cell density of 2x107 cells/well in a 96-well plate (Costar, Cat. No. 3599). The inventive compounds were subjected to serial dilution in a constant volume of 100% DMSO and used in the assay at 9 different concentrations in the range from 10 µM to 1 nM. It was ensured here that the DMSO concentration present was always 0.1% DMSO for each of the 9 concentrations used. There was a 30-minute preincubation of the DCs with the inventive compounds. Thereafter, the DCs were then stimulated to produce IL-23 by means of 10 ng/ml of LPS (Sigma, *Escherichia coli* serotype 0127:B8, Cat. No. L3129) (TLR4 ligand) and 2.5 µg/ml of TLR-7/8 ligand R848 (Invivogen, Cat. No. tlrl-r848-5), both of which bring about the activation of the IRAK4-mediated signalling pathway, in an incubator (37°C, 95%rH, 5% CO_2) for 24 hours. After this incubation time of 24 hours, the supernatants were removed and analysed with the aid of a commercially available hIL-23 ELISA (eBiosciences, Cat. No. 88-7237-88), which was conducted according to the manufacturer's instructions. The results of the inhibition of IL-23 in human DCs are shown by way of example for Example Compound 12 in Figure 1.

In vitro TLR-7/8- or TLR-9-induced IFNα production of human plasmacytoid dendritic cells (pDCs)

With the aid of this test, the effect of the inventive compounds of the general formula (I) on the production of IFNα (interferon-alpha), a key cytokine in the pathogenesis of systemic lupus erythematosus (Mathian et al., Arthritis Rheum, 2009; Crow M.K., Rheum Dis Clin N Am, 2010), can be studied in human pDCs. For this purpose, as described above, human PBMCs were isolated from whole blood and the plasmacytoid DCs (pDCs) were isolated therefrom with the aid of a commercially available cell separation kit (Miltenyi Biotech, Plasmacytoid Dendritic Cell Isolation Kit II, Cat. No. 130-097-415) The pDCs thus obtained were resuspended in complete medium (RPMI 1640 + GlutaMax [*Gibco*, Cat. No. 61870-010] supplemented with 10% FBS [Gibco, Cat. No. 10493-106] and 50 U penicillin/streptomycin [Gibco, Cat. No. 15140-114]) and plated out in a cell density of $5x10^4$ cells/well in a 96-well microtitre plate (Costar, Cat. No. 3599). The inventive compounds were subjected to serial dilution in a constant volume of 100% DMSO and used in the assay at 9 different concentrations in the range from 10 µM to 1 nM. It was ensured here that the DMSO concentration present was always 0.1% DMSO for each of the 9 concentrations used. There was a 30-minute preincubation of the pDCs with the inventive compounds. The pDCs were stimulated either with a TLR7/8 ligand (imiquimod, R837, Invivogen, Cat. No. tlrl-imq) or with a TLR-9 ligand (CPG-A, ODN2216, Invivogen, Cat. No. tlrl-2216-1) and this led to activation of the IRAK-4-mediated signalling pathways. After incubation for 24 hours, the cell culture supernatants were removed and analysed by means of a

commercially available human IFNα ELISA (IFNalpha Multi-Subtype ELISA Kit, pbl Assay Science, Cat. No. 41105-1). The results of the inhibition of IFNα in human plasmacytoid DCs are shown by way of example for Example Compound 12 in Figure 2.

***In vivo* model of TLR-mediated inflammation**

The inventive compounds of the general formula (I) were examined for their *in vivo* efficacy in a model of *in vivo* TLR-mediated inflammation. This mechanistic model particularly shows the potential effect of the inventive compounds on TLR4-mediated disorders, since an LPS-mediated inflammation model was used. In this model, female Balb/c mice (about 8 weeks old; Charles River Laboratories, Germany) were divided into groups of 5 animals each. The control group was treated with the vehicle in which the substance had been dissolved (substance vehicle) and also with the vehicle in which the LPS had been dissolved. As well as the substrate treatment groups, the positive control group was also administered intraperitoneally (i.p.) with 0.2 mg in each case of LPS/kg body weight (Sigma, Cat. No. L4391) (lipopolysaccharides from *E. coli* 0111:B4). In addition, the positive control group was treated with the substance vehicle described above. The substance was administered orally 16 hours before induction of inflammation by administration of LPS. To examine the effect of the inventive compounds on the inflammation, a final blood sample was taken from the animals after 1.5 hours. The concentration of particular cytokines in the plasma was determined using the Mouse ProInflammatory 7-Plex Tissue Culture Kit (MSD, Cat. No. K15012B) in accordance with the manufacturer's instructions. IRAK4 inhibitors are effective in the TLR-mediated inflammation model. Figure 3 shows the amount of TNF-α in the plasma, which is reduced in a dose-dependent manner by administration of Example Compound 11 in comparison with the LPS-induced concentration.

