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Thompson et al.

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(54) **SUBSTITUTED
TETRAHYDRO-1H-PYRAZOLO
[3,4-C]PYRIDINES COMPOSITIONS
COMPRISING THEM, AND USE**

(75) Inventors: **Fabienne Thompson**, Paris (FR);
Catherine Souaille, Choisy le Roi (FR);
Fabrice Viviani, Louvres (FR); **Michel
Tabart**, La Norville (FR); **Patrick
Mailliet**, Fontenay Sous Bois (FR);
Teresa Damiano, Paris (FR);
Marie-Pierre Cherrier, Ivy sur Seine
(FR); **Francois Clerc**, Antony (FR);
Frank Halley, Sevres (FR); **Herve
Bouchard**, Thiais (FR); **Laurence
Gauzy-Lazo**, Paris (FR); **Bernard
Baudoin**, Chaville (FR)

(73) Assignee: **Aventis Pharma S.A.**, Antony (FR)

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patent is extended or adjusted under 35
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(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**

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C07D 515/02 (2006.01)

(52) **U.S. Cl.** 546/119; 546/120

(58) **Field of Classification Search** 546/119,
546/120; 514/303
See application file for complete search history.

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

FR	2827861	1/2003
WO	02/12242	* 2/2002
WO	WO 02/12242	2/2002
WO	WO 03/024967	3/2003
WO	WO 2004/064778	8/2004

OTHER PUBLICATIONS

Hetian et al., The journal of biological chemistry, 2002, vol. 277, pp.
43137-43142.*

Dorte Krehan et al., Aza-THIP and Related Analogues of THIP as
GABAc Antagonists, Bioorganic & Medicinal Chemistry (2003, pp.
4891-4896, vol. 11).

Povl Krogsgaard-Larsen et al., GABA Agonists. Synthesis and struc-
ture-activity studies on analogues of isoguvacine and THIP, Eur. J.
Med. Chem.- (1979, pp. 157-167, vol. 14, No. 2).

* cited by examiner

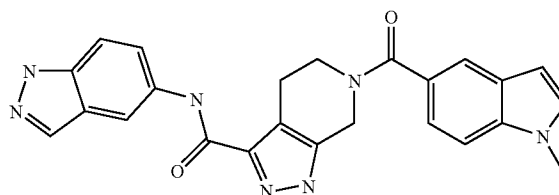
Primary Examiner—D. Margaret Seaman

Assistant Examiner—Nilooofar Rahmani

(74) *Attorney, Agent, or Firm*—Kelly L. Bender; Paul R.
Darkes

(57) **ABSTRACT**

Substituted tetrahydro-1H-pyrazolo[3,4-c]pyridines, compo-
sitions comprising them and use. The present invention
relates in particular to novel substituted tetrahydro-1H-pyra-
zolo[3,4-c]pyridines having therapeutic activity, which can
be used in particular in oncology.



11 Claims, No Drawings

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SUBSTITUTED
TETRAHYDRO-1H-PYRAZOLO
[3,4-C]PYRIDINES COMPOSITIONS
COMPRISING THEM, AND USE

CROSS REFERENCE TO RELATED
 APPLICATIONS

This application is a division of U.S. application Ser. No. 10/888,611, filed Jul. 09, 2004, now allowed, which is incorporated herein by reference in its entirety; and which claims the benefit of priority of French Patent Application No. 03/08,441, filed Jul. 10, 2003 and French Patent Application No. 03/08,442, filed Jul. 10, 2003.

The present invention relates to novel chemical compounds, particularly novel tetrahydro-1H-pyrazolo[3,4-c]pyridines, compositions comprising the, and to their use as medicinal products.

More particularly, the invention relates to novel tetrahydro-1H-pyrazolo-[3,4-c]pyridines exhibiting anticancer activity, and in particular kinase-inhibiting activity, especially Tie2-inhibiting activity.

Only a few tetrahydro-1H-pyrazolo[3,4-c]pyridines are known.

Thus, WO 02/012442 discloses tetrahydro-1H-pyrazolo[3,4-c]pyridines substituted in the 5-position with an optionally substituted amino group. These products are useful in the treatment of cancer and of other diseases related to cell proliferation.

P. Krogsgaard-Larsen et al. in Eur. J. Med. Chemical—Chim. Ther. (1979), 14(2), p. 157-164, discloses two tetrahydro-1H-pyrazolo[3,4-c]pyridines substituted in the 3-position with a hydroxyl group.

WO 96112720 claims tetrahydro-1H-pyrazolo[3,4-c]pyridines substituted in the 3-position with substituents chosen from H, alkyl, alkylene, cycloalkyl and methylenecycloalkyl, and in the 1- and 6-positions with varied substituents. These products are described as inhibitors (i) of phosphodiesterase type IV (PDE-IV), and (ii) of tumour necrosis factor (TNF), and are, as a result, considered to be useful in the treatment of inflammatory diseases. No example of a compound according to the invention is disclosed.

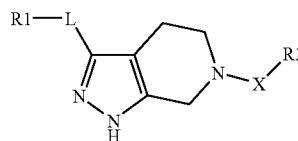
Attempts to obtain effective inhibitors of Tie2 have already been successful in the past (in this respect, see, for example, WO 98/02434; WO 98/41525; WO 99/10325; WO 99/17770; WO 99/54286; WO 99/21859; WO 99/55335; WO 00/17202; WO 00/17203; WO 00/27822; WO 00/75139; WO 01/37835; WO 01/57008; WO 01/72751; WO 02/060382; WO 02/076396; WO 02/076463; WO 02/076954; WO 02/076984; WO 02/076985; WO 02/080926; WO 03/004488).

However, none of those documents discloses 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine derivatives as defined below, exhibiting activity against kinases, in particular Tie2.

To this effect, the products in accordance with the invention, according to its first aspect, satisfy formula (I) below:

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(I)



and its tautomers, in which:

L is chosen from a bond, CH₂, CO, SO₂, CONH, COO, NHCO, NH, NHSO₂, SO₂NH, NHCONH, CH₂NH and NHCH₂,

X is chosen from a bond, CH₂, CO, SO₂, CONH and COO;

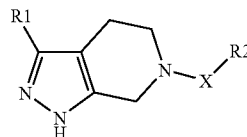
R1 is chosen from OH, H, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, which is optionally substituted, and, when X is a bond, then R1 may also be halogen;

R2 is H or is chosen from alkyl, alkylene, cycloalkyl, heterocyclyl, aryl, heteroaryl, which is optionally substituted;

the substituents being chosen independently from R3, O—R3, halogen, NO₂, SO₂—R3, CO—R3, SO₂NH—R3, CONH—R3, N—(R3)₂, NHCO—R3, NHSO₂—R3, NHCONH—R3, NHSO₂NH—R3, OCO—R3, COO—R3, OSO₂—R3, SO₂O—R3, OCONH—R3 and OSO₂NH—R3, where each R3 is chosen independently from H, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, heterocyclyl, which is optionally substituted with halogen, aryl, heteroaryl, R4, OR4 or N(R4)₂, each R4 being chosen independently from H, C₁-C₄ alkyl and halogenated C₁-C₄ alkyl.

Products in accordance with the invention, according to its first aspect, are more particularly chosen from products of formula (II) below:

(II)



and its tautomers, in which:

X is chosen from a bond, CH₂, CO, SO₂, CONH and COO;

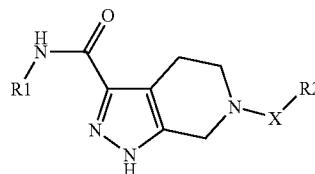
R1 is chosen from alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, which is optionally substituted;

R2 is H or is chosen from alkyl, alkylene, cycloalkyl, heterocyclyl, aryl, heteroaryl, which is optionally substituted;

the substituents being chosen independently from R3, O—R3, halogen, NO₂, to SO₂—R3, CO—R3, SO₂NH—R3, CONH—R3, N—(R3)₂, NHCO—R3, NHSO₂—R3, NHCONH—R3, NHSO₂NH—R3, OCO—R3, COO—R3, OSO₂—R3, SO₂O—R3, OCONH—R3 and OSO₂NH—R3, where each R3 is chosen independently from H, alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, heterocyclyl, which is optionally substituted with halogen, aryl, heteroaryl, R4, OR4 or N(R4)₂, where each R4 is chosen independently from H and C₁-C₄ alkyl.

Products in accordance with the invention, according to its first aspect, are more particularly chosen from products of formula (III) below:

(III)



and its tautomers, in which:

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X is chosen from a bond, CH₂, CO, SO₂, CONH and COO;
R1 is chosen from alkyl, cycloalkyl, heterocyclyl, aryl,
heteroaryl, which is optionally substituted;

R2 is H or is chosen from alkyl, alkylene, cycloalkyl,
heterocyclyl, aryl, heteroaryl, which is optionally substituted;

in which the substituents are chosen independently from
R3, O—R3, halogen, NO₂, SO₂—R3, CO—R3, SO₂NH—
R3, CONH—R3, N—(R3)₂, NHCO—R3, NHSO₂—R3,
NHCONH—R3, NHSO₂NH—R3, OCO—R3, COO—R3,
OSO₂—R3, SO₂O—R3, OCONH—R3 and OSO₂NH—R3,
in which each R3 is chosen independently from H, alkyl,
cycloalkyl, alkenyl, aryl, heteroaryl, heterocyclyl, which is
optionally substituted with halogen, aryl, heteroaryl, OR4 or
N(R4)₂, and in which each R4 is chosen independently from
H and C₁-C₄ alkyl.

A product in accordance with the invention is advanta-
geously chosen from the products according to its first aspect,
in which R1 is heteroaryl, which is optionally substituted, in
which a preferred heteroaryl is chosen from benzimidazolyl,
indolyl, pyrrolyl, optionally substituted with halogen, R4 or
O—R4.

More particularly, a preferred heteroaryl is chosen from
benzimidazol-2-yl, indol-2-yl, pyrrol-2-yl, optionally substi-
tuted with halogen, R4 or O—R4.

A product in accordance with the invention according to its
first aspect advantageously has a substituent R2 chosen from
phenyl, pyridyl, thienyl, C₁-C₄ alkyl, and C₃-C₇ cycloalkyl,
which is optionally substituted.

X may advantageously be chosen from CO and SO₂.

A product in accordance with the invention according to its
first aspect is advantageously chosen from the products of
formula (I) in which R1 is H.

A preferred product is advantageously chosen from the
products of formula (I) in which R1 is substituted aryl.

According to a first preferred embodiment, a preferred
product is advantageously chosen from the products of for-
mula (I) in which R1-L is R1-NH—CO, and more preferably
when R1 is H.

Very preferably, and according to a second preferred
embodiment, a preferred product is advantageously chosen
from (i) the products of formula (I), or (ii) preferably the
products according to the first preferred embodiment, in
which X is a bond, and in which R2 is chosen from substituted
aryl and substituted heteroaryl.

According to a third preferred embodiment, a more pre-
ferred product is chosen from the products in accordance with
the invention according to its second embodiment, in which
R2 is chosen from:

aryl substituted with NHSO₂—R3 or NHCONH—R3, and
heteroaryl substituted with NHSO₂—R3 or NHCONH—
R3.

Products according to the third preferred embodiment are
advantageously chosen from:

aryl substituted with NHSO₂—R3 or NHCONH—R3, and
heteroaryl substituted with NHSO₂—R3 or NHCONH—
R3,

in which aryl is phenyl and in which heteroaryl is chosen from
pyridyl and pyrimidyl.

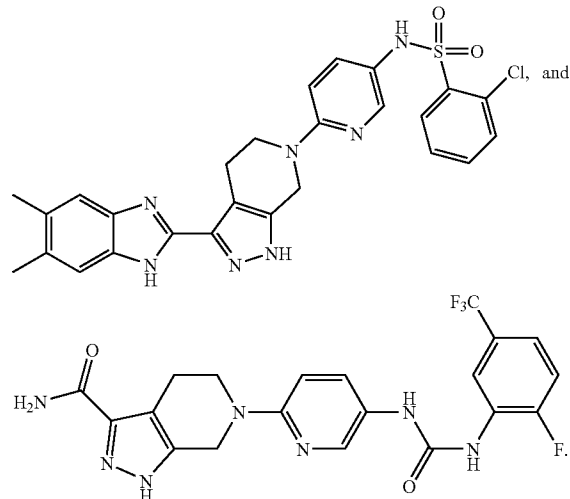
According to a fourth embodiment, products according to
the third preferred embodiment are advantageously chosen
from:

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aryl substituted with NHSO₂—R3 or NHCONH—R3, and
heteroaryl substituted with NHSO₂—R3 or NHCONH—
R3,

in which R3 is chosen from substituted aryl and substituted
heteroaryl, in which R3 is advantageously substituted with a
substituent selected from the group consisting of halogen, R4,
OR4 and N(R4)₂, in which each R4 is chosen independently
from H, C₁-C₄ alkyl and halogenated C₁-C₄ alkyl.

According to a fifth embodiment, products according to the
fourth preferred embodiment are advantageously chosen
from:



A product in accordance with the invention according to its
first aspect may be in:

- 1) racemic form, or
- 2) a form enriched in a stereoisomer, or
- 3) a form enriched in an enantiomer;

and may optionally be salified.

According to a second aspect, the invention relates to phar-
maceutical compositions comprising a product as defined
above, in combination with a pharmaceutically acceptable
excipient.

According to a third aspect, the invention relates to the use
of a product as defined above, as an agent for modulating the
activity of a kinase. A preferred kinase will advantageously be
chosen from Tie2 and KDR. Tie2 is more preferred.

According to its third aspect, the invention relates to the use
of a product as defined above, for producing a medicinal
product that is useful for treating a pathological condition, in
particular cancer.

Products in accordance with the invention can be obtained
by methods well known to those skilled in the art, in particular
as regards the techniques of coupling between an acid and an
amine; see, for example, J. March, Advanced organic chem-
istry, (J. Wiley & Sons, ed.), fourth edition, 1992.

The products of the invention are useful as agents which
inhibit a reaction catalysed by a kinase. Tie2 is a kinase for
which the products of the invention will be particularly useful
as inhibitors. These products can also be used as inhibitors of
other kinases, such as KDR.

Reasons for which the kinases are chosen are given below:
Tie2

Tie-2 (TEK) is a member of a family of tyrosine kinase receptors specific for endothelial cells. Tie2 is the first receptor with tyrosine kinase activity for which both the agonist (angiopoietin 1 or Ang1), which stimulates autophosphorylation of the receptor and cell signalling [S. Davis et al (1996) *Cell* 87, 1161-1169] and the antagonist (angiopoietin 2 or Ang2) [P. C. Maisonpierre et al. (1997) *Science* 277, 55-60] are known. Angiopoietin 1 can synergize with VEGF in the final stages of neoangiogenesis [Asahara T. *Circ. Res.* (1998) 233-240]. Knockout experiments and transgenic manipulations of the expression of Tie2 or of Ang1 result in animals which exhibit vascularization defects [D. J. Dumont et al (1994) *Genes Dev.* 8, 1897-1909 and C. Suri (1996) *Cell* 87, 1171-1180]. The binding of Ang1 to its receptor results in autophosphorylation of the kinase domain of Tie2, which is essential for neovascularization and for the recruitment and the interaction of the vessels with pericytes and smooth muscle cells; these phenomena contribute to the maturing and the stability of the newly formed vessels [P. C. Maisonpierre et al (1997) *Science* 277, 55-60]. Lin et al (1997), *J. Clin. Invest.* 100, 8: 2072-2078 and Lin P. (1998) *PNAS* 95, 8829-8834, have shown inhibition of tumour growth and vascularization and a decrease in lung metastases during adenoviral infections or during injections of the Tie-2 (Tek) extracellular domain in breast tumour and melanoma xenograph models.

Tie2 inhibitors can be used in situations where neovascularization takes place inappropriately (i.e. in diabetic retinopathy, chronic inflammation, psoriasis, Kaposi's sarcoma, chronic neovascularization due to macular degeneration, rheumatoid arthritis, infantile haemangioma and cancers).

KDR

KDR (Kinase insert Domain Receptor), also known as VEGF-R2 (Vascular Endothelial Growth Factor Receptor 2), is expressed only in endothelial cells. This receptor binds to the angiogenic growth factor VEGF and thus acts as a mediator to a transduction signal via the activation of its intracellular kinase domain. Direct inhibition of kinase activity of VEGF-R2 makes it possible to reduce the phenomenon of angiogenesis in the presence of exogenous VEGF (Vascular Endothelial Growth Factor) (Strawn et al., *Cancer Research*, 1996, vol. 56, p. 3540-3545). This process has been demonstrated in particular using VEGF-R2 mutants (Millauer et al., *Cancer Research*, 1996, vol. 56, p. 1615-1620). The VEGF-R2 receptor does not appear to have any function in adults other than that related to the angiogenic activity of VEGF. Consequently, a selective inhibitor of the kinase activity of VEGF-R2 should only show slight toxicity.

In addition to this central role in the dynamic angiogenic process, recent results suggest that VEGF expression contributes to the survival of tumour cells after chemotherapy and radiotherapy, emphasizing the potential synergy of KDR inhibitors with other agents (Lee et al. *Cancer Research*, 2000, vol. 60, p. 5565-5570).

EXPERIMENTAL SECTION

Method A: Analysis by LC/MS

The LC/MS analyses were carried out on a Micromass model LCT device connected to an HP 1100 device. The abundance of the products was measured using an HP G1315A diode array detector over a wavelength of 200-600 nm and a Sedex 65 light scattering detector. The mass spectra were acquired over a range of from 180 to 800. The data were analysed using the Micromass MassLynx software. Separation was carried out on a Hypersil BDS C18, 3 µm (50×4.6 mm) column, eluting with a linear gradient of from 5 to 90% of acetonitrile comprising 0.05% (v/v) of trifluoroacetic acid (TFA) in water comprising 0.05% (v/v) TFA, over 3.5 min at a flow rate of 1 ml/min. The total analysis time, including the period for re-equilibrating the column, is 7 min.