***In vivo* model of IL-1β-mediated inflammation**

To evaluate the potential efficacy of the inventive compounds of the general formula (I) in IL-1β-mediated disorders, IL-1β was administered i.p. to female Balb/c mice (about 8 weeks old, Charles River Laboratories, Germany) and the effect of the inventive compounds on IL-1β-mediated cytokine secretion was examined. There were 5 animals in each group. The control group was treated with the vehicles used for dissolving the substance and the IL-1β. The substance treatment groups and the positive control group were each administered with 90 µg of IL-1β /kg body weight (R&D, Cat. No. 401-ML/CF). The substance or its vehicle in the positive control group was administered 6 hours before the administration of IL-1β. 2 hours after administration of the IL-1β, TNF-α was determined in the plasma after the final removal of blood using the Mouse ProInflammatory 7-Plex Tissue Culture Kit (MSD, Cat. No. K15012B) in accordance with the manufacturer's instructions. Administration of IL-1β led to an elevated TNF-α plasma concentration which was inhibited by treatment with Example Compounds 11 and 12. This is illustrated by Figure 4.

***In vivo* adjuvant-induced arthritis model**

To determine the anti-inflammatory activity of the inventive compounds of the general formula (I), they were examined for their *in vivo* efficacy in an arthritis model. For this

purpose, male Lewis rats (about 100-125 g, Charles River Laboratories, Germany) were each administered subcutaneously with 100 µl of a complete Freund's adjuvant (CFA) solution (*M. tuberculosis* H37Ra [Difo Lab, Cat. No. -231141] dissolved in Incomplete Freund´s adjuvant [Difco Lab, Cat. No. -263910]) into the tailhead on day 0. There were n = 8 rats in each group. Both a healthy control group and a disease control group were included in the study. Each control group was given p.o. treatment only with the vehicle of the test substance. The treatment with different dosages of the test substance was conducted in a preventative manner, i.e. starting from day 0, by oral administration. On day 0, the starting condition of the animals was additionally determined in terms of the disease activity scores (rating of the severity of arthritis based on a points system). In this points system (score), according to the extent of joint inflammation, points were awarded from 0 to 4 for the presence of an erythema including joint swelling (0 = none; 1 = slight; 2 = moderate; 3 = distinct; 4 = severe) for both hind paws and added up. To determine the anti-inflammatory efficacy of the compounds, the disease status of the animals was scored by means of disease activity scoring starting from day 8, when the animals first exhibit signs of arthritis, and subsequently 3 times per week, until the end (day 20). Statistical analysis was effected using single-factor variance analysis (ANOVA) and comparison with the control group by means of multiple comparative analysis (Dunnett's test).

The s.c. administration of CFA in rats leads to acute arthritis with distinct joint inflammation in rats. This induced arthritis was inhibited by the treatment with Example Compound 11. This is illustrated by Figure 5.

***In vivo* collagen antibody-induced arthritis model in mice**

The anti-inflammatory effect of the inventive compounds of the general formula (I) was examined in a further murine arthritis model. For this purpose, female Balb/c mice (about 9 weeks old, Charles River Laboratories, Kingston, Canada) were each injected intravenously on day 0 with 200 µl of a collagen antibody cocktail (10 mg/ml; ArthritoMab, MD Bioproducts) into the tail vein (except for the healthy control group included in the study). On day 6, these mice then each received a further intraperitoneal injection of 200 µl of LPS. There were n = 10 mice in each group. Both a healthy control group and a disease control group were included in the study. Each control group was given p.o. treatment only with the vehicle of the test substance. The treatment with different dosages of the test substance was conducted in a preventative manner, i.e. starting from day 0, by oral administration. Over the course of the experiment, the extent of disease was scored on the basis of the points award system for the disease activity score on all four paws. In this awarding of points, no points are awarded for a healthy paw, whereas points from 1 [mild inflammation, for example, of the toe(s)] to 4 [severe inflammation extending over the entire paw] are awarded in each case for the particular extent of joint inflammation that has arisen from the toes through the metatarsal joint to the ankle joint, as explained as follows:

- ***0 = normal***
- 1 = erythema and mild swelling limited to the tarsal or ankle or toes

- 2 = erythema and mild swelling extending from the ankle to the metatarsus (2 segments)
- 3 = erythema and moderate swelling extending from the ankle as far as the metatarsal joints
- 4 = erythema and severe swelling encompassing the metatarsus, foot and toes

For this parameter, the starting condition was determined beforehand one day before the start of the experiment (day -1) and this disease activity score was subsequently scored three times per week from day 8 onwards. Statistical analysis was effected using single-factor variance analysis (ANOVA) and comparison with the control group by means of multiple comparative analysis (Dunnett's test).

The i.v. administration of a collagen antibody cocktail including the subsequent i.p. administration of LPS in mice leads to acute arthritis with distinct joint inflammation in mice. This induced arthritis was inhibited by the treatment with Example Compound 12. This is illustrated by Figure 6.