Method B: Purification by LC/MS:

The products were purified by LC/MS using a Waters FractionLynx system composed of a Waters model 600 gradient pump, a Waters model 515 regeneration pump, a Waters Reagent Manager dilution pump, a Waters model 2700 auto-injector, two Rheodyne model LabPro valves, a Waters model 996 diode array detector, a Waters model ZMD mass spectrometer and a Gilson model 204 fraction collector. The system was controlled by the Waters FractionLynx software. Separation was carried out alternately on two Waters Symmetry columns (C₁₈, 5 µm, 19×50 mm, catalogue reference 186000210), one column undergoing regeneration with a 95/5 (v/v) water/acetonitrile mixture comprising 0.07% (v/v) of trifluoroacetic acid, while the other column was being used for separation. The columns were eluted using a linear gradient of from 5 to 95% of acetonitrile comprising 0.07% (v/v) of trifluoroacetic acid in water comprising 0.07% (v/v) of trifluoroacetic acid, at a flow rate of 10 ml/min. At the outlet of the separation column, one-thousandth of the effluent is separated by means of an LC Packing Accurate, diluted with methyl alcohol at a flow rate of 0.5 ml/min and sent to the detectors, in a proportion of 75% to the diode array detector and the remaining 25% to the mass spectrometer. The rest of the effluent (999/1000) is sent to the fraction collector, where the flow is discarded for as long as the mass of the expected product is not detected by the FractionLynx software. The molecular formulae of the expected products are supplied to the FractionLynx software, which actuates the collection of the product when the mass signal detected corresponds to the ion [M+H]⁺ and/or to [M+Na]⁺. In certain cases, depending on the results of the analytical LC/MS, when an intense ion corresponding to [M+2H]⁺⁺ was detected, the value corresponding to half the calculated molecular mass (MW/2) is also supplied to the FractionLynx software. Under these conditions, the collection is also actuated when the mass signal of the ion [M+2H]⁺⁺ and/or [M+Na+H]⁺⁺ are detected.

Method C: EI Analysis

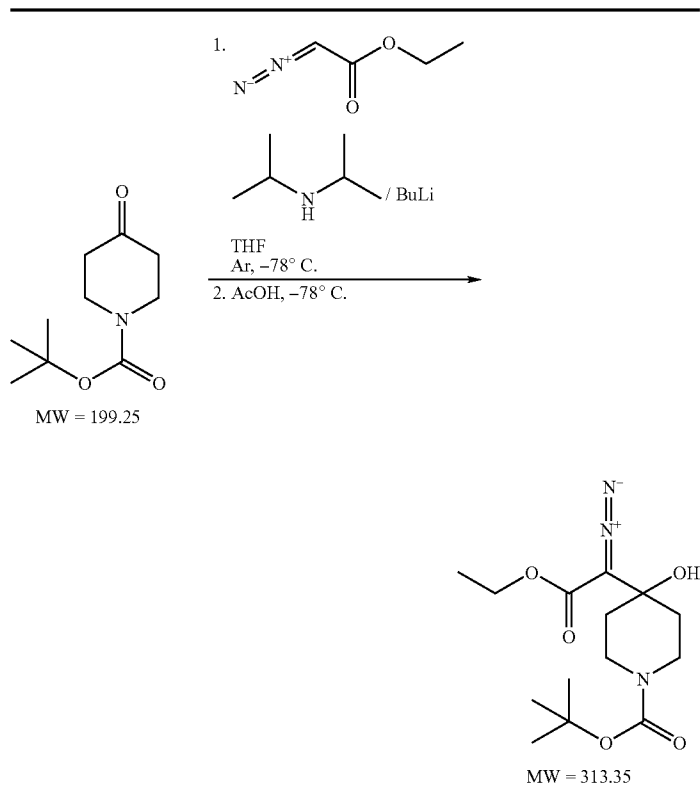
The mass spectra were produced by electron impact (70 eV) on a Finnigan SSQ 7000 spectrometer.

Method D: NMR Analysis

The NMR spectra were produced on a Bruker Avance 300 spectrometer and a Bruker Avance DRX 400 spectrometer.

tert-Butyl 4-(diazoethoxycarbonylmethyl)-4-hydroxypiperidine-1-carboxylate

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CAS	Name	d	MM	eq	mmol	g	ml
1 79099-07-3	N-Boc-piperidinone		199.25	1.00	50.19	10.00	
2 623-73-4	Ethyl diazoacetate	1.085	114.1	1.05	52.70	6.01	5.54
3 109-72-8	1.6 M BuLi hexane			1.60	80.30		50.19
4 108-18-9	Diisopropylamine	0.720	101.19	1.60	80.30	8.13	11.29
109-99-9	THF on 4 molecular sieve			10			500
6 64-19-7	100% AcOH	1.050	60.05	5.00	250.94	15.07	14.35

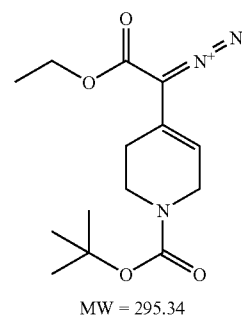
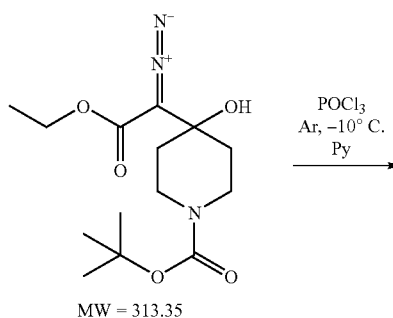
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A freshly prepared solution of LDA (prepared by the dropwise addition, under an inert atmosphere at -78°C ., of 50.19 ml of 1.6 M of BuLi in hexane to a solution of 11.29 ml of diisopropylamine in 200 ml of dry THF) is added dropwise, under an inert atmosphere at -78°C ., onto 10.0 g of N-Boc-piperidinone in suspension and 5.54 ml of ethyl diazoacetate in 300 ml of dry THF. The mixture is stirred at -78°C . for 4 hours and is then decomposed at -78°C . with 14.35 ml of concentrated AcOH. The mixture obtained is left at ambient temperature overnight, and the solvent is then evaporated off

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under reduced pressure, to $\frac{1}{10}$ of its initial volume, diluted in diisopropyl ether, and washed 4 times with a saturated NaHCO_3 solution. The organic phase is dried over MgSO_4 . The hydrated salt is removed by filtration and the dry filtrate is concentrated under reduced pressure so as to give 15.12 g of a viscous yellow oil. LC/MS: RT=2.84; $[\text{M}+1]^+=304.33$. The product is used as it is for the subsequent step.

tert-Butyl 4-(diazoethoxycarbonylmethyl)-3,6-dihydro-2H-pyridine-1-carboxylate

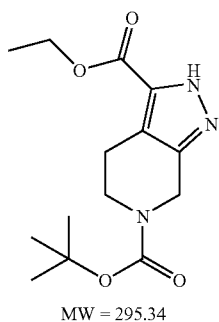
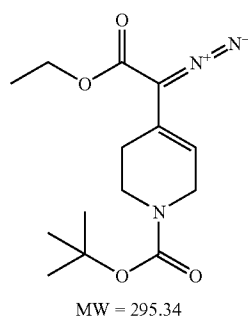


CAS	Name	d	MM	eq	mmol	g	ml
1	P-31391-106-4		313.35	1	48.25	15.12	
2	10025-87-3 POCl_3	1.67	153.33	2	96.51	14.80	8.86
3	110-86-1 Pyridine (4 Å m.s.)	0.983	79.1	20	965.06	76.34	77.66
4	108-20-3 iPr_2O			5vol			250
5	1310-73-2 0.1 M NaOH		40	1	48.25		483

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78.0 ml of dry pyridine are added to a solution of 15.12 g of tert-butyl 4-(diazoethoxycarbonylmethyl)-4-hydroxypiperidine-1-carboxylate into 250 ml of iPr₂O. The mixture is cooled to -10° C. and 8.86 ml of POCl₃ are added slowly with vigorous stirring. The mixture is then left to return to ambient temperature for 12 hours with stirring. The reaction mixture is decomposed with 500 ml of a 0.1 M NaOH solution, and is then extracted 3 times with EtOAc. The organic phase is washed with a saturated NaCl solution and dried over MgSO₄. The hydrated salt is removed by filtration and the dry filtrate is concentrated under reduced pressure to 1/10 of its initial volume. LC/MS: RT=4.57; [M+1]⁺=296.31 The product is used as it is for the subsequent step.

6-tert-Butyl 3-ethyl 2,4,5,7-tetrahydropyrazolo[3,4-c]pyridyl-3,6-dicarboxylate



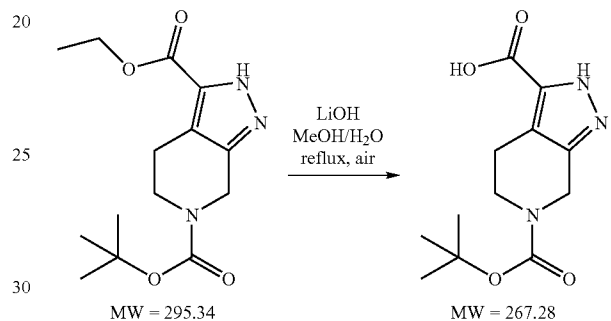
CAS	Name	d	MM	eq	mmol	mg	ml
1	P-31391-120-4		285.35	1.0	48.25		
2	108-83-3 PhMe						150

The solution of tert-butyl 4-(diazoethoxycarbonylmethyl)-3,6-dihydro-2H-pyridyl-1-carboxylate in Py/EtOAc obtained in the preceding step is added dropwise to 150 ml of

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toluene reflux. The azeotrope Py/PhMe is distilled at a rate equivalent to the rate of addition. One hour after the end of addition, the solution is left to cool to ambient temperature, the solvent is evaporated off under reduced pressure and the crude product obtained (15.05 g) is purified by flash chromatography (SiO₂, CH₂Cl₂/MeOH 1% NH₃ 7M_(MeOH) 40:1 then 30:1 then 20:1). The solvent is evaporated off and 10.05 g (71% over 3 steps) of a black solid are obtained: LC/MS: RT=3.88; [M+1]⁺=296.27.

(tert-Butyl 2,4,5,7-tetrahydropyrazolo[3,4-c]pyridyl-6-carboxylate)-3-carboxylic acid



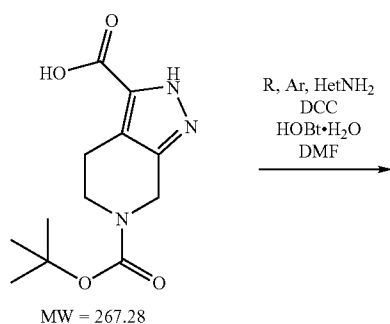
CAS	Name	d	MM	eq	mmol	g	ml
1	P-31391-123-1		295.34	1.0	34.03	10.05	
2	1310-66- LiOH.H ₂ O		41.96	1.1	37.43	1.57	
3	67-56-1 MeOH				10		375
4	7732-18- H ₂ O				1 vol		38

1.57 g of LiOH and 38 ml of water are added to a solution of 10.05 g of 6-tert-butyl 3-ethyl 2,4,5,7-tetrahydropyrazolo[3,4-c]pyridyl-3,6-dicarboxylate in 375 ml of MeOH. The mixture obtained is refluxed overnight. The solution is cooled to ambient temperature and is then acidified to pH=2 with 50 ml of a 1M HCl solution. The solution is then extracted 4 times with EtOAc. The organic phase is washed with a saturated NaCl solution and then dried over Na₂SO₄. The salt obtained is removed by filtration and the solvent is evaporated off under reduced pressure so as to produce 8.90 g (98%) of a white solid. LC/MS: RT=3.21; [M+1]⁺=268.23.

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Preparation of a Library of Products:

tert-Butyl 3-(alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, etc.)-2,4,5,7-tetrahydropyrazolo [3,4-c]pyridine-6-carboxylate



CAS	Name	d	MM	eq	mmol	g	ml
1	P-31391-031-5		267.28	1.0	3.741	1.00	
	amine			2.0	6.744		
2	538-75-0		206.33	1.0	3.741	0.772	
3	2592-95-2		153.13	1.5	5.612	0.859	
4	68-12-2			5 vol.			19

General Method:

DCC and HOBT·H₂O in solution in DMF with 2 eq of amine (R, Ar, or Het)-NH₂ are added to a solution of 1 eq of tert-butyl (2,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridyl-6-carboxylate)-3-carboxylic acid in DMF and the mixture is stirred at ambient temperature for 3 h. The solvent is evaporated off under reduced pressure at 35° C. overnight. The crude product obtained is purified by flash chromatography (SiO₂, CH₂Cl₂/MeOH 1% NH₃ 7M_(MeOH) 20:1 then 10:1 then 5:1, according to the products).

List of amines R1-NH₂ used (Table 1) [Comment: R1-NH₂=(R, Ar, or Het)-NH₂]:

TABLE 1

Reference number of the amine	Structure
1	
2	

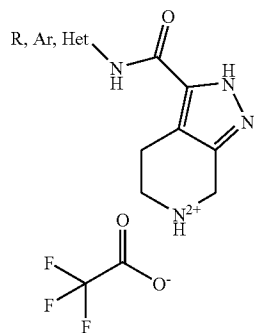
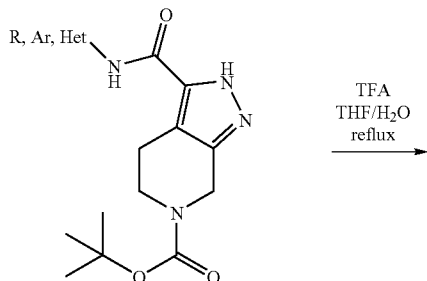
14

TABLE 1-continued

Reference number of the amine	Structure
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	

15

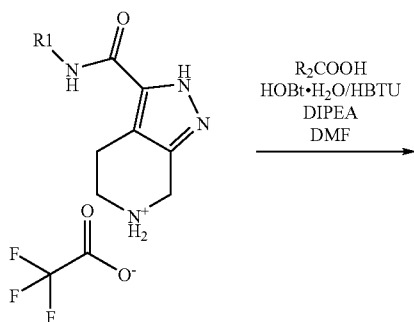
3-(Alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, etc.)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridin-6-ium trifluoroacetate



General Method:

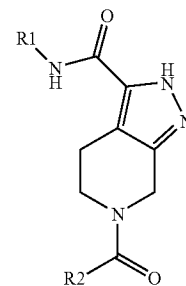
16 eq of TFA are added to 1 eq of tert-butyl 3-(alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, etc.)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridine-6-carboxylate in a 1:1 THF/water solution, and the solution is refluxed for 2 h. The solvent is evaporated off under reduced pressure and the viscous oil collected is dried under vacuum overnight. The product thus obtained is used without purification in the subsequent step.

6-(Alkyl, aryl, heteroaryl, etc.)carbonyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-(alkyl, aryl, hetyl, etc.)amide



16

-continued



General Method:

A solution of 2.5M HOBt·H₂O (2 eq) in DMF, a solution of 0.833M HBTU in DMF (2 eq), a solution of 2.5M DIPEA (4 eq) in DMF and a suspension or a solution at an appropriate concentration of an R₂COOH (2 eq) in DMF are added, in order, to a solution of 1 eq of 3-(alkylcarbamoyl, arylcarbamoyl, heteroarylcarbamoyl, etc.)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridin-6-ium trifluoroacetate in DMF. The solutions are stirred overnight at ambient temperature and are then acidified with 100 μl of 100% AcOH, filtered and purified by preparative LC/MS.

List of the acids R₂COOH used (Table 2):

TABLE 2

Reference number of the acid	Nomenclature
1	1-Phenyl-1-cyclopropylcarboxylic acid
2	Acetic acid
3	Propionic acid
4	Crotonic acid
5	Vinylacetic acid
6	Pyruvic acid
7	Sarcosine
8	Methoxyacetic acid
9	Lactic acid
10	3,3-Dimethylacrylic acid
11	Cyclopropylacetic acid
12	Valeric acid
13	N,N-dimethylglycine
14	3-Mercaptopropionic acid
15	(Methylthio)acetic acid
16	Pyrrole-2-carboxylic acid
17	1-Cyanocyclopropanecarboxylic acid
18	2-Furoic acid
19	4-Pyrazolecarboxylic acid
20	Imidazole-4-carboxylic acid
21	1-Cyclopentenecarboxylic acid
22	Acid
23	Acetoxyacetic acid
24	Hydantoic acid
25	Benzoic acid
26	Nicotinic acid
27	2-Pyrazinecarboxylic acid
28	o-Toluic acid
29	Phenylacetic acid
30	Salicylic acid
31	2-Fluorobenzoic acid
32	3-Cyanobenzoic acid
33	4-Vinylbenzoic acid
34	2-Phenylpropionic acid
35	N-Methylantranilic acid
36	2-Methoxybenzoic acid
37	2-Hydroxyphenylacetic acid

17

TABLE 2-continued

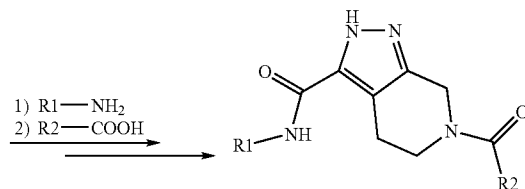
Reference number of the acid	Nomenclature
38	4-Hydroxymethylbenzoic acid
39	2-Fluorophenylbenzoic acid
40	2,6-Difluorobenzoic acid
41	Indole-3-carboxylic acid
42	3,5-Dimethylphenylacetic acid
43	3-(Dimethylamino)benzoic acid
44	Piperonylic acid
45	DL-tropic acid
46	3-Methoxyphenylacetic acid
47	3-Methoxysalicylic acid
48	4-(Methylthio)benzoic acid
49	2-Chlorophenylacetic acid
50	2-Naphthoic acid
51	2-Chloro-6-fluorobenzoic acid
52	1-Methylindole-3-carboxylic acid
53	3-Acetamidobenzoic acid
54	4-(Dimethylamino)salicylic acid
55	2,3-Dimethoxybenzoic acid
56	4-Chlorophenylpropionic acid
57	2-Chloromandelic acid
58	2-Chloro-6-fluorophenylacetic acid
59	1-Phenyl-1-cyclopentanecarboxylic acid
60	2,6-Dichlorobenzoic acid
61	3-Methyl-2-phenylvaleric acid
62	4-Phenylbenzoic acid
63	2-Chloro-4-nitrobenzoic acid
64	2-Benzylbenzoic acid
65	2-Phenoxybenzoic acid
66	2-Ethoxy-1-naphthoic acid
67	4-(4-N-Propylphenyl)benzoic acid
68	3,5-Dibromosalicylic acid
69	2,6-Dichlorophenylacetic acid
70	Cyanoacetic acid

18

Results

The following products are prepared according to the process described above.

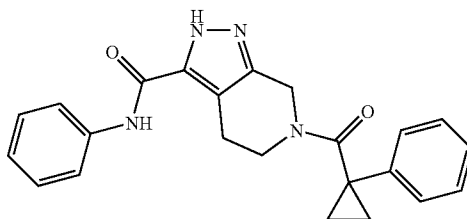
Scheme A



In order to simplify the representation of the products in Table 3 which follows, the pyrazolopiperidine ring presented in Scheme A is symbolized by the letter H, the amines R1-NH₂ which are linked to H are symbolized by the letter B followed by a number ranging from 1 to 15, corresponding to the products listed in Table 1, and the acids R2-COOH which are linked to H are symbolized by the letter A followed by a number from 1 to 70, corresponding to the products listed in Table 2.

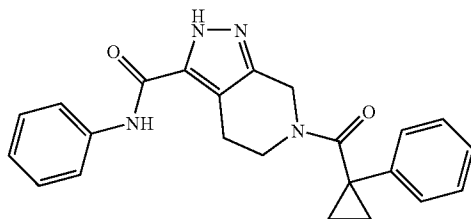
Thus, a product referred to as A1-H—B1 corresponds to the following structure:

TABLE 3



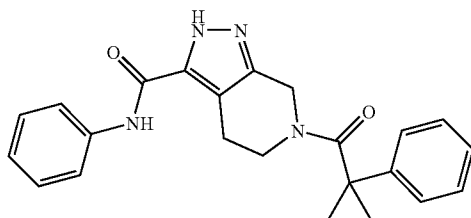
A1-H-B1	A2-H-B1	A3-H-B1	A4-H-B1	A5-H-B1	A6-H-B1	A7-H-B1
A1-H-B2	A2-H-B2	A3-H-B2	A4-H-B2	A5-H-B2	A6-H-B2	A7-H-B2
A1-H-B3	A2-H-B3	A3-H-B3	A4-H-B3	A5-H-B3	A6-H-B3	A7-H-B3
A1-H-B4	A2-H-B4	A3-H-B4	A4-H-B4	A5-H-B4	A6-H-B4	A7-H-B4
A1-H-B5	A2-H-B5	A3-H-B5	A4-H-B5	A5-H-B5	A6-H-B5	A7-H-B5
A1-H-B6	A2-H-B6	A3-H-B6	A4-H-B6	A5-H-B6	A6-H-B6	A7-H-B6
A1-H-B7	A2-H-B7	A3-H-B7	A4-H-B7	A5-H-B7	A6-H-B7	A7-H-B7
A1-H-B8	A2-H-B8	A3-H-B8	A4-H-B8	A5-H-B8	A6-H-B8	A7-H-B8
A1-H-B9	A2-H-B9	A3-H-B9	A4-H-B9	A5-H-B9	A6-H-B9	A7-H-B9
A1-H-B10	A2-H-B10	A3-H-B10	A4-H-B10	A5-H-B10	A6-H-B10	A7-H-B10
A1-H-B11	A2-H-B11	A3-H-B11	A4-H-B11	A5-H-B11	A6-H-B11	A7-H-B11
A1-H-B12	A2-H-B12	A3-H-B12	A4-H-B12	A5-H-B12	A6-H-B12	A7-H-B12
A1-H-B13	A2-H-B13	A3-H-B13	A4-H-B13	A5-H-B13	A6-H-B13	A7-H-B13
A1-H-B14	A2-H-B14	A3-H-B14	A4-H-B14	A5-H-B14	A6-H-B14	A7-H-B14
A1-H-B15	A2-H-B15	A3-H-B15	A4-H-B15	A5-H-B15	A6-H-B15	A7-H-B15
A8-H-B1	A9-H-B1	A10-H-B1	A11-H-B1	A12-H-B1	A13-H-B1	A14-H-B1
A8-H-B2	A9-H-B2	A10-H-B2	A11-H-B2	A12-H-B2	A13-H-B2	A14-H-B2
A8-H-B3	A9-H-B3	A10-H-B3	A11-H-B3	A12-H-B3	A13-H-B3	A14-H-B3
A8-H-B4	A9-H-B4	A10-H-B4	A11-H-B4	A12-H-B4	A13-H-B4	A14-H-B4
A8-H-B5	A9-H-B5	A10-H-B5	A11-H-B5	A12-H-B5	A13-H-B5	A14-H-B5
A8-H-B6	A9-H-B6	A10-H-B6	A11-H-B6	A12-H-B6	A13-H-B6	A14-H-B6
A8-H-B7	A9-H-B7	A10-H-B7	A11-H-B7	A12-H-B7	A13-H-B7	A14-H-B7
A8-H-B8	A9-H-B8	A10-H-B8	A11-H-B8	A12-H-B8	A13-H-B8	A14-H-B8
A8-H-B9	A9-H-B9	A10-H-B9	A11-H-B9	A12-H-B9	A13-H-B9	A14-H-B9
A8-H-B10	A9-H-B10	A10-H-B10	A11-H-B10	A12-H-B10	A13-H-B10	A14-H-B10

TABLE 3-continued



A8-H-B11	A9-H-B11	A10-H-B11	A11-H-B11	A12-H-B11	A13-H-B11	A14-H-B11
A8-H-B12	A9-H-B12	A10-H-B12	A11-H-B12	A12-H-B12	A13-H-B12	A14-H-B12
A8-H-B13	A9-H-B13	A10-H-B13	A11-H-B13	A12-H-B13	A13-H-B13	A14-H-B13
A8-H-B14	A9-H-B14	A10-H-B14	A11-H-B14	A12-H-B14	A13-H-B14	A14-H-B14
A8-H-B15	A9-H-B15	A10-H-B15	A11-H-B15	A12-H-B15	A13-H-B15	A14-H-B15
A15-H-B1	A16-H-B1	A17-H-B1	A18-H-B1	A19-H-B1	A20-H-B1	A21-H-B1
A15-H-B2	A16-H-B2	A17-H-B2	A18-H-B2	A19-H-B2	A20-H-B2	A21-H-B2
A15-H-B3	A16-H-B3	A17-H-B3	A18-H-B3	A19-H-B3	A20-H-B3	A21-H-B3
A15-H-B4	A16-H-B4	A17-H-B4	A18-H-B4	A19-H-B4	A20-H-B4	A21-H-B4
A15-H-B5	A16-H-B5	A17-H-B5	A18-H-B5	A19-H-B5	A20-H-B5	A21-H-B5
A15-H-B6	A16-H-B6	A17-H-B6	A18-H-B6	A19-H-B6	A20-H-B6	A21-H-B6
A15-H-B7	A16-H-B7	A17-H-B7	A18-H-B7	A19-H-B7	A20-H-B7	A21-H-B7
A15-H-B8	A16-H-B8	A17-H-B8	A18-H-B8	A19-H-B8	A20-H-B8	A21-H-B8
A15-H-B9	A16-H-B9	A17-H-B9	A18-H-B9	A19-H-B9	A20-H-B9	A21-H-B9
A15-H-B10	A16-H-B10	A17-H-B10	A18-H-B10	A19-H-B10	A20-H-B10	A21-H-B10
A15-H-B11	A16-H-B11	A17-H-B11	A18-H-B11	A19-H-B11	A20-H-B11	A21-H-B11
A15-H-B12	A16-H-B12	A17-H-B12	A18-H-B12	A19-H-B12	A20-H-B12	A21-H-B12
A15-H-B13	A16-H-B13	A17-H-B13	A18-H-B13	A19-H-B13	A20-H-B13	A21-H-B13
A15-H-B14	A16-H-B14	A17-H-B14	A18-H-B14	A19-H-B14	A20-H-B14	A21-H-B14
A15-H-B15	A16-H-B15	A17-H-B15	A18-H-B15	A19-H-B15	A20-H-B15	A21-H-B15
A22-H-B1	A23-H-B1	A24-H-B1	A25-H-B1	A26-H-B1	A27-H-B1	A28-H-B1
A22-H-B2	A23-H-B2	A24-H-B2	A25-H-B2	A26-H-B2	A27-H-B2	A28-H-B2
A22-H-B3	A23-H-B3	A24-H-B3	A25-H-B3	A26-H-B3	A27-H-B3	A28-H-B3
A22-H-B4	A23-H-B4	A24-H-B4	A25-H-B4	A26-H-B4	A27-H-B4	A28-H-B4
A22-H-B5	A23-H-B5	A24-H-B5	A25-H-B5	A26-H-B5	A27-H-B5	A28-H-B5
A22-H-B6	A23-H-B6	A24-H-B6	A25-H-B6	A26-H-B6	A27-H-B6	A28-H-B6
A22-H-B7	A23-H-B7	A24-H-B7	A25-H-B7	A26-H-B7	A27-H-B7	A28-H-B7
A22-H-B8	A23-H-B8	A24-H-B8	A25-H-B8	A26-H-B8	A27-H-B8	A28-H-B8
A22-H-B9	A23-H-B9	A24-H-B9	A25-H-B9	A26-H-B9	A27-H-B9	A28-H-B9
A22-H-B10	A23-H-B10	A24-H-B10	A25-H-B10	A26-H-B10	A27-H-B10	A28-H-B10
A22-H-B11	A23-H-B11	A24-H-B11	A25-H-B11	A26-H-B11	A27-H-B11	A28-H-B11
A22-H-B12	A23-H-B12	A24-H-B12	A25-H-B12	A26-H-B12	A27-H-B12	A28-H-B12
A22-H-B13	A23-H-B13	A24-H-B13	A25-H-B13	A26-H-B13	A27-H-B13	A28-H-B13
A22-H-B14	A23-H-B14	A24-H-B14	A25-H-B14	A26-H-B14	A27-H-B14	A28-H-B14
A22-H-B15	A23-H-B15	A24-H-B15	A25-H-B15	A26-H-B15	A27-H-B15	A28-H-B15
A29-H-B1	A30-H-B1	A31-H-B1	A32-H-B1	A33-H-B1	A34-H-B1	A35-H-B1
A29-H-B2	A30-H-B2	A31-H-B2	A32-H-B2	A33-H-B2	A34-H-B2	A35-H-B2
A29-H-B3	A30-H-B3	A31-H-B3	A32-H-B3	A33-H-B3	A34-H-B3	A35-H-B3
A29-H-B4	A30-H-B4	A31-H-B4	A32-H-B4	A33-H-B4	A34-H-B4	A35-H-B4
A29-H-B5	A30-H-B5	A31-H-B5	A32-H-B5	A33-H-B5	A34-H-B5	A35-H-B5
A29-H-B6	A30-H-B6	A31-H-B6	A32-H-B6	A33-H-B6	A34-H-B6	A35-H-B6
A29-H-B7	A30-H-B7	A31-H-B7	A32-H-B7	A33-H-B7	A34-H-B7	A35-H-B7
A29-H-B8	A30-H-B8	A31-H-B8	A32-H-B8	A33-H-B8	A34-H-B8	A35-H-B8
A29-H-B9	A30-H-B9	A31-H-B9	A32-H-B9	A33-H-B9	A34-H-B9	A35-H-B9
A29-H-B10	A30-H-B10	A31-H-B10	A32-H-B10	A33-H-B10	A34-H-B10	A35-H-B10
A29-H-B11	A30-H-B11	A31-H-B11	A32-H-B11	A33-H-B11	A34-H-B11	A35-H-B11
A29-H-B12	A30-H-B12	A31-H-B12	A32-H-B12	A33-H-B12	A34-H-B12	A35-H-B12
A29-H-B13	A30-H-B13	A31-H-B13	A32-H-B13	A33-H-B13	A34-H-B13	A35-H-B13
A29-H-B14	A30-H-B14	A31-H-B14	A32-H-B14	A33-H-B14	A34-H-B14	A35-H-B14
A29-H-B15	A30-H-B15	A31-H-B15	A32-H-B15	A33-H-B15	A34-H-B15	A35-H-B15
A36-H-B1	A37-H-B1	A38-H-B1	A39-H-B1	A40-H-B1	A41-H-B1	A42-H-B1
A36-H-B2	A37-H-B2	A38-H-B2	A39-H-B2	A40-H-B2	A41-H-B2	A42-H-B2
A36-H-B3	A37-H-B3	A38-H-B3	A39-H-B3	A40-H-B3	A41-H-B3	A42-H-B3
A36-H-B4	A37-H-B4	A38-H-B4	A39-H-B4	A40-H-B4	A41-H-B4	A42-H-B4
A36-H-B5	A37-H-B5	A38-H-B5	A39-H-B5	A40-H-B5	A41-H-B5	A42-H-B5
A36-H-B6	A37-H-B6	A38-H-B6	A39-H-B6	A40-H-B6	A41-H-B6	A42-H-B6
A36-H-B7	A37-H-B7	A38-H-B7	A39-H-B7	A40-H-B7	A41-H-B7	A42-H-B7
A36-H-B8	A37-H-B8	A38-H-B8	A39-H-B8	A40-H-B8	A41-H-B8	A42-H-B8
A36-H-B9	A37-H-B9	A38-H-B9	A39-H-B9	A40-H-B9	A41-H-B9	A42-H-B9
A36-H-B10	A37-H-B10	A38-H-B10	A39-H-B10	A40-H-B10	A41-H-B10	A42-H-B10
A36-H-B11	A37-H-B11	A38-H-B11	A39-H-B11	A40-H-B11	A41-H-B11	A42-H-B11
A36-H-B12	A37-H-B12	A38-H-B12	A39-H-B12	A40-H-B12	A41-H-B12	A42-H-B12
A36-H-B13	A37-H-B13	A38-H-B13	A39-H-B13	A40-H-B13	A41-H-B13	A42-H-B13
A36-H-B14	A37-H-B14	A38-H-B14	A39-H-B14	A40-H-B14	A41-H-B14	A42-H-B14
A36-H-B15	A37-H-B15	A38-H-B15	A39-H-B15	A40-H-B15	A41-H-B15	A42-H-B15
A43-H-B1	A44-H-B1	A45-H-B1	A46-H-B1	A47-H-B1	A48-H-B1	A49-H-B1
A43-H-B2	A44-H-B2	A45-H-B2	A46-H-B2	A47-H-B2	A48-H-B2	A49-H-B2

TABLE 3-continued

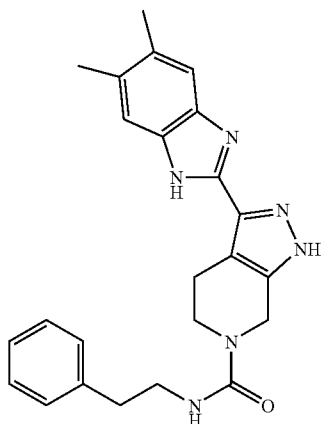


A43-H-B3	A44-H-B3	A45-H-B3	A46-H-B3	A47-H-B3	A48-H-B3	A49-H-B3
A43-H-B4	A44-H-B4	A45-H-B4	A46-H-B4	A47-H-B4	A48-H-B4	A49-H-B4
A43-H-B5	A44-H-B5	A45-H-B5	A46-H-B5	A47-H-B5	A48-H-B5	A49-H-B5
A43-H-B6	A44-H-B6	A45-H-B6	A46-H-B6	A47-H-B6	A48-H-B6	A49-H-B6
A43-H-B7	A44-H-B7	A45-H-B7	A46-H-B7	A47-H-B7	A48-H-B7	A49-H-B7
A43-H-B8	A44-H-B8	A45-H-B8	A46-H-B8	A47-H-B8	A48-H-B8	A49-H-B8
A43-H-B9	A44-H-B9	A45-H-B9	A46-H-B9	A47-H-B9	A48-H-B9	A49-H-B9
A43-H-B10	A44-H-B10	A45-H-B10	A46-H-B10	A47-H-B10	A48-H-B10	A49-H-B10
A43-H-B11	A44-H-B11	A45-H-B11	A46-H-B11	A47-H-B11	A48-H-B11	A49-H-B11
A43-H-B12	A44-H-B12	A45-H-B12	A46-H-B12	A47-H-B12	A48-H-B12	A49-H-B12
A43-H-B13	A44-H-B13	A45-H-B13	A46-H-B13	A47-H-B13	A48-H-B13	A49-H-B13
A43-H-B14	A44-H-B14	A45-H-B14	A46-H-B14	A47-H-B14	A48-H-B14	A49-H-B14
A50-H-B1	A51-H-B1	A52-H-B1	A53-H-B1	A54-H-B1	A55-H-B1	A56-H-B1
A50-H-B2	A51-H-B2	A52-H-B2	A53-H-B2	A54-H-B2	A55-H-B2	A56-H-B2
A50-H-B3	A51-H-B3	A52-H-B3	A53-H-B3	A54-H-B3	A55-H-B3	A56-H-B3
A50-H-B4	A51-H-B4	A52-H-B4	A53-H-B4	A54-H-B4	A55-H-B4	A56-H-B4
A50-H-B5	A51-H-B5	A52-H-B5	A53-H-B5	A54-H-B5	A55-H-B5	A56-H-B5
A50-H-B6	A51-H-B6	A52-H-B6	A53-H-B6	A54-H-B6	A55-H-B6	A56-H-B6
A50-H-B7	A51-H-B7	A52-H-B7	A53-H-B7	A54-H-B7	A55-H-B7	A56-H-B7
A50-H-B8	A51-H-B8	A52-H-B8	A53-H-B8	A54-H-B8	A55-H-B8	A56-H-B8
A50-H-B9	A51-H-B9	A52-H-B9	A53-H-B9	A54-H-B9	A55-H-B9	A56-H-B9
A50-H-B10	A51-H-B10	A52-H-B10	A53-H-B10	A54-H-B10	A55-H-B10	A56-H-B10
A50-H-B11	A51-H-B11	A52-H-B11	A53-H-B11	A54-H-B11	A55-H-B11	A56-H-B11
A50-H-B12	A51-H-B12	A52-H-B12	A53-H-B12	A54-H-B12	A55-H-B12	A56-H-B12
A50-H-B13	A51-H-B13	A52-H-B13	A53-H-B13	A54-H-B13	A55-H-B13	A56-H-B13
A50-H-B14	A51-H-B14	A52-H-B14	A53-H-B14	A54-H-B14	A55-H-B14	A56-H-B14
A50-H-B15	A51-H-B15	A52-H-B15	A53-H-B15	A54-H-B15	A55-H-B15	A56-H-B15
A57-H-B1	A58-H-B1	A59-H-B1	A60-H-B1	A61-H-B1	A62-H-B1	A63-H-B1
A57-H-B2	A58-H-B2	A59-H-B2	A60-H-B2	A61-H-B2	A62-H-B2	A63-H-B2
A57-H-B3	A58-H-B3	A59-H-B3	A60-H-B3	A61-H-B3	A62-H-B3	A63-H-B3
A57-H-B4	A58-H-B4	A59-H-B4	A60-H-B4	A61-H-B4	A62-H-B4	A63-H-B4
A57-H-B5	A58-H-B5	A59-H-B5	A60-H-B5	A61-H-B5	A62-H-B5	A63-H-B5
A57-H-B6	A58-H-B6	A59-H-B6	A60-H-B6	A61-H-B6	A62-H-B6	A63-H-B6
A57-H-B7	A58-H-B7	A59-H-B7	A60-H-B7	A61-H-B7	A62-H-B7	A63-H-B7
A57-H-B8	A58-H-B8	A59-H-B8	A60-H-B8	A61-H-B8	A62-H-B8	A63-H-B8
A57-H-B9	A58-H-B9	A59-H-B9	A60-H-B9	A61-H-B9	A62-H-B9	A63-H-B9
A57-H-B10	A58-H-B10	A59-H-B10	A60-H-B10	A61-H-B10	A62-H-B10	A63-H-B10
A57-H-B11	A58-H-B11	A59-H-B11	A60-H-B11	A61-H-B11	A62-H-B11	A63-H-B11
A57-H-B12	A58-H-B12	A59-H-B12	A60-H-B12	A61-H-B12	A62-H-B12	A63-H-B12
A57-H-B13	A58-H-B13	A59-H-B13	A60-H-B13	A61-H-B13	A62-H-B13	A63-H-B13
A57-H-B14	A58-H-B14	A59-H-B14	A60-H-B14	A61-H-B14	A62-H-B14	A63-H-B14
A57-H-B15	A58-H-B15	A59-H-B15	A60-H-B15	A61-H-B15	A62-H-B15	A63-H-B15
A64-H-B1	A65-H-B1	A66-H-B1	A67-H-B1	A68-H-B1	A69-H-B1	A70-H-B1
A64-H-B2	A65-H-B2	A66-H-B2	A67-H-B2	A68-H-B2	A69-H-B2	A70-H-B2
A64-H-B3	A65-H-B3	A66-H-B3	A67-H-B3	A68-H-B3	A69-H-B3	A70-H-B3
A64-H-B4	A65-H-B4	A66-H-B4	A67-H-B4	A68-H-B4	A69-H-B4	A70-H-B4
A64-H-B5	A65-H-B5	A66-H-B5	A67-H-B5	A68-H-B5	A69-H-B5	A70-H-B5
A64-H-B6	A65-H-B6	A66-H-B6	A67-H-B6	A68-H-B6	A69-H-B6	A70-H-B6
A64-H-B7	A65-H-B7	A66-H-B7	A67-H-B7	A68-H-B7	A69-H-B7	A70-H-B7
A64-H-B8	A65-H-B8	A66-H-B8	A67-H-B8	A68-H-B8	A69-H-B8	A70-H-B8
A64-H-B9	A65-H-B9	A66-H-B9	A67-H-B9	A68-H-B9	A69-H-B9	A70-H-B9
A64-H-B10	A65-H-B10	A66-H-B10	A67-H-B10	A68-H-B10	A69-H-B10	A70-H-B10
A64-H-B11	A65-H-B11	A66-H-B11	A67-H-B11	A68-H-B11	A69-H-B11	A70-H-B11
A64-H-B12	A65-H-B12	A66-H-B12	A67-H-B12	A68-H-B12	A69-H-B12	A70-H-B12
A64-H-B13	A65-H-B13	A66-H-B13	A67-H-B13	A68-H-B13	A69-H-B13	A70-H-B13
A64-H-B14	A65-H-B14	A66-H-B14	A67-H-B14	A68-H-B14	A69-H-B14	A70-H-B14
A64-H-B15	A65-H-B15	A66-H-B15	A67-H-B15	A68-H-B15	A69-H-B15	A70-H-B15