***In vivo* NASH mouse model**

To experimentally induce NASH, 45 male 2-day-old C57BL/6 mice were each injected subcutaneously with 200 µg of streptozotocin (STZ; Sigma-Aldrich, USA). From an age of 4 weeks, these animals are fed ad libitum with a high-fat diet (HFD; 57 kcal% fat, #HFD32 from CLEA, Japan). At an age of 6 weeks, the animals are randomized into 3 groups (15 animals per group). While one of the groups does not receive any treatment, the other 2 groups are given daily oral treatment either with vehicle or the test substance over 4 weeks. On completion of the 4-week treatment, all animals are sacrificed painlessly under anaesthesia, and the livers are removed and fixed for the histological study in Bouin's solution (H. Denk, "Fixierung histologischer Präparate" [Fixing of Histological Preparations], in: P. Böck (ed.): "Romeis Mikroskopische Technik" [Romei's Microscopy Techniques], Urban & Schwarzenberg, Munich-Vienna-Baltimore 1989, 17th edition, page 97, ISBN 3-541-11227-1). Thereafter, the liver samples are embedded in paraffin and 5 µm-thick paraffin sections are produced. Histological sections of each liver are stained a) for the determination of the NAFLD activity score (NAS) with haematoxylin-eosin (HC), and b) for the determination of liver fibrosis with Picro-Sirius red (Waldeck, Germany). The NAFLD activity score is determined in the haematoxylin-eosin sections with modification on the basis of the criteria recommended by D.E. Kleiner et al., Hepatology 41 (2005), 1313-1321 (Table 1). For the histological quantification of fibrotic areas, 5 digital photos (DFC280; Leica, Germany) are taken for each section under 200-fold microscope enlargement and the percentage of fibrosis is determined with the aid of the ImageJ Software (National Institute of Health, USA).

***In vivo* db/db mouse model**

30 male 8-week-old db/db mice are used. This model is a recognized model for obesity, insulin resistance and type 2 diabetes (Aileen JF King; The use of animal models in diabetes research; British Journal of Pharmacology 166 (2012), 877–894). During the experiment, the animals receive a standard diet (RM1(E) 801492, SDS) and

tap water ad libitum. The animals are randomized into 3 groups (10 animals per group) and treated orally with the test substance over 6 weeks. During the study period, blood is taken from the animals at different times (before commencement of treatment, 3 weeks after commencement of treatment and 2 days before the end of treatment) to determine insulin sensitivity parameters (e.g. HbA1c, glucose content, insulin content). In addition, an OGTT (oral glucose tolerance test) is conducted 1 day before commencement of treatment and 2 days after the end of treatment, likewise as a parameter for determination of insulin sensitivity. In addition, the HOMA-IR index (fasting insulin level (mU/l) * fasting glucose level (mmol/l) / 22.5) is calculated.

***In vivo* B-cell lymphoma-associated xenotransplantation model**

The anti-tumour activity of the inventive compounds of the general formula (I) is studied in murine xenotransplantaion models. For this purpose, female C.B-17 SCID mice are implanted subcutaneously with tumour cell lines of human B-cell lymphoma, e.g. TMD-8. With a mean tumour size of 20-30 mm², oral monotherapeutic treatment commences with an inventive compound or treatment by administration of an inventive compound in combination with a standard therapy, each administered orally. However, the animals are randomized beforehand. The treatment is ended as soon as the untreated control group has large tumours. The tumour size and body weight are determined three times per week. Decreases in body weight are a measure of treatment-related toxicity (> 10% = critical, stoppage in treatment until recovery, > 20% = toxic, termination). The tumour area is detected by means of an electronic caliper gauge [length (mm) x width (mm)]. At the end of the study, the tumour weight is also determined. The anti-tumour efficacy defines the ratio of tumour weight of treatment vs. control (T/C) [tumour weight of the treatment group on day x/tumour weight of the control group on day x] or the ratio of the tumour area of treatment vs. control [tumour area of the treatment group on day x/tumour area of the control group on day x]. A compound having a T/C greater than 0.5 is defined as active (effective). Statistical analysis is effected using single-factor ANOVA and comparison with the control group by means of pair-by-pair comparative analysis (Dunnett's test).

Figure 1: Inhibition of IL-23 in human monocyte-generated DCs for Example Compound 12. Data are shown as mean values with standard deviations.

Figure 2: Inhibition of INF-α in (A) imiquimod (R837)- or (B) CpG-A-stimulated human plasmacytoid DCs for Example Compound 12. Data are shown as mean values with standard deviations.

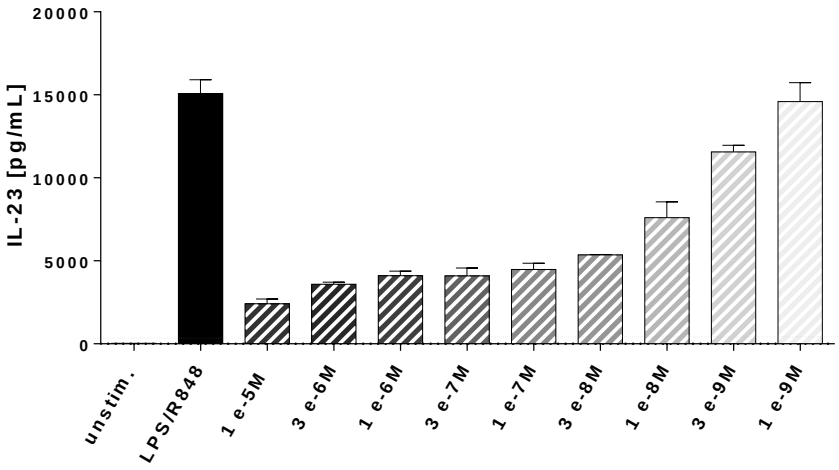
Figure 3: Treatment of an LPS-induced inflammation with Example Compound 11 leads to a reduced amount of secreted TNF-α Data are shown as mean values with standard deviations.