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EXAMPLE 1

3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridine-6-carboxylic acid 2-phenylethylamide



3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo-[3,4-c]pyridine-6-carboxylic acid 2-phenylethylamide can be prepared in the following way:

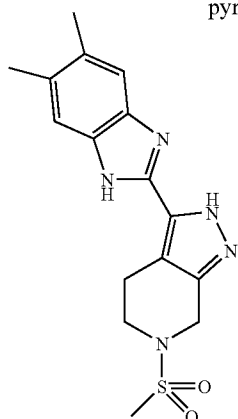
10 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine are suspended in 0.3 ml of tetrahydrofuran. 7.8 μ l of 2-phenylethyl isocyanate are added and the reaction mixture is stirred at ambient temperature for 20 hours and then concentrated under reduced pressure.

The evaporation residue is purified by LC/MS (method B). After purification by LC/MS, the fractions containing the 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridine-6-carboxylic acid 2-phenylethylamide are combined and loaded onto SCX phase (500 mg of CUBCX1-HL phase). The SCX phase is subsequently washed with methanol and then extracted with a solution of 2M ammonia in methanol. The extraction solution obtained is then concentrated under reduced pressure. 1.2 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridine-6-carboxylic acid 2-phenylethylamide are thus obtained in the form of a white powder, the characteristics of which are as follows:

LC/MS (method A): molecular ion detected: 415.29; retention time=3.48 minutes

EXAMPLE 2

3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-methanesulphonyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine



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3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-methanesulphonyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine can be prepared in the following way:

10 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine are suspended in 0.3 ml of dichloromethane. 15.8 μ l of triethylamine are added, along with 4.5 μ l of methanesulphonyl chloride. The reaction mixture is stirred at ambient temperature for 20 hours and is then concentrated under reduced pressure.

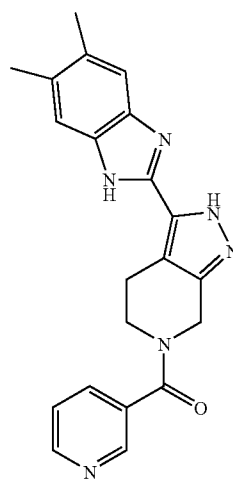
The evaporation residue is purified by LC/MS (method B). After purification by LC/MS, the fractions containing 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-methanesulphonyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine are combined and loaded onto SCX phase (500 mg of CUBCX1-HL phase). The SCX phase is subsequently washed with methanol and then extracted with a solution of 2M ammonia in methanol. The extraction solution obtained is then concentrated under reduced pressure. 4.2 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-methanesulphonyl-4,5,6,7-tetrahydro-2H-pyrazolo-[3,4-c]pyridine are thus obtained in the form of a white powder, the characteristics of which are as follows:

LC/MS (method A): molecular ion detected: 346.30; retention time=3.08 minutes.

¹H NMR (300 MHz, (CD₃)₂SO, δ in ppm): 2.32 (broad s: 6H); 3.02 (s: 3H); 3.03 (mt: 2H); 3.52 (broad t, J=5 Hz: 2H); 4.45 (broad s: 2H); 7.24 (broad s: 1H); 7.42 (broad s: 1H); 12.45 (unresolved peak: 1H); 13.07 (unresolved peak: 1H).

EXAMPLE 3

[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]-3-pyridinylmethanone



[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo-[3,4-c]pyridin-6-yl]-3-pyridinylmethanone can be prepared in the following way:

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10 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine are suspended in 0.3 ml of DMF. 6.9 mg of nicotinic acid are added, followed by 7.6 mg of HOBt and 8.7 μ l of diisopropylcarbodiimide. The reaction mixture is stirred at ambient temperature for 20 hours and is then concentrated under reduced pressure.

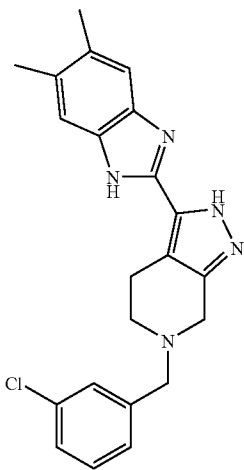
The evaporation residue is purified by LC/MS (method B). After purification by LC/MS, the fractions containing the [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-3-pyridinylmethanone are combined and loaded onto SCX phase (500 mg of CUBCX1-HL phase). The SCX phase is subsequently washed with methanol and then extracted with a solution of 2M ammonia in methanol. The extraction solution obtained is then concentrated under reduced pressure. 5.3 mg of [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-3-pyridinylmethanone are thus obtained in the form of a white powder, the characteristics of which are as follows:

LC/MS (method A): molecular ion detected: 373.31; retention time=2.87 minutes

^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$, at a temperature of 373K, δ in ppm): 2.35 (s: 6H); from 2.90 to 3.10 (mt: 2H); 3.76 (unresolved peak: 2H); 4.76 (broad s: 2H); 7.27 (unresolved peak: 1H); 7.40 (unresolved peak: 1H); 7.51 (dd, J=8 and 5 Hz: 1H); 7.90 (broad d, J=8 Hz: 1H); 8.70 (mt: 2H); from 11.80 to 12.20 (broad unresolved peak: 1H); from 12.50 to 13.00 (broad unresolved peak: 1H).

EXAMPLE 4

6-(3-Chlorobenzyl)-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine



6-(3-Chlorobenzyl)-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine can be prepared in the following way: 10 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine are suspended in 0.3 ml of methanol. 12.7 μ l of 3-chlorobenzaldehyde are added, followed by 4.7 mg of

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NaBH_3CN . The reaction mixture is stirred at ambient temperature for 20 hours and is then concentrated under reduced pressure.

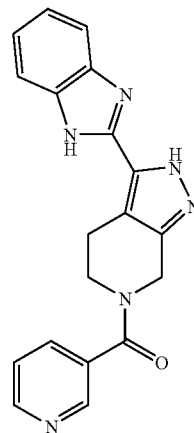
The evaporation residue is purified by LC/MS (method B). After purification by LC/MS, the fractions containing the 6-(3-chlorobenzyl)-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine are combined and loaded onto a SCX phase (500 mg of CUBCX1-HL phase). The SCX phase is subsequently washed with methanol and then extracted with a solution of 2M ammonia in methanol. The extraction solution obtained is then concentrated under reduced pressure. 4 mg of 6-(3-chlorobenzyl)-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine are thus obtained in the form of a white powder, the characteristics of which are as follows:

LC/MS (method A): molecular ion detected: 392.26; retention time 3.18 minutes.

^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$, at a temperature of 373K, δ in ppm): 2.35 and 2.36 (2 s: 6H in total); 2.83 (t, J=5.5 Hz: 2H); from 2.90 to 3.00 (mt: 2H); 3.62 (broad s: 2H); 3.78 (s: 2H); from 7.25 to 7.50 (mt: 6H); 11.91 (unresolved peak: 1H); from 12.30 to 12.60 (broad unresolved peak: 1H).

EXAMPLE 5

[3-(1H-Benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-3-pyridinylmethanone



[3-(1H-Benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-3-pyridinylmethanone can be prepared in the following way:

15 mg of 3-(1H-benzimidazol-2-yl)-2,4,5,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine hydrochloride are suspended in 0.5 ml of DMF. 24.3 mg of diisopropylethylamine are added, followed by 12.7 mg of HOBt, 11.9 mg of diisopropylcarbodiimide and 11.6 mg of nicotinic acid. The reaction mixture is stirred at ambient temperature for 20 hours and then concentrated under reduced pressure.

The evaporation residue is purified by LC/MS (method B). After purification by LC/MS, the fractions containing the [3-(1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-3-pyridinylmethanone are combined and loaded onto SCX phase (500 mg of CUBCX1-HL phase). The

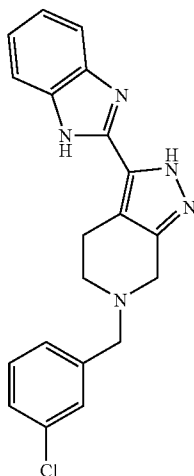
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SCX phase is subsequently washed with methanol and then extracted with a solution of 2M ammonia in methanol. The extraction solution obtained is then concentrated under reduced pressure. 7.7 mg of [3-(1H-benzimidazol-2-yl)-2, 4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-3-pyridinyl-methanone are thus obtained in the form of a white powder, the characteristics of which are as follows:

LC/MS (method A): molecular ion detected: 345.22; retention time=1.95 minutes

EXAMPLE 6

6-(3-Chlorobenzyl)-3-(1H-benzimidazol-2-yl)-4,5, 6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine



6-(3-Chlorobenzyl)-3-(1H-benzimidazol-2-yl)-4,5, 6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine can be prepared in the following way:

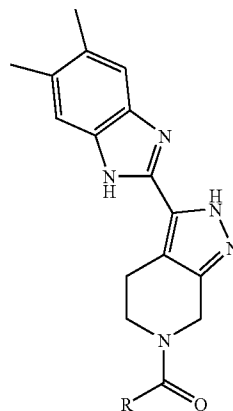
15 mg of 3-(1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine hydrochloride are suspended in 0.5 ml of methanol. 26.5 mg of 3-chlorobenzaldehyde are added, followed by 7.9 mg of NaBH₃CN. The reaction mixture is stirred at ambient temperature for 20 hours and is then concentrated under reduced pressure.

The evaporation residue is purified by LC/MS (method B). After purification by LC/MS, the fractions containing the 6-(3-chlorobenzyl)-3-(1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine are combined and loaded onto SCX phase (500 mg of CUBCX1-HL phase). The SCX phase is subsequently washed with methanol and extracted with a solution of 2M ammonia in methanol. The extraction solution obtained is then concentrated under reduced pressure. 6.9 mg of 6-(3-chlorobenzyl)-3-(1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine are thus obtained in the form of a white powder, the characteristics of which are as follows: LC/MS (method A): molecular ion detected: 364.22; retention time=2.19 minutes

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EXAMPLE 7

Preparation of an Amide Library



The amide library can be prepared in the following way;
The 19 acids (Table 4) are weighed and placed in 19 individual test tubes.

Table 4: Acids used

TABLE 4

Acids used			
Entry	Name	Amount	
1	ISOBUTYRIC ACID	3.3 mg	
2	BENZOIC ACID	4.6 mg	
3	2,3-DICHLOROBENZOIC ACID	7.1 mg	
4	PHENYLACETIC ACID	5.1 mg	
5	ACETIC ACID	2.2 mg	
6	CYCLOPROPANECARBOXYLIC ACID	3.2 mg	
7	2-CHLOROBENZOIC ACID	5.9 mg	
8	3-CHLOROBENZOIC ACID	5.9 mg	
9	4-CHLOROBENZOIC ACID	5.9 mg	
10	ISOVALERIC ACID	3.8 mg	
11	HYDROCINNAMIC ACID	5.6 mg	
12	VINYLAACETIC ACID	3.2 mg	
13	BUTYRIC ACID	3.3 mg	
14	2-FUROIC ACID	4.2 mg	
15	PIVALIC ACID	3.8 mg	
16	N,N-DIMETHYLGLYCINE	3.9 mg	
17	VALERIC ACID	3.8 mg	
18	THIOPHENE-2-CARBOXYLIC ACID	4.8 mg	
19	4-METHYLSULPHONYLBENZOIC ACID	7.5 mg	

152 mg of HOBt and 142 mg of diisopropylcarbodiimide are solubilized in 12 ml of DMF and the solution obtained is distributed in each of the 19 test tubes, at a rate of 600 µl per tube.

200 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine hydrochloride are suspended in 4 ml of DMF in the presence of 290 mg of N,N-diisopropylethylamine, and the suspension obtained is distributed into each of the 19 test tubes, at a rate of 200 µl per tube.

The 19 reaction mixtures are shaken by means of orbital shaking at ambient temperature for 20 hours.

For each reaction mixture, a 10 µl sample is taken and diluted in 40 µl of DMSO (Gilson Liquid Handler Quad-Z

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215). Each sample in solution in DMSO thus obtained is analysed by LC/MS (method A).

The 19 reaction mixtures are then evaporated to dryness and the evaporation residues are each solubilized in 500 µl of DMSO, and the solutions obtained are then purified by LC/MS (method B).

After purification by LC/MS, the fractions containing the desired compounds are (optionally combined) loaded onto SCX phase (500 mg of CUBCX1-HL phase). The SCX phases are subsequently washed with methanol and then

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extracted with a solution of 2M ammonia in methanol. The extraction solutions are collected in tared glass tubes, evaporated to dryness (Savant AES 2000 or Genevac HT8 centrifugal evaporator), weighed (Mettler Toledo Automated Workstation LA200) and diluted to 10 mM in DMSO (Gilson Liquid Handler Quad-Z 215). Each solution obtained is analysed by LC/MS (method A).

The following compounds (Table 5) were isolated and characterized by means of their retention time and molecular peak in mass spectrometry (method A).

TABLE 5

Entry	Name	Amide library obtained		
		Amount of product obtained	Retention time (minutes)	Molecular ion detected
1	1-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo-[3,4-c]pyridin-6-yl]-2-methylpropan-1-one	5.8 mg	3.08	338.23
2	[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]-pyridin-6-yl]phenylmethanone	6.8 mg	2.68	372.21
3	(2,3-Dichlorophenyl)-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-methanone	12 mg	3.05	440.13
4	1-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo-[3,4-c]pyridin-6-yl]-2-phenylethanone	7.9 mg	2.99	386.23
5	1-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo-[3,4-c]pyridin-6-yl]ethanone	2.7 mg	2.4	310.19
6	Cyclopropyl-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-methanone	3.4 mg	2.57	336.21
7	(2-Chlorophenyl)-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-methanone	11.2 mg	2.97	406.18
8	(3-Chlorophenyl)-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-methanone	12.1 mg	3.31	406.16
9	(4-Chlorophenyl)-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-methanone	11.5 mg	3.51	406.17
10	1-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]-pyridin-6-yl]-3-methylbutan-1-one	4.8 mg	2.72	352.24
11	1-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]-pyridin-6-yl]-3-phenylpropan-1-one	11.9 mg	2.95	400.24
12	1-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo-[3,4-c]pyridin-6-yl]but-3-en-1-one	10.1 mg	2.72	336.22

TABLE 5-continued

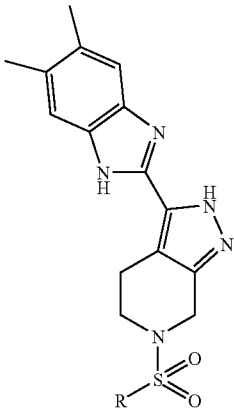
Amide library obtained		Amount of product obtained	Retention time (minutes)	Molecular ion detected
Entry	Name			
13	1-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]butan-1-one	7 mg	2.66	338.23
14	[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]furan-2-yl-methanone	9.5 mg	2.67	362.19
15	1-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-2,2-dimethylpropan-1-one	9.3 mg	2.8	352.24
16	2-Dimethylamino-1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]ethanone	4.7 mg	2.55	353.23
17	1-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]pentan-1-one	5.4 mg	2.78	352.24
18	[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]thiophen-2-yl-methanone	7.2 mg	2.75	378.17
19	[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-(4-methanesulphonyl-phenyl)methanone	14.3 mg	2.79	450.19

EXAMPLE 8

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Preparation of a Sulphonamide Library

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The sulphonamide library can be prepared in the following way:

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190 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6, 60
7-tetrahydro-2H-pyrazolo[3,4-c]pyridine hydrochloride are
suspended in 2 ml of dichloromethane in the presence of 150
μl of triethylamine, and the suspension obtained is distributed
into 17 test tubes, at a rate of 500 μl per tube. The 17 sulphonyl 65
chlorides (Table 6) are weighed and added to each of the 17
test tubes.