Figure 4: Treatment of an IL-1β-induced inflammation with Example Compounds 11 (left) and 12 (right) leads to a dose-dependent reduction in the amount of secreted TNF-α. Data are shown as mean values with standard deviations.

Figure 5: Anti-inflammatory effects of Example Compound 11 in an animal model of rheumatoid arthritis (adjuvant-induced rat model). Significant and dose-dependent inhibition of rheumatic joint inflammation measured on the basis of the disease activity score. The data corresponds to the mean values + standard deviations. Single-factor ANOVA variance analysis with subsequent multiple comparative analysis with the CFA control group by means of Dunnett's test; *p < 0.05; **p < 0.01;***p < 0.001; ****p < 0.0001.

Figure 6: Anti-inflammatory effects of Example Compound 12 in an animal model of rheumatoid arthritis (collagen antibody-induced mouse model). Significant and dose-dependent inhibition of rheumatic joint inflammation measured on the basis of the disease activity score. The data corresponds to the mean values + standard deviations. The statistical significances between collagen antibody (AK) control and the treatment groups were calculated by means of single-factor ANOVA variance analysis with subsequent multiple comparative analysis (Dunnett's test) (*p < 0.05; **p < 0.01;***p < 0.001; ****p < 0.0001).

Figure 1: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10000
5000
0
unstim.
LPS/R848
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3 e-6M
1 e-6M
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1 e-7M
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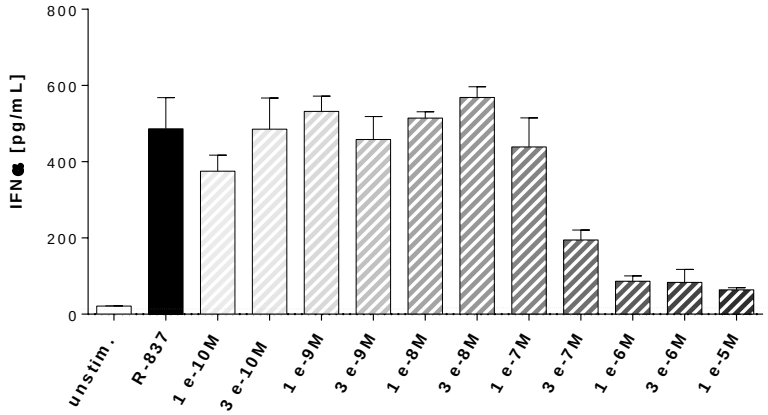
3 e-9M
1 e-9M

Figure 2:

A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600
400
200
0
IFN● [pg/mL]
unstim.
R-837
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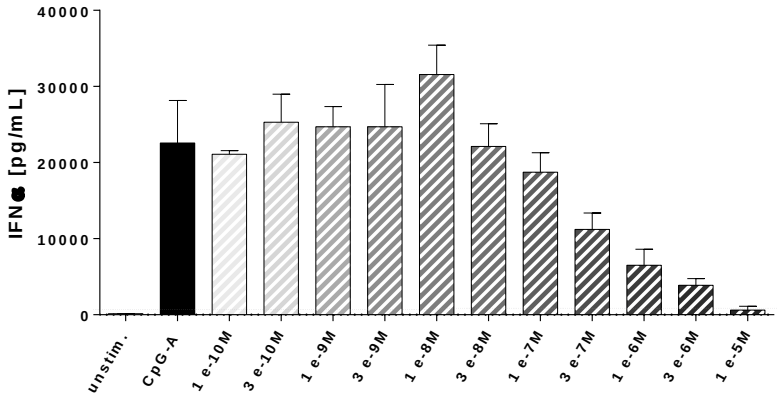
3 e-6M
1 e-5M

B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30000
20000
10000
0
IFN [pg/mL]
unstim.
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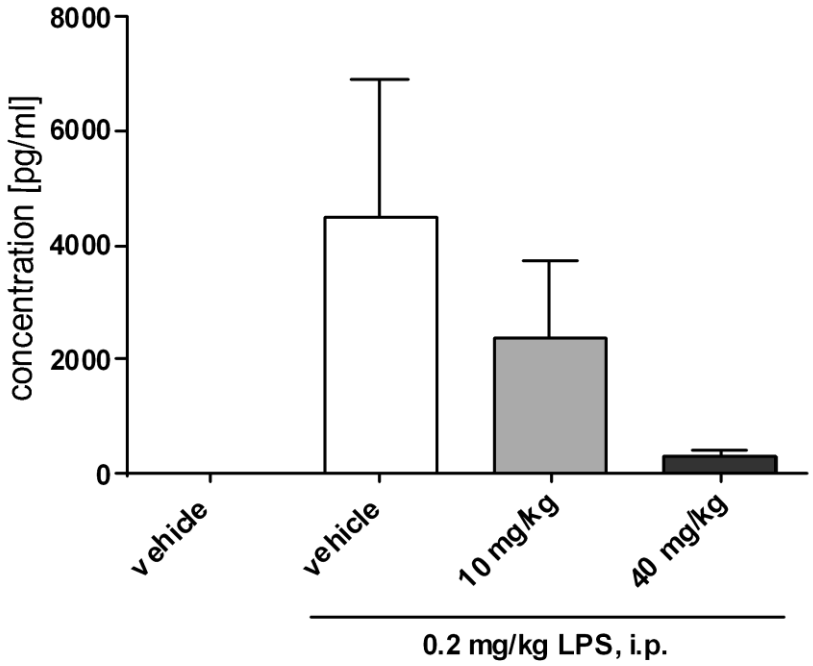
1 e-5M

Figure 3: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vehicle
vehicle
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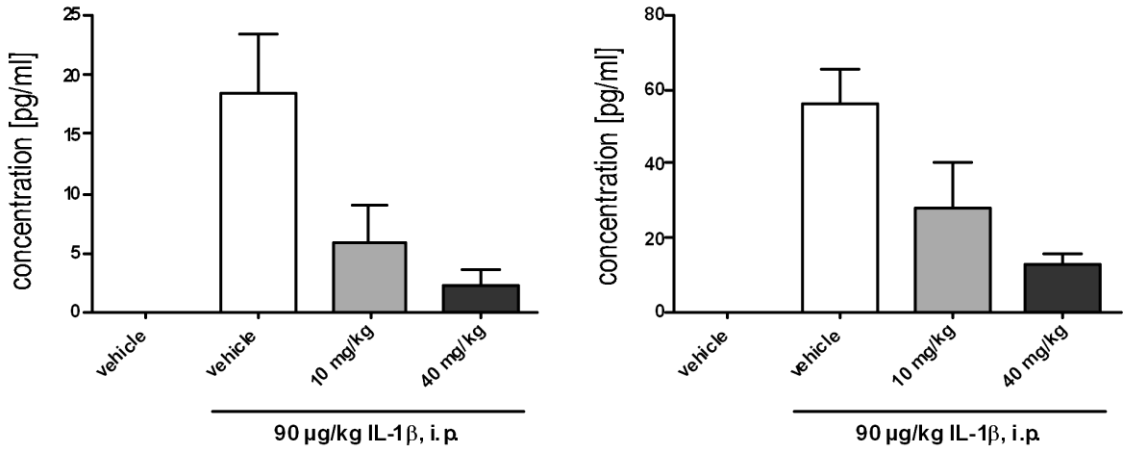
40 mg/kg
0.2 mg/kg LPS, i.p.

Figure 4: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20
15
10
5
0
vehicle
vehicle
10 mg/kg
40 mg/kg
90 µg/kg IL-1β, i.p.
concentration [pg/ml]
80
60
40
20
0
vehicle
vehicle
10 mg/kg
40 mg/kg
90 µg/kg IL-1β, i.p.

Figure 5:

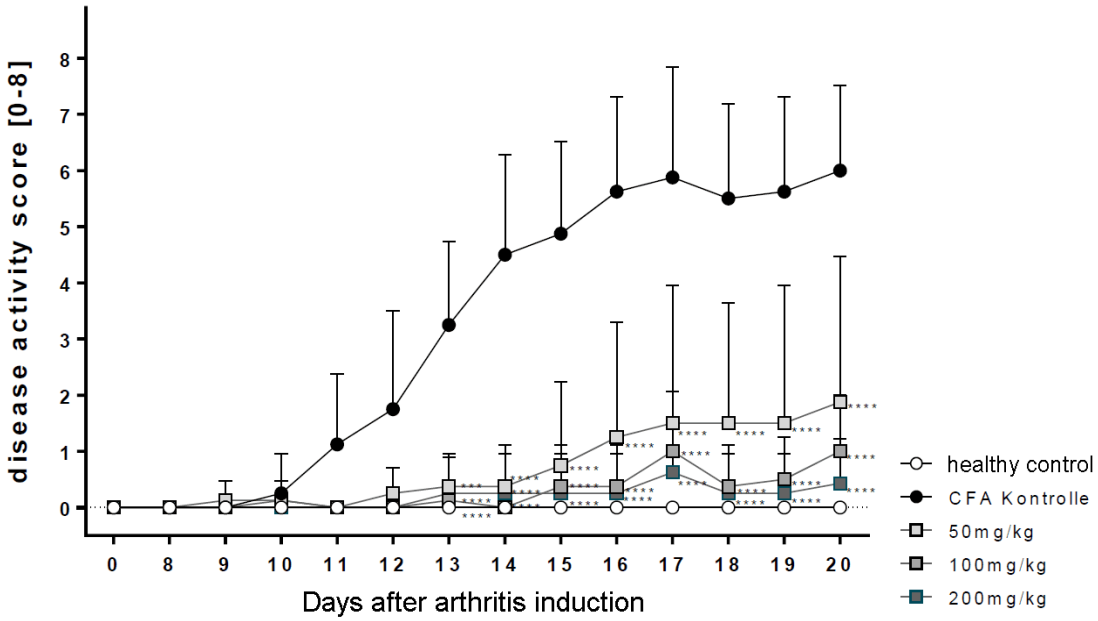
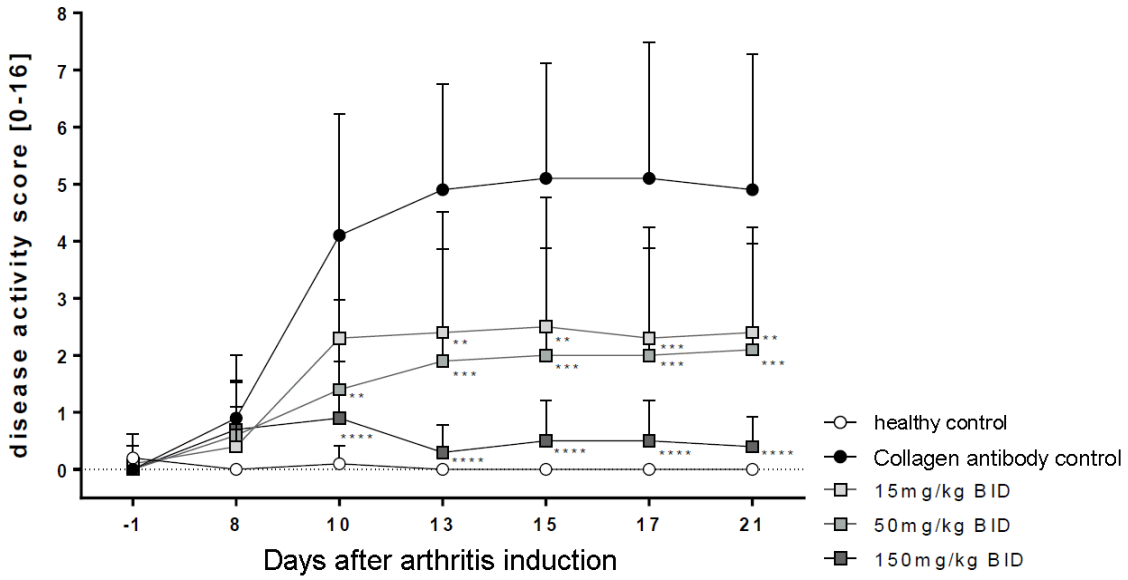