TABLE 6

<u>Sulphonyl chlorides used</u>		
Entry	Name	Quantity
1	BENZENESULPHONYL CHLORIDE	9.9 mg
2	ALPHA-TOLUENESULPHONYL CHLORIDE	10.7 mg
3	2,3-DICHLOROBENZENESULPHONYL CHLORIDE	13.8 mg
4	4-CHLOROBENZENESULPHONYL CHLORIDE	11.9 mg
5	2,2,2-TRIFLUOROETHANESULPHONYL CHLORIDE	10.2 mg
6	ETHANESULPHONYL CHLORIDE	7.2 mg
7	1-PROPANESULPHONYL CHLORIDE	8 mg
8	1-BUTANESULPHONYL CHLORIDE	8.8 mg
9	2-CHLOROBENZENESULPHONYL CHLORIDE	11.9 mg
10	3-CHLOROBENZENESULPHONYL CHLORIDE	11.9 mg
11	[(4-FLUOROPHENYL)METHYL]SULPHONYL CHLORIDE	11.7 mg
12	4-METHOXYBENZENESULPHONYL CHLORIDE	11.6 mg
13	P-TOLUENESULPHONYL CHLORIDE	10.7 mg
14	O-TOLUENESULPHONYL CHLORIDE	10.7 mg
15	3-METHYLBENZENESULPHONYL CHLORIDE	10.7 mg
16	3-METHOXYBENZENESULPHONYL CHLORIDE	11.6 mg
17	2-METHOXY-4-METHYLBENZENESULPHONYL CHLORIDE	12.4 mg

The 17 reaction mixtures are shaken by means of orbital shaking at ambient temperature for 20 h.

For each reaction mixture, a 10 µl sample is taken and diluted in 40 µl of DMSO (Gilson Liquid Handler Quad-Z 215). Each sample in solution in DMSO thus obtained is analysed by LC/MS (method A).

The 17 reaction mixtures are then evaporated to dryness and the evaporation residues are each solubilized in 1 ml of DMSO in the presence of a drop of an aqueous 5N hydrochloric acid solution, and the solutions obtained are purified by LC/MS (method B). After purification by LC/MS, the fractions containing the desired compounds are (optionally

combined) loaded onto SCX phase (500 mg of CUBCX1-HL phase). The SCX phases are subsequently washed with methanol and then extracted with a solution of 2M ammonia in methanol. The extraction solutions are collected in tared glass tubes, evaporated to dryness (Savant AES 2000 or Genevac HT8 centrifugal evaporator), weighed (Mettler Toledo Automated Workstation LA200) and diluted to 10 mM in DMSO (Gilson Liquid Handler Quad-Z 215). Each solution obtained is analysed by LC/MS (method A).

The following compounds (Table 7) were isolated and characterized by means of their retention time and molecular peak in mass spectrometry (method A).

TABLE 7

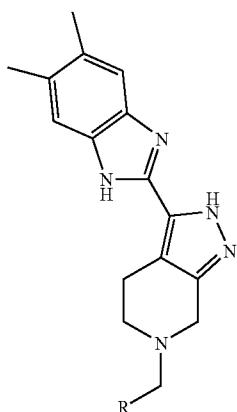
<u>Sulphonamide library obtained</u>				
Entry	Name	Amount of product obtained	Retention time (minutes)	Molecular ion detected
1	6-Benzenesulphonyl-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	1.4 mg	3.41	408.18
2	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-phenylmethanesulphonyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	0.7 mg	3.51	422.2
3	6-(2,3-Dichlorobenzenesulphonyl)-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	6.4 mg	3.25	476.1
4	6-(4-Chlorobenzenesulphonyl)-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	5.9 mg	3.19	442.12
5	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(2,2,2-trifluoroethanesulphonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	1.7 mg	3.06	414.14
6	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-ethanesulphonyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	5.2 mg	2.63	360.17
7	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(propane-1-sulphonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	4.3 mg	2.8	374.19
8	6-(Butane-1-sulphonyl)-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	5.6 mg	2.94	388.2

TABLE 7-continued

<u>Sulphonamide library obtained</u>				
Entry	Name	Amount of product obtained	Retention time (minutes)	Molecular ion detected
9	6-(2-Chlorobenzenesulphonyl)-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]-pyridine	5.6 mg	3.38	442.13
10	6-(3-Chlorobenzenesulphonyl)-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]-pyridine	6.9 mg	3.71	442.13
11	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(4-fluorophenylmethanesulphonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]-pyridine	0.7 mg	3.05	440.18
12	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(4-methoxybenzenesulphonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]-pyridine	7.5 mg	2.99	438.19
13	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(toluene-4-sulphonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	7.3 mg	3.22	422.2
14	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(toluene-2-sulphonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	4.8 mg	3.16	422.19
15	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(toluene-3-sulphonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	5.1 mg	3.13	422.19
16	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(3-methoxybenzenesulphonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]-pyridine	6.9 mg	3.07	438.18
17	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(2-methoxy-4-methyl-benzene-sulphonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	0.8 mg	3.34	452.19

EXAMPLE 9

Preparation of an Amine Library



The amine library can be prepared in the following way:

180 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine hydrochloride are suspended in 2.7 ml of methanol and the suspension obtained is distributed into 16 test tubes, at a rate of 150 μ l per tube.

The 16 aldehydes (Table 8) are weighed and added to each of the 16 test tubes.

TABLE 8

<u>Aldehydes used</u>		
Entry	Name	Quantity
40	1 ISOBUTYRALDEHYDE	8.1 mg
	2 FORMALDEHYDE	3.4 mg
45	3 BENZALDEHYDE	11.9 mg
	4 PHENYLACETALDEHYDE	13.5 mg
	5 2,3-DICHLOROBENZALDEHYDE	19.6 mg
	6 FURFURAL	10.8 mg
	7 4-CHLOROBENZALDEHYDE	15.8 mg
	8 2-THIOPHENECARBOXALDEHYDE	12.6 mg
50	9 NICOTINALDEHYDE	12 mg
	10 TRIMETHYLACETALDEHYDE	9.7 mg
	11 ACETALDEHYDE	4.9 mg
	12 ISOVALERALDEHYDE	9.7 mg
	13 PROPIONALDEHYDE	6.5 mg
	14 3-PHENYLPROPIONALDEHYDE	15.1 mg
55	15 BUTYRALDEHYDE	8.1 mg
	16 CYCLOPROPANECARBOXALDEHYDE	7.9 mg

A solution of 85 mg of NaBH_3CN in 2.7 ml of methanol is then also distributed into the 16 test tubes, at a rate of 150 μ l per tube. The 16 reaction mixtures are shaken by means of orbital shaking at ambient temperature for 20 h. 100 μ l of methanol are then added to each of the 16 tubes.

For each reaction mixture, a 10 μ l sample is taken and diluted in 40 μ l of DMSO (Gilson Liquid Handler Quad-Z 215). Each sample in solution in DMSO thus obtained is analysed by LC/MS (method A).

The 16 reaction mixtures are then evaporated to dryness and the evaporation residues are each solubilized in 500 μ l of DMSO and filtered through sintered glass, and the residual solutions are then purified by LC/MS (method B). After purification by LC/MS, the fractions containing the desired compounds are (optionally combined) loaded onto SCX phase (500 mg of CUBCX1-HL phase). The SCX phases are subsequently washed with methanol and then extracted with a solution of 2M ammonia in methanol. The extraction solu-

tions are collected in tared glass tubes, evaporated to dryness (Savant AES 2000 or Genevac HT8 centrifugal evaporator), weighed (Mettler Toledo Automated Workstation LA200) and diluted to 10 mM in DMSO (Gilson Liquid Handler Quad-Z 215). Each solution obtained is analysed by LC/MS (method A).

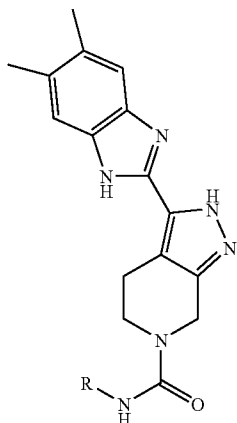
The following compounds (Table 9) were isolated and characterized by means of their retention time and molecular peak in mass spectrometry (method A).

TABLE 9

		Amine library obtained		
Entry	Name	Amount of product obtained	Retention time (minutes)	Molecular ion detected
1	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-isobutyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	5.9 mg	2.62	324.32
2	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	3.5 mg	2.49	282.29
3	6-Benzyl-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	8.2 mg	2.74	358.3
4	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-phenethyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	6.4 mg	2.84	372.32
5	6-(2,3-Dichlorobenzyl)-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	8.6 mg	2.95	426.23
6	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-furan-2-ylmethyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	5.9 mg	2.64	348.27
7	6-(4-Chlorobenzyl)-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	4.7 mg	2.9	392.26
8	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-thiophen-2-ylmethyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	8.4 mg	2.71	364.24
9	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-pyridin-3-ylmethyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	11.7 mg	2.55	359.29
10	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(2,2-dimethylpropyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	3.7 mg	2.72	338.32
11	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-ethyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	5 mg	2.55	296.27
12	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(3-methylbutyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	5.9 mg	2.76	338.3
13	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-propyl-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	6.4 mg	2.62	310.29
14	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(3-phenylpropyl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	4.2 mg	2.97	386.31
15	6-Butyl-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	4.5 mg	2.68	324.28
16	6-Cyclopropylmethyl-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine	3.9 mg	2.62	322.27

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EXAMPLE 10

Preparation of a Urea Library



The urea library can be prepared in the following way:
120 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine hydrochloride are suspended in 3.6 ml of tetrahydrofuran in the presence of 190 μ l of triethylamine, and the suspension obtained is distributed into each of the 9 test tubes, at a rate of 300 μ l per tube.

The 9 isocyanates (Table 10) are weighed and added to each of the 9 test tubes.

TABLE 10

<u>Isocyanates used</u>		
Entry	Name	Amount
1	PHENYL ISOCYANATE	6.7 mg
2	BENZYL ISOCYANATE	7.5 mg
3	2-CHLOROPHENYL ISOCYANATE	8.6 mg

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TABLE 10-continued

<u>Isocyanates used</u>			
Entry	Name	Amount	
5	4	3-CHLOROPHENYL ISOCYANATE	8.6 mg
	5	4-CHLOROPHENYL ISOCYANATE	8.6 mg
	6	N-BUTYL ISOCYANATE	5.6 mg
10	7	2-THIENYL ISOCYANATE	7 mg
	8	2-METHOXYPHENYL ISOCYANATE	8.4 mg
	9	O-TOLYL ISOCYANATE	7.5 mg

The 9 reaction mixtures are shaken by means of orbital shaking at ambient temperature for 2 hours, and are then evaporated to dryness.

Evaporation residues are each solubilized in 1 ml of DMSO and, for each solution obtained, a 10 μ l sample is taken and diluted in 40 μ l of DMSO (Gilson Liquid Handler Quad-X 215). Each sample in solution in DMSO thus obtained is analysed by LC/MS (method A).

The residual solutions are purified by LC/MS (method B). After purification by LC/MS, the fractions containing the desired compounds are (optionally) evaporated to dryness (entries 1, 3, 6, 8 and 9) or loaded onto SCX phase (500 mg of CUBCX1-HL phase; entries 2, 4, 5 and 7). The SCX phases are subsequently washed with methanol and then extracted with a solution of 2M ammonia in methanol. The extraction solutions are collected in tared glass, evaporated to dryness (Savant AES 2000 or Genevac HT8 centrifugal evaporator), weighed (Mettler Toledo Automated Workstation LA200) and diluted to 10 mM in DMSO (Gilson Liquid Handler Quad-Z 215). Each solution obtained is analysed by LC/MS (method A).

The following compounds (Table 11) were isolated and characterized by means of their retention time and molecular peak in mass spectrometry (method A).

TABLE 11

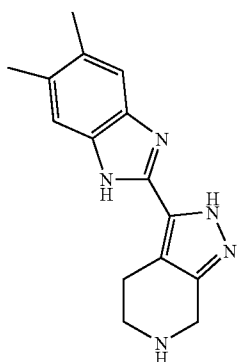
<u>Urea library obtained</u>				
Entry	Name	Amount of product obtained	Retention time (minutes)	Molecular ion detected
1	3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridine-6-carboxylic acid phenylamide bistrifluoroacetate	14.6 mg	3.04	387.28
2	3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridine-6-carboxylic acid benzylamide	1.8 mg	2.78	401.29
3	3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridine-6-carboxylic acid (2-chlorophenyl)amide bistrifluoroacetate	16 mg	2.92	421.25
4	3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridine-6-carboxylic acid (3-chlorophenyl)amide	7.9 mg	3.89	421.24
5	3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo-	9.8 mg	3.36	421.25

TABLE 11-continued

Urea library obtained		Amount of product obtained	Retention time (minutes)	Molecular ion detected
Entry	Name			
6	[3,4-c]pyridine-6-carboxylic acid (4-chlorophenyl)amide 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo-[3,4-c]pyridine-6-carboxylic acid butylamide bistrifluoroacetate	2.4 mg	2.8	367.31
7	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo-[3,4-c]pyridine-6-carboxylic acid thiophen-2-ylamide	3.8 mg	2.77	393.24
8	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo-[3,4-c]pyridine-6-carboxylic acid (2-methoxyphenyl)amide bistrifluoroacetate	14.4 mg	3.14	417.28
9	3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo-[3,4-c]pyridine-6-carboxylic acid o-tolylamide bistrifluoroacetate	16.2 mg	2.68	401.29

EXAMPLE 11

3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine



3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo-[3,4-c]pyridine can be prepared in the following way:

9 ml of water and 2.8 ml of trifluoroacetic acid are added to a solution of 670 mg of tert-butyl 3-(2-amino-4,5-dimethylphenylcarbamoyl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridine-6-carboxylate in 9 ml of THF. After stirring for 2 hours at 80° C., the reaction medium is concentrated under reduced pressure. It is then taken up in water and the precipitate formed is recovered by filtration through sintered glass, washed with an aqueous 1 N sodium hydroxide solution and dried. The aqueous phase obtained is subsequently extracted with dichloromethane and the organic phase is then dried over magnesium sulphate and concentrated under reduced pressure. The residue obtained and the precipitate are combined and then solubilized in methanol with a few drops of DMF. This solution is then loaded onto MEGA BE-SCX phase. The SCX phase is subsequently washed with methanol and

extracted with a solution of 2M ammonia in methanol. The extraction solution obtained is then concentrated under reduced pressure.

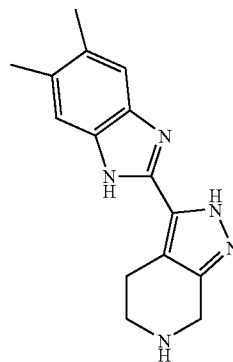
46 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine are thus obtained in the form of a beige powder, the characteristics of which are as follows:

EI:	m/z=267 m/z=238 m/z=209	M ⁺ [M —NHCH ₂] ⁺ [M —C ₃ H ₈ N] ⁺	base peak
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¹H NMR (300 MHz, (CD₃)₂SO, δ in ppm): 2.31 and 2.32 (2 s: 6H in total); 2.81 (broad t, J=5 Hz: 2H); 2.92 (broad t, J=5 Hz: 2H); 3.83 (broad s: 2H); 7.22 (broad s: 1H); 7.40 (broad s: 1H); 12.28 (unresolved peak: 1H); 12.73 (unresolved peak: 1H).

EXAMPLE 12

3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine hydrochloride



HCl

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3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine can be prepared in the following way:

9 ml of an aqueous 5N hydrochloric acid solution are added to a solution of 1.7 g of tert-butyl 3-(2-amino-4,5-dimethylphenylcarbamoyl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridine-6-carboxylate in 40 ml of ethanol. After stirring at 80° C. for 60 hours, the reaction medium is brought back to ambient temperature. The precipitate formed is recovered by filtration through sintered glass and dried. 1.04 g of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine hydrochloride are thus obtained in the form of a beige powder, the characteristics of which are as follows:

El:	m/z = 267	M ⁺	base peak
	m/z = 238	[M - CH ₂ NH] ⁺	
	m/z = 209	[M - C ₃ H ₈ N] ⁺	
	m/z = 36	[HCl] ⁺	

¹H NMR (300 MHz, (CD₃)₂SO with addition of a few drops of CD₃COOD, δ in ppm): 2.40 (s: 6H); 3.23 (broad t, J=5.5 Hz: 2H); 3.45 (t, J=5.5 Hz: 2H); 4.45 (s: 2H); 7.54 (s: 2H).

tert-Butyl 3-(2-amino-4,5-dimethylphenylcarbamoyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridine-6-carboxylate can be prepared in the following way:

8.5 g of HBTU and also 2.9 g of diisopropylethylamine are added, at ambient temperature, to a solution of 3 g of (tert-butyl 2,4,5,7-tetrahydropyrazolo-[3,4-c]pyridine-6-carboxylate)-3-carboxylic acid in 50 ml of anhydrous DMF. After twenty minutes' stirring at ambient temperature, 3.06 g of 4,5-diamino-o-xylene are added. After stirring at ambient temperature for 60 hours, the reaction medium is diluted in 3 l of an aqueous NaHCO₃ solution at pH greater than 7, containing 20 g of NaCl. The aqueous phase is extracted three times with 1 l of ethyl acetate, and the combined organic phases are then dried over magnesium sulphate and concentrated under reduced pressure. The crude residue obtained is taken up in 150 ml of dichloromethane and the insoluble material is removed by filtration through sintered glass. The filtrate is then concentrated under reduced pressure and purified by chromatography on silica (20-45 μm Amicon) with a gradient of from 50 to 100% of ethyl acetate in cyclohexane. The fractions containing the desired product are combined and concentrated under reduced pressure. 4.37 g of tert-butyl 3-(2-aminophenylcarbamoyl)-2,4,5,7-tetrahydro-pyrazolo [3,4-c]pyridine-6-carboxylate are thus obtained in the form of a beige powder, the characteristics of which are as follows:

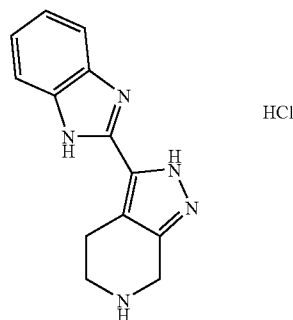
El:	m/z = 385	M ⁺	base peak
	m/z = 329	[M - C ₄ H ₈] ⁺	
	m/z = 312	[M - C ₄ H ₉ O] ⁺	
	m/z = 57	[C ₄ H ₉] ⁺	

¹H NMR (300 MHz, (CD₃)₂SO, δ in ppm): 1.46 (s: 9H); 2.10 and 2.12 (2 s: 3H each); 2.77 (mt: 2H); 3.58 (t, J=5.5 Hz: 2H); 4.53 (s: 2H); 4.57 (unresolved peak: 2H); 6.60 (s: 1H); 7.14 (broad s: 1H); 9.10 (unresolved peak: 1H); 13.08 (unresolved peak: 1H).

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EXAMPLE 13

3-(1H-Benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo-[3,4-c]pyridine hydrochloride



3-(1H-Benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine hydrochloride can be prepared in the following way:

2.2 ml of an aqueous 5N hydrochloric acid solution are added to a solution of 200 mg of tert-butyl 3-(2-aminophenylcarbamoyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridine-6-carboxylate in 1 ml of ethanol. After stirring for 20 hours at 80° C., the reaction medium is brought back to ambient temperature. The insoluble material is removed by filtration through sintered glass and the filtrate is concentrated under reduced pressure. 84 mg of 3-(1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine hydrochloride are thus obtained in the form of an orange-coloured powder, the characteristics of which are as follows:

LC/MS (method A): molecular ion detected: 240.26; retention time=1.68 minutes

tert-Butyl 3-(2-aminophenylcarbamoyl)-2,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridine-6-carboxylate can be prepared in the following way:

425 mg of HBTU and also 145 mg of diisopropylethylamine are added, at ambient temperature, to a solution of 150 mg of (tert-butyl 2,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridine-6-carboxylate)-3-carboxylic acid in 1 ml of anhydrous DMF. After stirring for twenty minutes at ambient temperature, 121 mg of orthophenylenediamine are added.

After stirring at ambient temperature for 20 hours, the reaction medium is diluted in 100 ml of water and 50 ml of ethyl acetate. The aqueous phase is extracted three times with 50 ml of ethyl acetate and the combined organic phases are then dried over magnesium sulphate and concentrated under reduced pressure. The crude residue obtained is purified by HPLC (reverse phase C18 Lichroprep 12 μm) with a linear gradient of from 5 to 95% of acetonitrile comprising 0.07% (v/v) of trifluoroacetic acid in water comprising 0.07% (v/v) of trifluoroacetic acid, at a flow rate of 10 ml/min. The fractions containing the desired product are combined and loaded onto MEGA BE-SCX phase. The SCX phase is subsequently washed with methanol and extracted with a solution of 2M ammonia in methanol. The extraction solution obtained is then concentrated under reduced pressure. 200 mg of tert-butyl 3-(2-aminophenylcarbamoyl)-2,4,5,7-tetrahydropyrazo-

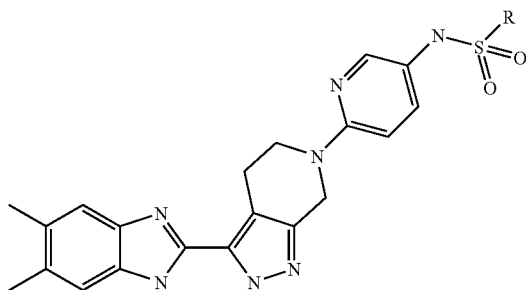
45

zolo[3,4-c]pyridine-6-carboxylate are thus obtained in the form of a beige powder, the characteristics of which are as follows:

LC/MS (method A): molecular ion detected: 358.34; retention time=3.19 minutes.

EXAMPLE 14

Preparation of a Sulphonamide Library



The sulphonamide library can be prepared in the following way:

40 mg of 6-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]pyridin-3-ylamine are suspended in 2 ml of dichloromethane and the solution obtained is distributed into 4 test tubes, at a rate of 500 µl per tube.

The 4 sulphonyl chlorides (Table 12) are weighed and added to each of the 4 test tubes, followed by 15.6 µl of triethylamine.

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TABLE 12

Sulphonyl chlorides used		
Entry	Name	Amount
1	THIOPHENE-2-SULPHONYL CHLORIDE	5.6 mg
2	4-METHOXYBENZENESULPHONYL CHLORIDE	6.3 mg
3	2-CHLOROBENZENESULPHONYL CHLORIDE	6.4 mg
4	2-METHOXY-4-METHYLBENZENESULPHONYL CHLORIDE	6.8 mg

The 4 reaction mixtures are shaken by means of orbital shaking at 40° C. for 15 h.

For each reaction mixture, a 5 µl sample is taken and diluted in 100 µl of DMSO (Gilson Liquid Handler Quad-Z 215). Each sample in solution in DMSO thus obtained is analysed by LC/MS (method A).

The 4 reaction mixtures are then evaporated to dryness and the evaporation residues are each solubilized in 500 µl of DMSO and the solutions obtained are purified by LC/MS (method B). After purification by LC/MS, the fractions containing the desired compounds are (optionally combined) loaded onto SCX phase (500 mg of CUBCX1-HL phase). The SCX phases are subsequently washed with methanol and then extracted with a solution of 2M ammonia in methanol. The extraction solutions are collected in tared glass tubes, evaporated to dryness (Savant AES 2000 or Genevac HT8 centrifugal evaporator), weighed (Mettler Toledo Automated Workstation LA200) and diluted to 10 mM in DMSO (Gilson Liquid Handler Quad-Z 215). Each solution obtained is analysed by LC/MS (method A).

The following compounds (Table 13) were isolated and characterized by means of their retention time and molecular peak in mass spectrometry (method A)

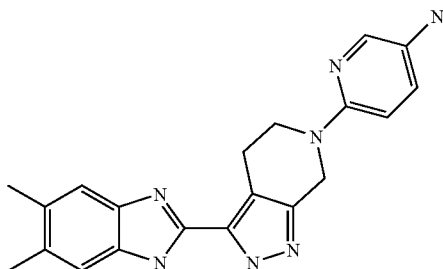
TABLE 13

Sulphonamide library obtained			
Entry	Name	Amount of product obtained	Retention time (minutes) Molecular ion detected
1	N-{6-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]pyridin-3-yl}thiophene-2-sulphonamide	2.9 mg	3.07 506.21
2	N-{6-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]pyridin-3-yl}-4-methoxybenzenesulphonamide	3.0 mg	3.20 530.25
3	2-Chloro-N-{6-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]pyridin-3-yl}benzenesulphonamide	3.0 mg	3.38 534.21
4	N-{6-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]pyridin-3-yl}-2-methoxy-4-methylbenzenesulphonamide	3.8 mg	3.38 544.26

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EXAMPLE 15

6-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydro-pyrazolo[3,4-c]pyridin-6-yl]pyridin-3-ylamine



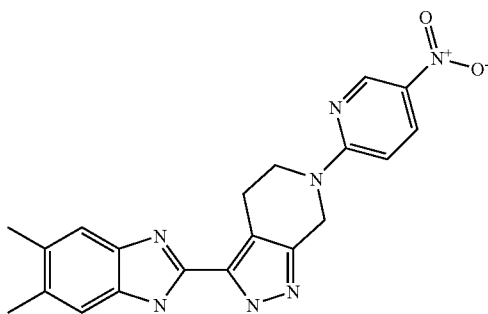
6-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo-[3,4-c]pyridin-6-yl]pyridin-3-ylamine can be prepared in the following way:

55 mg of Pd/CaCO₃ 10% are added to a solution of 545 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-(5-nitropyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine in 60 ml of ethanol. After stirring for 15 hours at 35° C. under 3 bar of hydrogen, the reaction medium is brought back to ambient temperature, filtered through celite and then concentrated under reduced pressure. 300 mg of 6-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-2,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl]-pyridin-3-ylamine are thus obtained in the form of a brown powder, the characteristics of which are as follows:

EI	m/z = 359 m/z = 266	M ⁺ (M - C ₅ H ₅ N ₂) ⁺	base peak
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EXAMPLE 16

3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(5-nitropyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine



3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-(5-nitropyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine can be prepared in the following way:

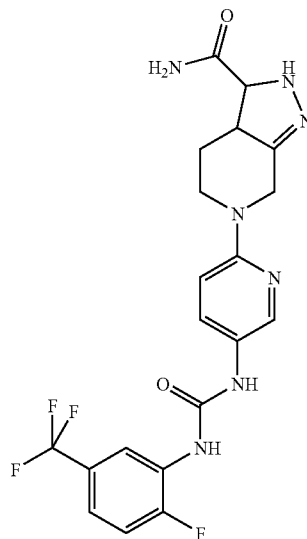
48

287 mg of 2-chloro-5-nitropyridine and 500 mg of potassium carbonate are added to a solution of 500 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine hydrochloride in 5 ml of dimethylformamide. After stirring for 20 hours at ambient temperature, the reaction medium is added to 50 ml of water. The precipitate formed is recovered by filtration through sintered glass, washed with 3 times 15 ml of water and then dried under reduced pressure. 548 mg of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-(5-nitropyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine are thus obtained in the form of a yellow powder, the characteristics of which are as follows:

EI:	m/z = 389 m/z = 266	M ⁺ (M - C ₅ H ₅ N ₂ O ₂) ⁺	base peak
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EXAMPLE 17

6-{5-[3-(2-Fluoro-5-trifluoromethylphenyl)ureido]pyridin-2-yl}-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxamide



6-{5-[3-(2-Fluoro-5-trifluoromethylphenyl)ureido]pyridin-2-yl}-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxamide can be prepared in the following way from ethyl 6-(5-tert-butoxycarbonylaminopyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate:

The ethyl ester of ethyl 6-(5-tert-butoxycarbonylaminopyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate is converted to carboxamide by amidation using a solution of aqueous ammonia, and results in the obtaining of 6-(5-tert-butoxycarbonylaminopyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxamide.

EI: m/z=358

The amine group of the 6-(5-tert-butoxycarbonylaminopyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxamide is deprotected in acid medium (trifluoroacetic

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acid in dichloromethane) and results in the obtaining of 6-(5-aminopyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxamide.

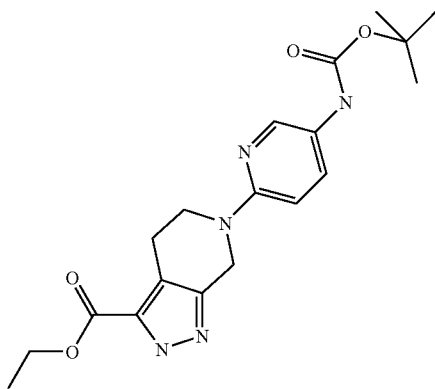
EI: $m/z=358$

The urea function is introduced onto the 6-(5-aminopyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxamide according to the method described in Example 1, using 2-fluoro-5-(trifluoromethyl)phenyl isocyanate, and results in the obtaining of 6-{3-(2-fluoro-5-trifluoromethylphenyl)-ureido}pyridin-2-yl}-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxamide.

EI: $m/z=463$

EXAMPLE 18

Ethyl 6-(5-tert-butoxycarbonylaminopyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate



Ethyl 6-(5-tert-butoxycarbonylaminopyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate can be prepared in the following way:

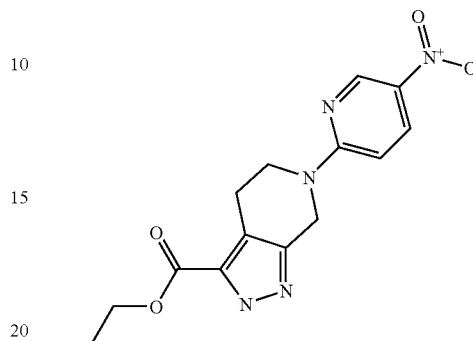
5 mg of Pd/C 10% and 38 mg of di-tert-butyl dicarbonate are added to a solution of 50 mg of ethyl 6-(5-nitropyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate in 6 ml of methanol. After stirring for 12 hours at ambient temperature under 3 bar of hydrogen, the reaction medium is filtered through celite and then concentrated under reduced pressure. The reaction crude obtained is purified by flash chromatography (SiO₂, CH₂Cl₂/MeOH gradient 75/25 to 25/75). 20 mg of ethyl 6-(5-tert-butoxycarbonylaminopyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate are thus obtained in the form of a white powder, the characteristics of which are as follows:

EI:	$m/z = 387$	M^+	
	$m/z = 331$	$(M - C_4H_8)^+$	base peak
	$m/z = 286$	$(m/z = 331 - CO_2H)^+$	
	$m/z = 194$	$C_9H_{12}N_3O_2^+$	
	$m/z = 57$	$C_4H_9^+$	

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EXAMPLE 19

Ethyl 6-(5-nitropyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate



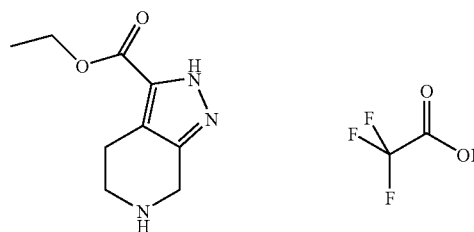
Ethyl 6-(5-nitropyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate can be prepared in the following way:

522 mg of 2-chloro-5-nitropyridine are added to a solution of 1 g of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine trifluoroacetate in 10 ml of pyridine. After stirring for 20 hours at ambient temperature, the reaction medium is concentrated under reduced pressure. The precipitate formed is recovered by filtration through sintered glass, washed with 3 times 15 ml of water, and dried under reduced pressure. The reaction crude obtained is purified by flash chromatography (SiO₂, cyclohexane/EtOAc gradient 75/25 to 25/75). 450 mg of ethyl 6-(5-nitropyridin-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate are thus obtained in the form of a yellow powder, the characteristics of which are as follows:

EI:	$m/z = 317$	M^+	base peak
	$m/z = 271$	$(M - NO_2)^+$	
	$m/z = 194$	$(M - C_5H_3N_2O_2)^+$	
	$m/z = 148$	$(m/z = 194 - C_2H_6O)^+$	

EXAMPLE 20

Ethyl 4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate trifluoroacetate



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Ethyl 4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate trifluoro-acetate can be prepared in the following way:

50 ml of water followed by 12 ml of trifluoroacetic acid are added to a solution of 3 g of 6-tert-butyl-3-ethyl 2,4,5,7-tetrahydropyrazolo[3,4-c]pyridyl-3,6-dicarboxylate in 50 ml of tetrahydrofuran. After stirring for 2 hours at reflux, the reaction medium is brought back to ambient temperature and a saturated aqueous Na_2CO_3 solution is added until a basic pH is obtained. The aqueous phase obtained is extracted 3 times with ethyl acetate. The combined organic phases are dried over magnesium sulphate and concentrated under reduced pressure. 1.49 g of ethyl 4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate trifluoroacetate are thus obtained, the characteristics of which are as follows:

EI:	m/z = 195	M^+	
	m/z = 166	$(\text{M} - \text{CH}_3\text{N})^+$	base peak
	m/z = 138	$(\text{M} - \text{C}_3\text{H}_7\text{N})^+$	
	m/z = 120	$(\text{m/z} = 166 - \text{C}_2\text{H}_6\text{O})^+$	
	m/z = 92	$(\text{m/z} = 120 - \text{CO})^+$	

Measurements of the Inhibitory Potential of the Products with Respect to the Activity of the Tie2 and KDR Kinases:

The inhibitory activity of the products with respect to the Tie2 and KDR kinases is tested according to the experimental protocols described below.

1. Tie2

The coding sequence of human Tie2 corresponding to amino acids 776-1124 of the intracellular domain was generated by PCR using the cDNA isolated from human placenta as model. This sequence was introduced into a baculovirus expression vector pFastBacGT in the form of a GST fusion protein.

The inhibitory effect of the molecules is determined in an assay for phosphorylation of PLC by Tie2 in the presence of GST-Tie2 purified to approximately 80% homogeneity. The substrate is made up of the SH2-SH3 fragments of PLC, the latter being expressed in the form of a GST fusion protein.

The kinase activity of Tie2 is measured in a 20 mM MOPS buffer, pH 7.2, containing 10 mM MgCl_2 , 10 mM MnCl_2 , 1 mM DTT and 10 mM of glycerophosphate. A reaction mixture made up of 70 μl of kinase buffer containing 100 ng of GST-Tie2 enzyme per well is placed in a flashplate 96-well plate kept on ice. 10 μl of the molecule to be tested, diluted in

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DMSO, at a concentration of at most 10% are then added. For a given concentration, each measurement is carried out in quadruplicate. The reaction is initiated by adding 20 μl of solution containing 2 μg of GST-PLC, 2 μM of cold ATP and 1 μCi of ^{33}P [ATP]. After incubation for 1 hour at 37° C., the reaction is stopped by adding 1 volume (100 μl) of 200 mM EDTA. After removal of the incubation buffer, the wells are washed three times with 300 μl of PBS. The radioactivity is measured on a Wallac MicroBeta 1450.

The inhibition of the Tie2 activity is calculated and expressed as percentage inhibition with respect to the control activity determined in the absence of compound.

2. KDR

The inhibitory effect of the compounds is determined in an assay for phosphorylation of substrate by the KDR enzyme *in vitro* using a scintillation technique (96-well plate, NEN).

The cytoplasmic domain of the human KDR enzyme was cloned in GST fusion form into the baculovirus expression vector pFastBac. The protein was expressed in SF21 cells and purified to approximately 60% homogeneity. The KDR kinase activity is measured in 20 mM MOPS, 10 mM MgCl_2 , 10 mM MnCl_2 , 1 mM DTT, 2.5 mM EGTA, 10 mM b-glycerophosphate, pH=7.2, in the presence of 10 mM MgCl_2 , 100 μM Na_3VO_4 and 1 mM NaF. 10 μl of the compound are added to 70 μl of kinase buffer containing 100 ng of KDR enzyme at 4° C. The reaction is initiated by adding 20 μl of solution containing 2 μg of substrate (SH2-SH3 fragment of PLC γ expressed in the form of an GST fusion protein), 2 μCi γ ^{33}P [ATP] and 2 μM cold ATP. After incubation for 1 hour at 37° C., the reaction is stopped by adding 1 volume (100 μl) of 200 mM EDTA. The incubation buffer is removed and the wells are washed three times with 300 μl of PBS. The radioactivity is measured in each well using a Top Count NXT (Packard) radioactivity counter.

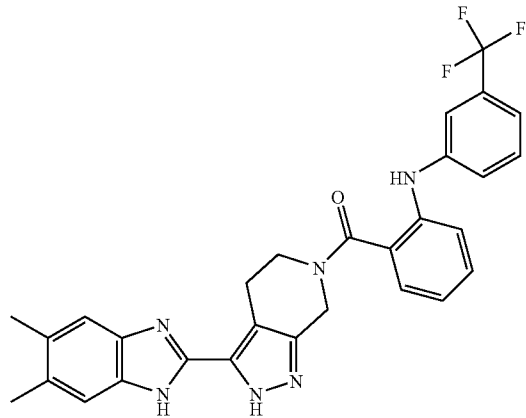
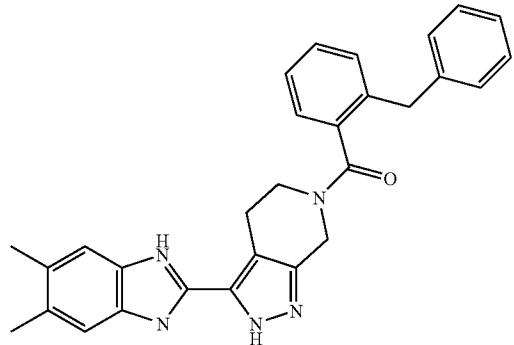
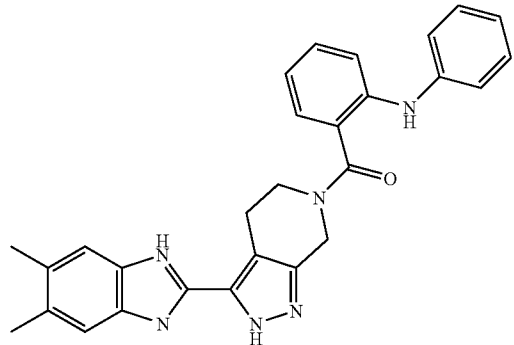
The background noise is determined by measuring the radioactivity in four different wells containing the radioactive ATP and the substrate alone.