disease activity score [0-8]
0
1
2
3
4
5
6
7
8
0
8
9
10
11
12
13
14
15
16
17
18
19
20
Days after arthritis induction
healthy control
CFA Kontrolle
50mg/kg
100mg/kg
200mg/kg

Figure 6:



(11) **9187**
(97) EP2892923 / 25/03/2020
(96) 13792452.8 / 05/09/2013
(22) 05/06/2020
(21) AL/P/ 2020/368
(54) **MOLEKULAT LIDHËSE IL-18**
30/06/2020
(30) 201261697981 P 07/09/2012 US
(71) Novartis AG
Lichtstrasse 35, 4056 Basel, CH
(72) DIEFENBACH-STREIBER, Beate (Morphosys AgLena-Christ-Strasse 48, 82152 Planegg); EBERTH, Adina (Morphosys AgLena-Christ-Strasse 48, 82152 Planegg); BRANNETTI, Barbara (Novartis Pharma AGPostfach, CH-4002 Basel); BARDROFF, Michael Otto (Novartis Pharma AGPostfach, CH-4002 Basel); CAMPBELL, Emma Michelle (Novartis Pharmaceuticals UK LimitedWimblehurst Road, Horsham Sussex RH12 5AB); KUNZ, Christian Carsten Silvester (Morphosys AgLena-Christ-Strasse 48, 82152 Planegg); MARSHALL, Sylwia (Novartis Pharmaceuticals UK LimitedWimblehurst Road, Horsham Sussex RH12 5AB); RONDEAU, Jean-Michel Rene (Novartis Pharma AGPostfach, CH-4002 Basel); SCHLAEPPI, Jean-Marc Alfred (Novartis Pharma AGPostfach, CH-4002 Basel) ;VAN HEEKE, Gino Anselmus (Novartis Pharmaceuticals UK LimitedWimblehurst Road, Horsham Sussex RH12 5AB)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)

(57) **1.** Një njeri plotësisht i izoluar ose antitrup kimerik ose një fragment i tij që lidhet në mënyre specifike IL-18, por nuk lidh kompleksin e proteinës lidhëse IL-18/IL-18, ku antitrupi i izoluar ose fragmenti i tij përfshin një fushë variable të zinxhirit të rëndë që përfshin SEQ ID NO: 14 dhe një fushë variable të zinxhirit të lehtë që përfshin SEQ ID NO: 16.

2. Antitrupi i izoluar ose fragmenti i tij sipas pretendimit 1, ku antitrupi i izoluar ose fragmenti i tij është një antitrup njerëzor plotësisht i izoluar ose fragmenti i tij.

3. Antitrupi i izoluar ose fragmenti i tij sipas pretendimit 1, ku antitrupi i izoluar ose fragmenti i tij është një fragment antitrupi zgjedhur nga grupi i perbërë prej një Fab, një Fab', një F(ab')2, dhe një scFv.

4. Antitrupi i izoluar ose fragmenti i tij sipas pretendimit 1, ku antitrupi i izoluar ose fragmenti i tij përfshin një zinxhir të rëndë që përfshin SEQ ID NO: 43 dhe një zinxhir të lehtë që përfshin prej SEQ ID NO: 45.

5. Një polinukleotid i izoluar që kodon antitrupin e izoluar ose fragmentin e tij të çdo njërit prej pretendimeve 1 deri në 4.