A total activity control is measured in four different wells containing all the reagents (γ ^{33}P -[ATP], KDR and PLC- γ substrate) but in the absence of compound.

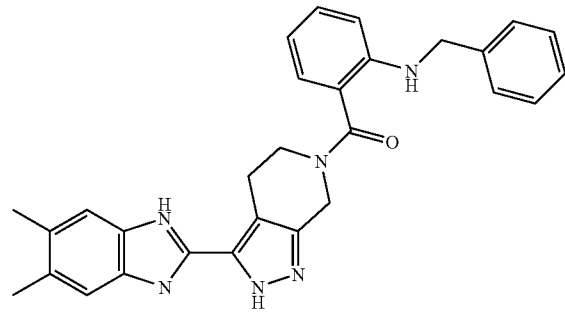
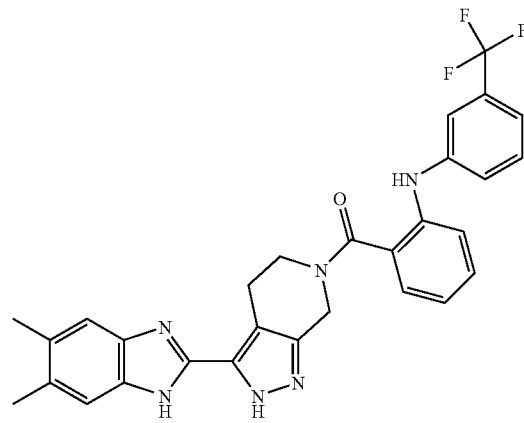
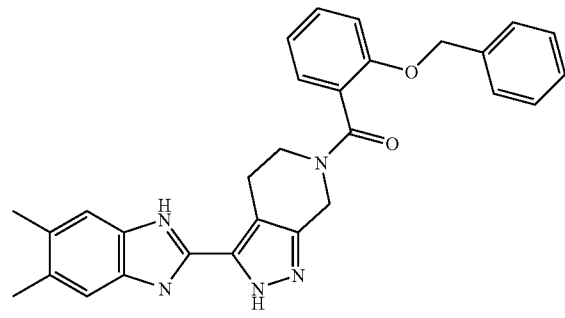
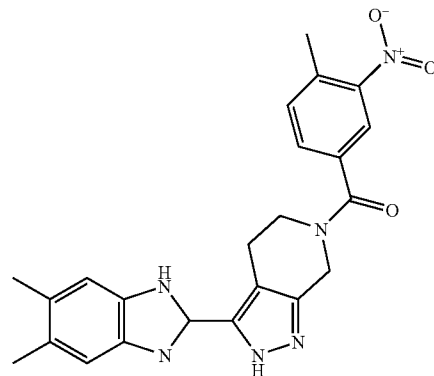
The inhibition of the KDR activity with the compound of the invention is expressed as percentage inhibition of the control activity determined in the absence of compound.

The compound SU5614 (Calbiochem) (1 μM) is included in each plate as inhibition control.

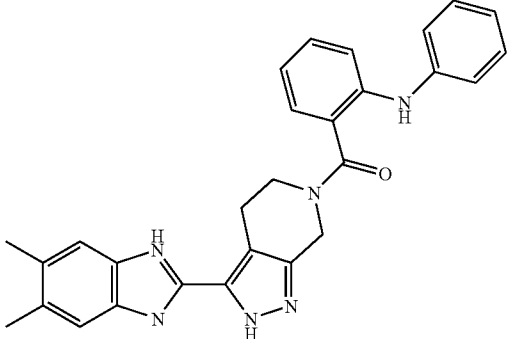
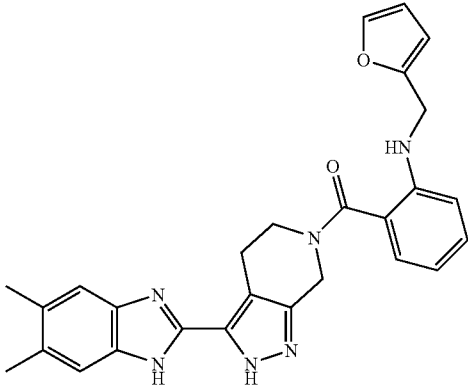
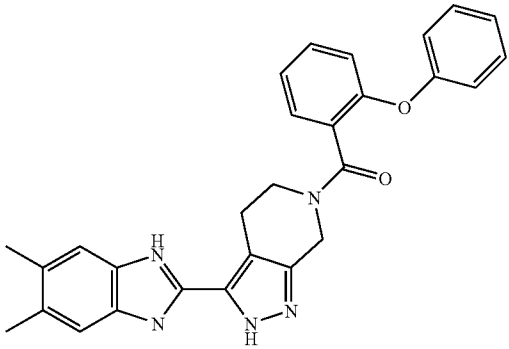
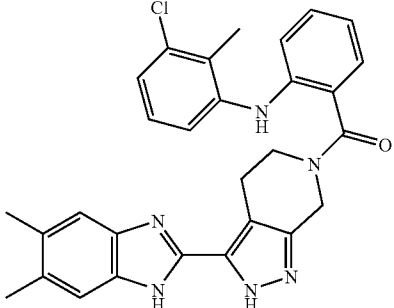
Results:

Chemistry	Tie2		KDR	
	% Inhib at 10 μ M (FRX)		% Inhib at 10 μ M	
	Assay 1	Assay 2	Assay 1	Assay 2
P-31378-112-3	78.7	79.1	59.0	56.5
				
P-31378-112-6	92.7	93.8	71.4	68.0
				
P-31378-112-2	92.6	92.6	98.1	97.4
				

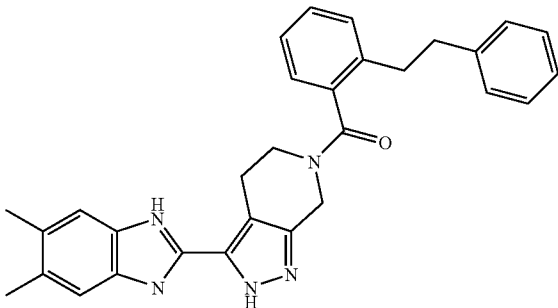
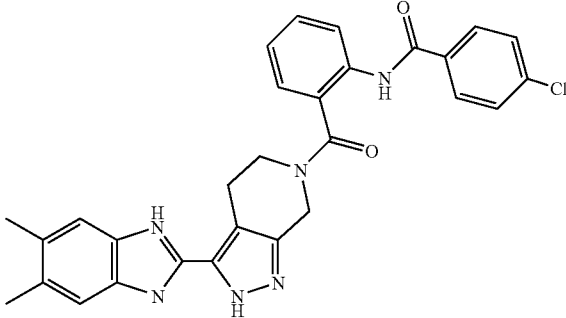
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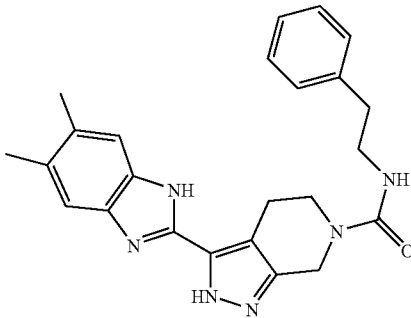
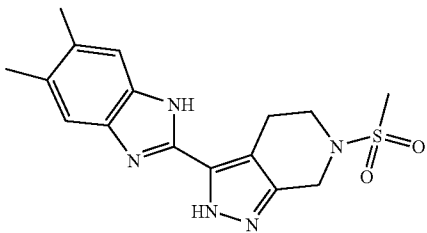
Chemistry	Tie2 % Inhib at 10 μ M (FRX)		KDR % Inhib at 10 μ M	
	Assay 1	Assay 2	Assay 1	Assay 2
P-31378-112-8	87.8	93.3	86.8	89.0
				
P-31378-112-4	83.1	87.2	56.2	50.1
				
P-31378-112-9	82.6	85.9	53.2	45.1
				
P-31378-112-14	69.7	73.8	19.5	13.0
				

-continued

Chemistry	Tie2 % Inhib at 10 μ M (FRX)		KDR % Inhib at 10 μ M	
	Assay 1	Assay 2	Assay 1	Assay 2
P-31378-112-1	83.1	88.1	96.5	96.7
				
P-31378-112-16	88.7	88.3	90.2	89.1
				
P-31378-112-5	87.1	86.4	94.7	95.4
				
P-31375-112-10	90.6	87.9	42.3	28.7
				

-continued

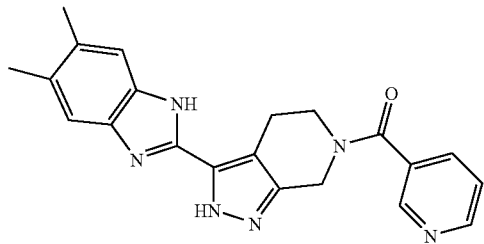
Chemistry	Tie2		KDR	
	% Inhib at 10 μ M (FRX)		% Inhib at 10 μ M	
	Assay 1	Assay 2	Assay 1	Assay 2
P-31378-112-7	92.7	92.0	68.6	64.3
				
P-31378-112-15	80.1	83.8	75.5	77.4
				

Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
	77.20	
Chemistry 2	78.10	
		
Chemistry 3		

-continued

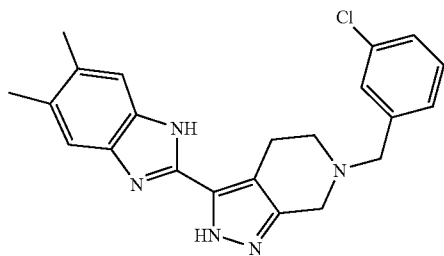
Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
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25.40



Chemistry 4

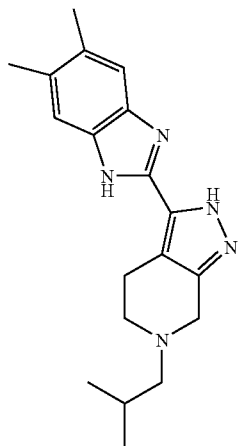
88.80



Chemistry 5

2.10

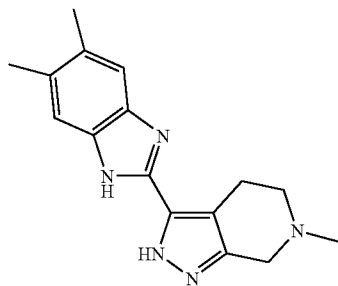
41.2



Chemistry 6

12.15

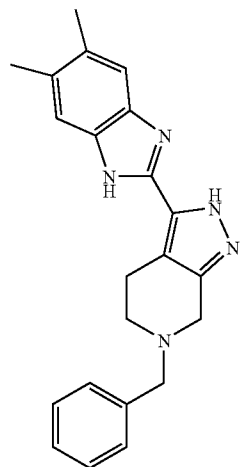
48.6



Chemistry 7

-continued

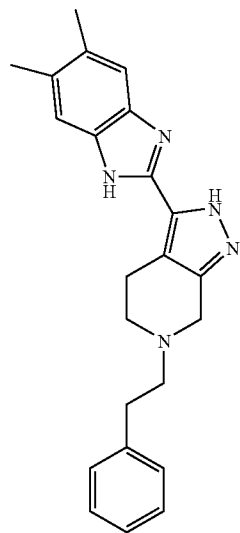
Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
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85.45

64.3

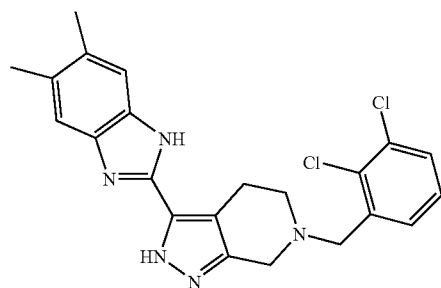
Chemistry 8



15.45

56.7

Chemistry 9

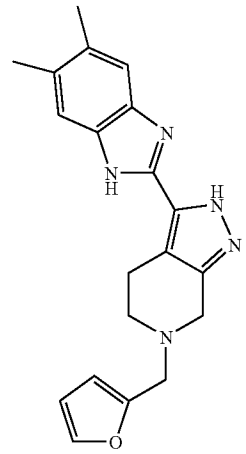
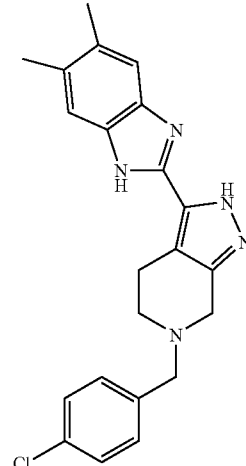
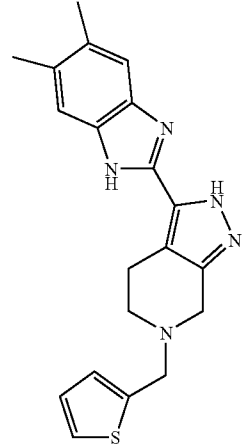


79.55

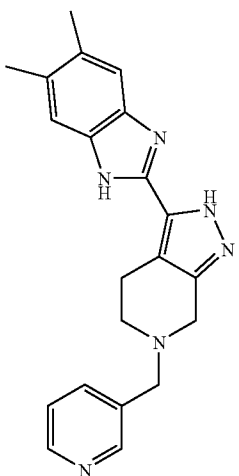
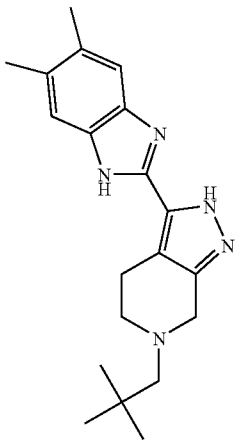
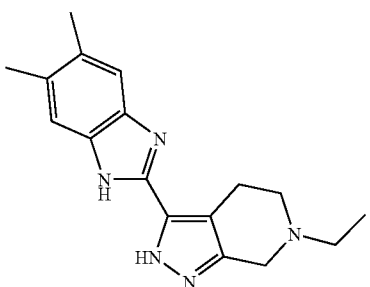
83.9

Chemistry 10

-continued

Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
	70.35	66.1
Chemistry 11	69.05	60.3
		
Chemistry 12	84.50	41.5
		
Chemistry 13		

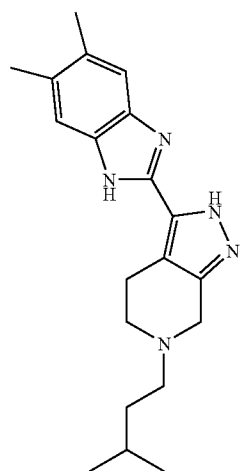
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Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
	14.85	50.5
Chemistry 14		
	39.30	69.4
Chemistry 15		
	-5.75	36.4

Chemistry 16

-continued

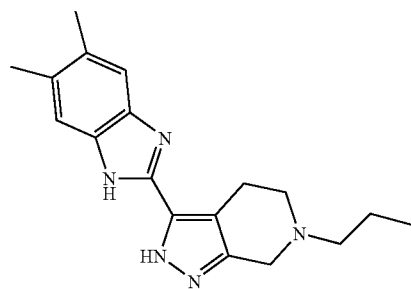
Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
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-2.90

50.7

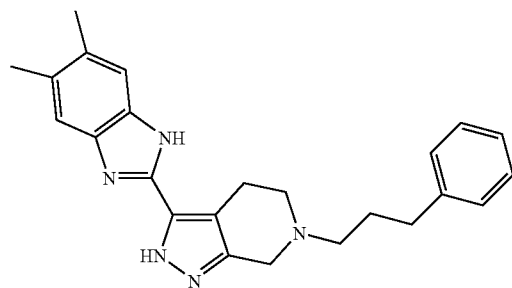
Chemistry 17



-3.70

55.0

Chemistry 18

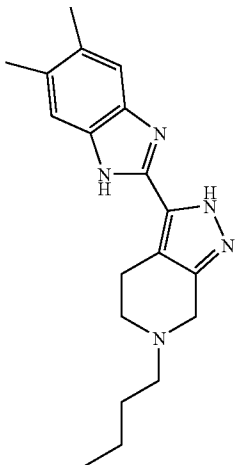
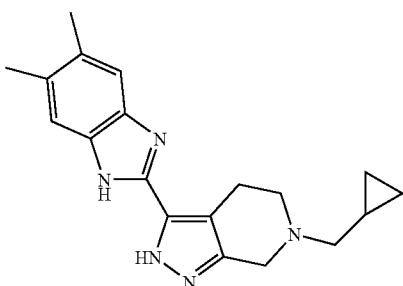
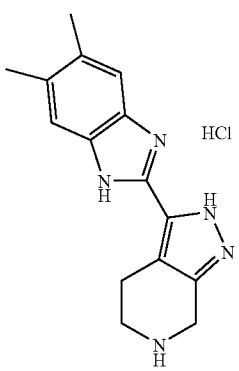
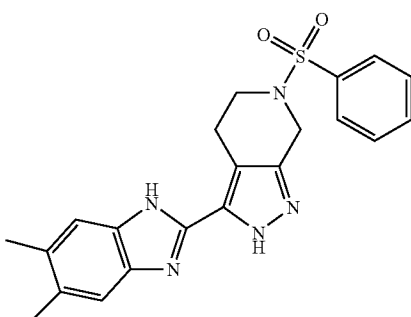


17.90

68.1

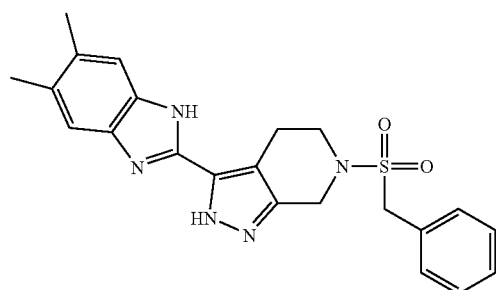
Chemistry 19

-continued

Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
	1.65	47.6
Chemistry 20		
	1.85	33.0
Chemistry 21		
	3.65	24.9
Chemistry 22		
	48	92.5
Chemistry 23		