6. Një polinukleotid i izoluar sipas pretendimit 5, që përfshin:
SEQ ID NO: 15 ose një sekuencë të paktën 90% identike me të; ose
SEQ ID NO: 17 ose një sekuencë të paktën 90% identike me të; ose
SEQ ID NO: 15 ose një sekuencë të paktën 90% identike me të, dhe SEQ ID NO: 17 ose një sekuencë të paktën 90% identike me të; ose
SEQ ID NO: 44 ose një sekuencë të paktën 90% identike me të; ose
SEQ ID NO: 46 ose një sekuencë të paktën 90% identike me të; ose
SEQ ID NO: 44 ose një sekuencë të paktën 90% identike me të, dhe SEQ ID NO: 46 ose një sekuencë të paktën 90% identike me të.

7. Një vektor shprehjeje ose klonimi që përfshin një ose më shumë polinukleotide sipas ndonjë prej pretendimit 5 ose 6.

8. Një qelizë pritëse që përfshin një ose më shumë vektorë shprehjeje ose klonimi sipas pretendimit 7.

9. Një qelizë pritëse e transfektuar ose e transformuar në mënyrë të qëndrueshme që përfshin një ose më shumë polinukleotide sipas ndonjë prej pretendimit 5 ose 6.

10. Një metodë për prodhimin e një njeriu plotesisht të izoluar, ose antitrupi kimerik ose fragmenti të tij që lidhet në mënyrë specifike IL-18, por nuk lidh kompleksin e proteinës lidhëse IL-18/IL-18, metodë e cila përfshin kultivimin e një qelize pritëse të pretendimit 8 nën kushtet e përshtatshme për prodhimin e antitrupit të izoluar ose fragmentit të tij.

11. Një kompozim farmaceutik që përfshin antitrupin e izoluar ose fragmentin e tij sipas çdo njërit prej pretendimeve 1 deri në 4 dhe një mbartës farmaceutik, ku kompozimi farmaceutik përfshin në mënyrë opsionale një përbërje terapeutike të dytë.

12. Kompozimi farmaceutik i pretendimit 11 i administrueshëm në formë intravenoze, inhalatore ose nën-lëkurë.

13. Antitrupi i izoluar ose fragmenti i tij sipas çdo njërit prej pretendimeve 1 deri në 4 ose kompozimi farmaceutik i pretendimit 11 ose 12 për përdorim në terapi.

14. Antitrupi i izoluar ose fragmenti i tij sipas çdo njërit prej pretendimeve 1 deri në 4 ose kompozimi farmaceutik i pretendimeve 11 ose 12 për përdorim në trajtimin dhe/ose parandalimin e sarkoidozëss, në veçanti sarkoidozës pulmonare, limfohistiocitoza hemofagocitike (HLH), limfohistiocitoza hemofagocitike familjare (FHL) dhe sindromave të tjera imunodeficente, Artriti i Qelizës Gjigande (GCA), sëmundja pulmonare obstruktive kronike (COPD), Sëmundja e Still e fillimit të të rriturve (AOSD), artriti idiopatik juvenil sistematik (SJIA), astma e rëndë, Uveiti, Atrofia Gjeografike, diabeti i tipit 1, diabeti i tipit 2 ose ateroskleroza dhe çdo kombinim i tyre në një pacient gjitar.

(11) **9188**
(97) EP3191081 / 25/03/2020
(96) 15762595.5 / 09/09/2015
(22) 12/06/2020
(21) AL/P/ 2020/387
(54) **FORMULIM QË PËRFSHIN GLIKOPIRROLATE, METODËN DHE APARATIN**
30/06/2020
(30) 14184164 09/09/2014 EP

(71) Vectura Limited
1 Prospect West, Chippenham, Wiltshire SN14 6FH, GB
(72) MANFORD, Fergus (c/o Vectura LimitedOne Prospect West, ChippenhamWiltshire SN14 6FH)
(74) Krenar LOLOÇI
Rr. Ibrahim Rugova, P.1/1, Kati II, Tiranë, Shqipëri (Albania)

(57) 1. Një metodë për përgatitjen e një formulimi pluhur të thatë, metodë që përfshin glikopirrolate të pamikronizuar me bluarje co-jet dhe stearate magnezi me gaz bluarës që ka një lagështirë nën 20% Lagështirë Relative për të prodhuar grimca të përbëra të mikronizuara, ku grimcat e përbëra të mikronizuara më pas i nënshtrohen një hapi kushtëzimi, i cili përfshin ekspozimin e grimcave të përbëra të mikronizuara në lagështirë në nivelin e 10%-95% Lagështirë Relative në temperaturë midis 5°C deri në 88°C për të paktën 60 minuta.

2. Metoda sipas pretendimit 1, ku kushtëzimi ka filluar brenda 30 minutave të përfundimit të bluarjes, brenda 25 minutave, brenda 20 minutave, brenda 15 minutave, në mënyrë të preferuar brenda 10 minutave, në mënyrë më të preferuar brenda 5 minutave, në mënyrën më të preferuar menjëherë pas përfundimit të bluarjes co-jet të glikopirrolate dhe stearate magnezi.

3. Metoda sipas pretendimeve 1 deri në 2, ku stearate magnezi është bluar co-jet në një sasi prej nga 1 deri në 25 % (w/w), në mënyrë më të preferuar nga 2 deri në 20 % (w/w), në mënyrë më të preferuar 3 deri në 15 % (w/w), në mënyrë më të preferuar 4 deri në 10 % (w/w) por në mënyrë më të preferuar nga 5 deri në 7.5 % (w/w) stearate magnezi sipas peshës së kombinimit të bluarjes co-jet së glikopirrolate dhe stearate magnezi.

4. Metoda sipas pretendimeve 1 deri në 3, ku metoda më tej përfshin nënshtrimin e grimcave të përbëra të mikronizuara në një atmosferë ventilimi që ka lagështirë relative në nivelin nga 10%-95% RH, në mënyrë të preferuar nga 30-90% RH, 45-90% RH ose 50-88% RH ose në mënyrë më të preferuar 60-87%, në mënyrë të preferuar ku atmosfera është ajër.

5. Metoda sipas pretendimit 4, ku atmosfera ventiluese kalon mbi dhe nëpërmjet një krevati pluhur që përfshin grimca të përbëra të mikronizuara në një raport prej më pak se 100 cm^3 /s, më pak se 10 cm^3 /s, më pak se 5 cm^3 /s, më pak se 2 cm^3 /s, më pak se 1 cm^3 /s, në mënyrë të preferuar më pak se 0.8 cm^3 /s, në mënyrë të preferuar më pak se 0.6 cm^3 /s, në mënyrë të preferuar më pak se 0.4 cm^3 /s, në mënyrë të preferuar më pak se 0.2 cm^3 /s, në mënyrë të preferuar më pak se 0.1 cm^3 /s, në mënyrë më të preferuar afërsisht 0.001 cm^3 /s.

6. Metoda sipas pretendimeve 1 deri në 5, ku hapi kushtëzues përfshin trazim të pluhurit, opsionalisht ku trazimi është trazim i përhershëm i pluhurit.

7. Metoda sipas pretendimit 6, ku trazimi i pluhurit kryhet brenda 30 minutave të përfundimit të bluarjes, brenda 25 minutave, brenda 20 minutave, brenda 15 minutave, në mënyrë të preferuar brenda 10 minutave, në mënyrë më të preferuar brenda 5 minutave, në mënyrën më të preferuar menjëherë pas përfundimit të bluarjes së glikopirrolate dhe stearate magnezi.

8. Metoda sipas çdonjë prej pretendimeve parardhëse, ku formulimi përfshin më tej një agonist beta-2 adrenoceptor, në mënyrë të preferuar ku agonisti beta-2 adrenoceptor është salbutamol, metaproterenol, terbutaline, salmeterol, fenoterol, prokaterol, në mënyrë të preferuar, formoterol, karmoterol dhe kripërat farmaceutikisht të pranueshme të tyre, në mënyrë më të preferuar ku agonisti beta-2 adrenoceptor është (R)-5-[2-(5,6-dietil-indan-2-ilamino)-1-hidroksi-etil]-8-hidroksi-1H-kuinolin-2-one maleate.

9. Metoda sipas çdonjë prej pretendimeve parardhëse, ku formulimi përfshin më tej indakaterol dhe mometasone, në mënyrë të preferuar indakaterol maleate dhe mometasone furoate.

10. Një metodë për përgatitjen e një formulimi pluhur të thatë, metoda që përfshin glikopirrolate të pamikronizuar me bluarje co-jet dhe stearate magnezi me gaz bluarës që ka një lagështirë nën 20% Lagështirë Relative për të prodhuar grimca të përbëra të mikronizuara, ku grimcat e përbëra të mikronizuara më pas i nënshtrohen një hapi kushtëzimi, i cili përfshin ekspozimin e grimcave të përbëra të mikronizuara në lagështirë në nivelin e 10%-95% Lagështirë Relative në temperaturë midis 5°C deri në 88°C për të paktën 10 minuta.

11. Metoda sipas pretendimeve 1 deri në 10, ku grimcat e përbëra të mikronizuara janë përzier me një transportues, në mënyrë të preferuar laktozë, në mënyrë më të preferuar laktozë anhidroze, në mënyrë më të preferuar alfa-laktozë monohidrate, opsionalisht pas hapit kushtëzues.

12. Metoda sipas pretendimit 11, ku grimcat e përbëra të mikronizuara janë prezente në një sasi prej më pak se 5%, më pak se 4%, më pak se 3%, në mënyrë të preferuar më pak se 2%, në mënyrë të preferuar më pak se 1%, në mënyrë të preferuar më pak se 0.75%, në mënyrë të preferuar më pak se 0.5% sipas peshës së formulimit.

13. Metoda sipas pretendimeve 1 deri në 12, ku hapi kushtëzues ndodh nga shpërndarja e grimcave të përbëra të mikronizuara mbi një sipërfaqe, opsionalisht ku hapi kushtëzues ndodh në një shtresë.

14. Metoda sipas pretendimeve 1 deri në 13, ku hapi kushtëzues përfshin ekspozimin e grimcave të përbëra të mikronizuara në lagështirë për kohë të mjaftueshme për glikopirrolate amorfe për të ri-kristalizuar pas bluarjes co-jet, siç përcaktohet nga thithja dinamike e avullit.

15. Metoda sipas pretendimeve 1 deri në 14, ku gazi bluarës ka një lagështirë në mënyrë të preferuar nën 15% Lagështirë Relative, në mënyrë të preferuar nën 10% Lagështirë Relative, në mënyrë të preferuar nën 5% Lagështirë Relative, në mënyrë më të preferuar nën 2.5% Lagështirë Relative.