-continued

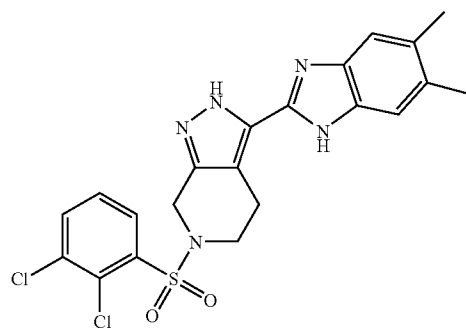
Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
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70.75

91.5

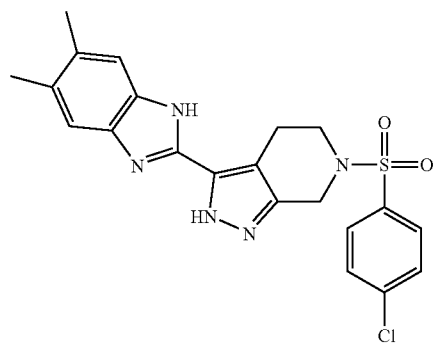
Chemistry 24



31.85

89.1

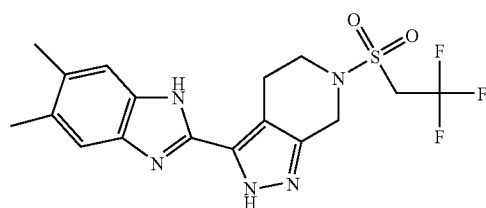
Chemistry 25



27.75

89.1

Chemistry 26



22.95

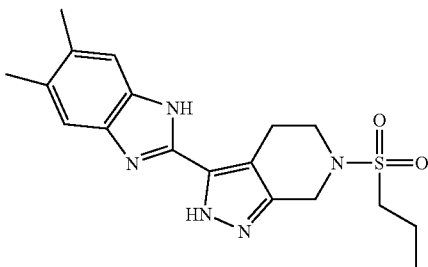
65.4

Chemistry 27

	KDR % Inhib.	Tie2 % Inhib.
Chemistry	10 μ M	10 μ M



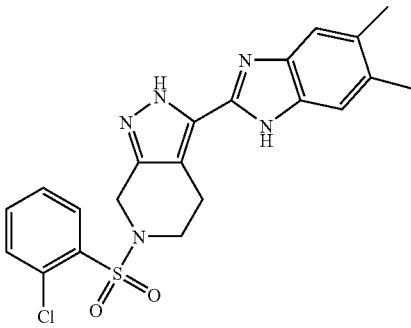
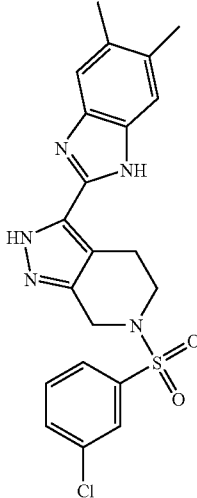
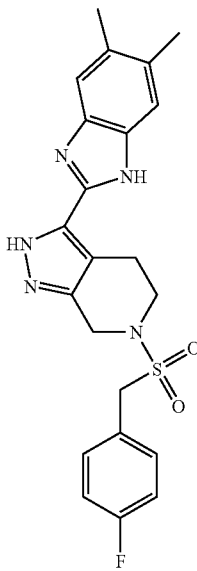
47.5



44.2

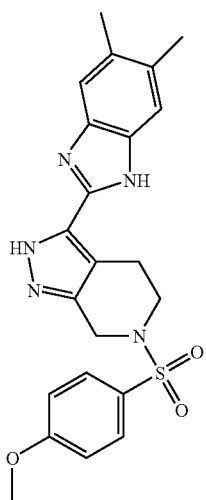


-continued

Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
 Chemistry 31	45.70	93.2
 Chemistry 32	46.45	91.5
 Chemistry 33	57.70	95.9

-continued

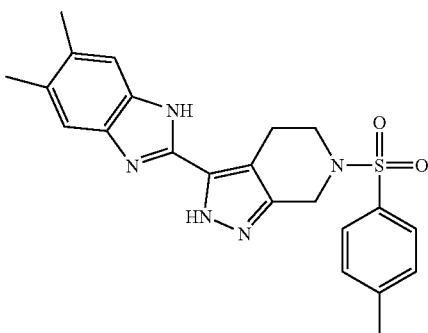
Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
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18.15

84.7

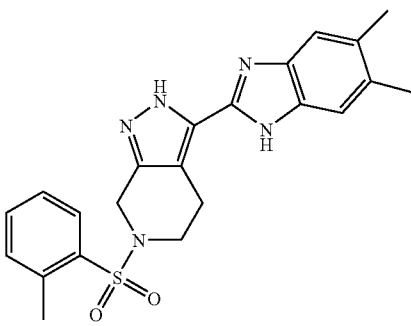
Chemistry 34



27.40

88.8

Chemistry 35



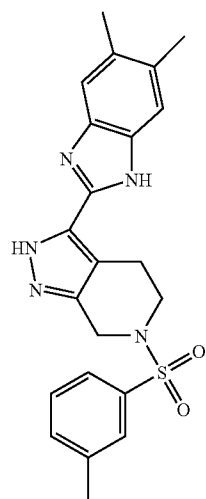
49.40

90.8

Chemistry 36

-continued

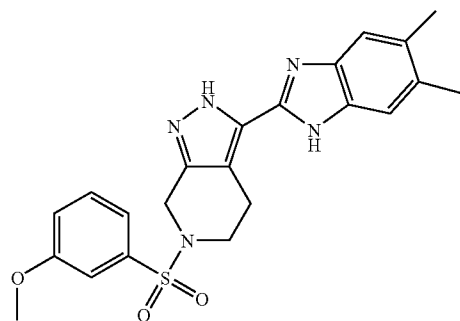
Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
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41.20

88.3

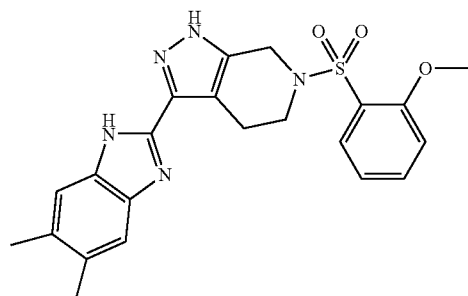
Chemistry 37



20.85

84.6

Chemistry 38

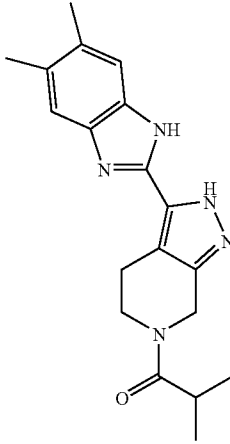
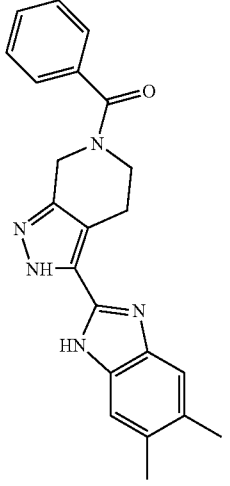
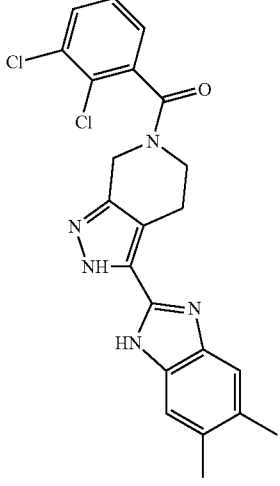


30.90

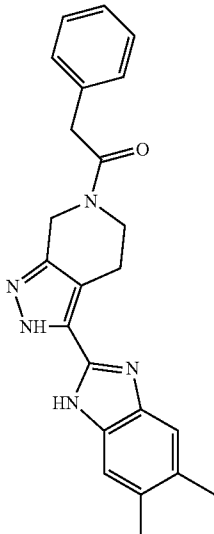
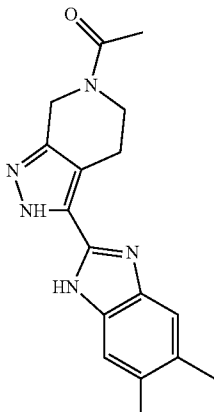
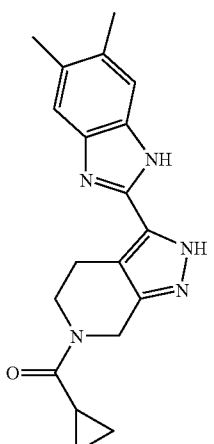
97.9

Chemistry 39

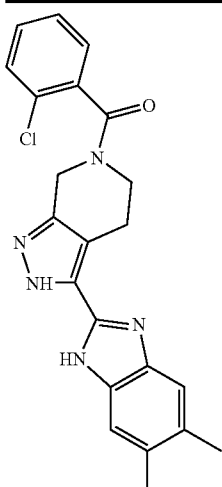
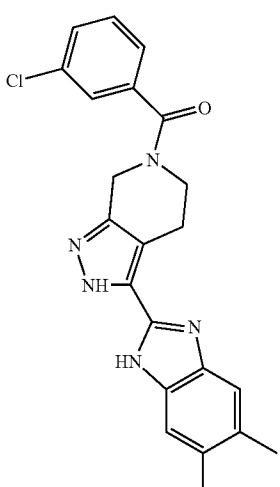
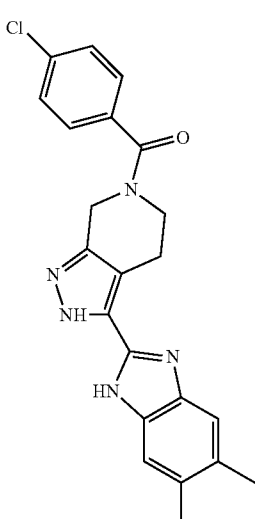
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Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
	14.40	83.4
Chemistry 40		
	72.50	86.3
Chemistry 41		
	52.65	97.4
Chemistry 42		

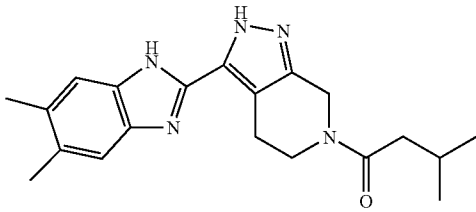
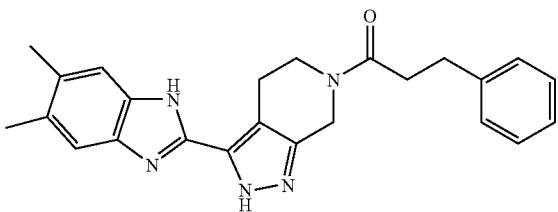
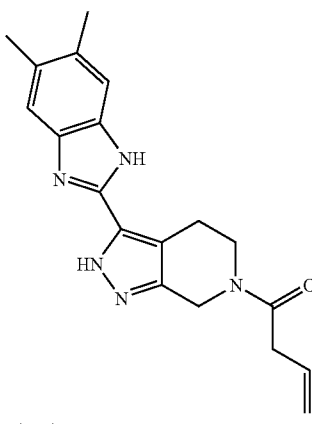
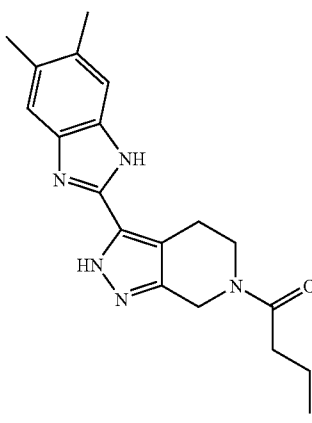
-continued

Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
	10.90	84.4
Chemistry 43		
	41.10	90.8
Chemistry 44		
	33.40	94.1
Chemistry 45		

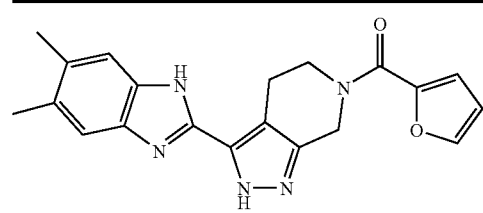
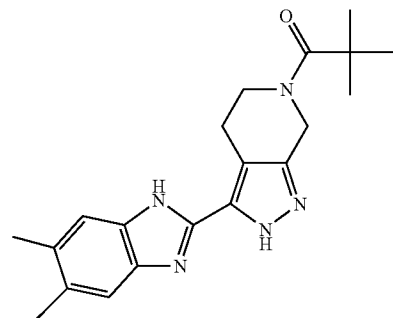
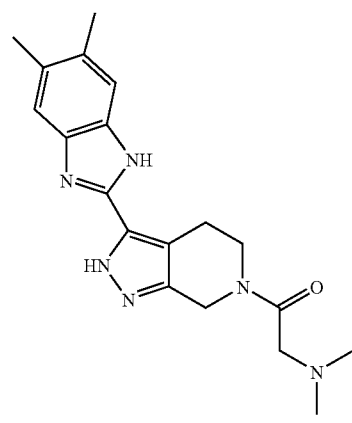
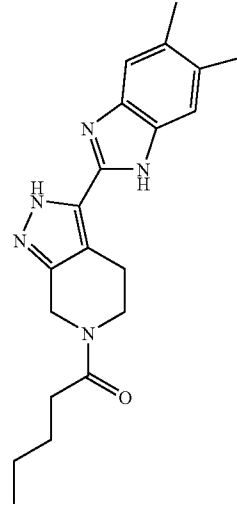
-continued

Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
	73.05	96.7
Chemistry 46	78.55	87.7
		
Chemistry 47	41.95	83.8
		
Chemistry 48		

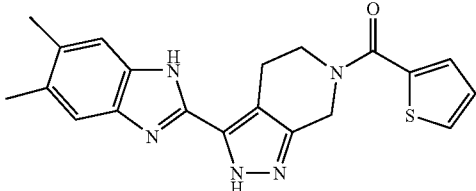
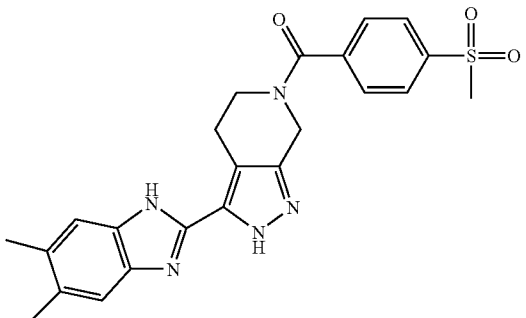
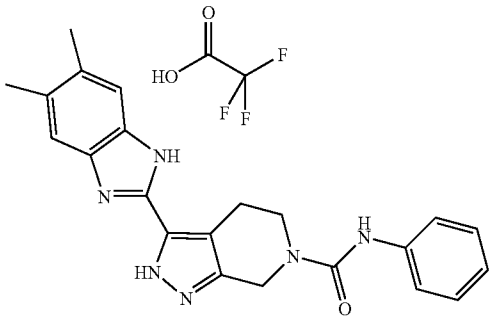
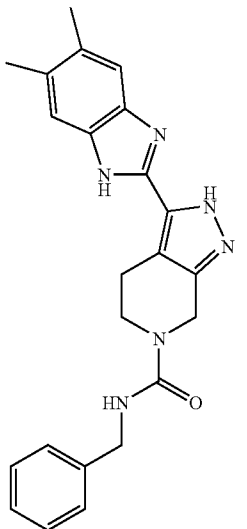
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Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
	12.20	84.8
Chemistry 49		
	74.75	82.4
Chemistry 50		
	38.70	72.9
Chemistry 51		
	29.35	89.3
Chemistry 52		

-continued

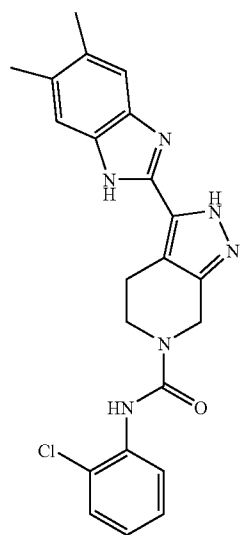
Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
	74.55	92.7
Chemistry 53		
	11.25	81.3
Chemistry 54		
	15.95	65.4
Chemistry 55		
	46.65	92.5
Chemistry 56		

-continued

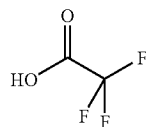
Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
	75.15	94.6
Chemistry 57		
	27.90	82.3
Chemistry 58		
	17.6	33.2
Chemistry 59		
	33.55	64.85
Chemistry 60		

-continued

Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
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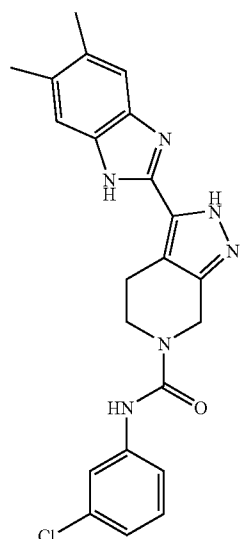


Chemistry 61



12.7

3.75

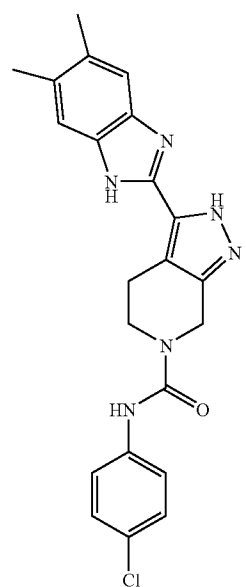


Chemistry 62

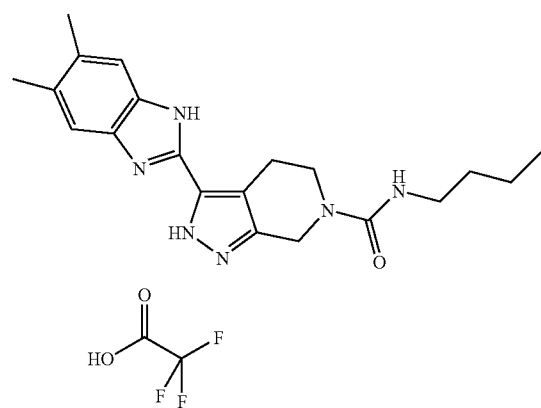
12.85

21

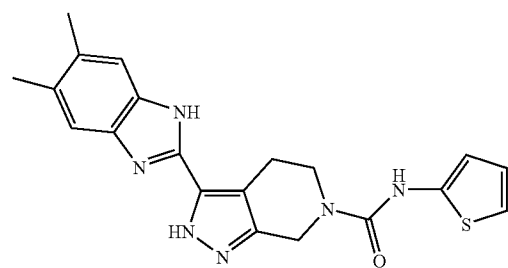
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Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
	-0.3	23.75

Chemistry 63

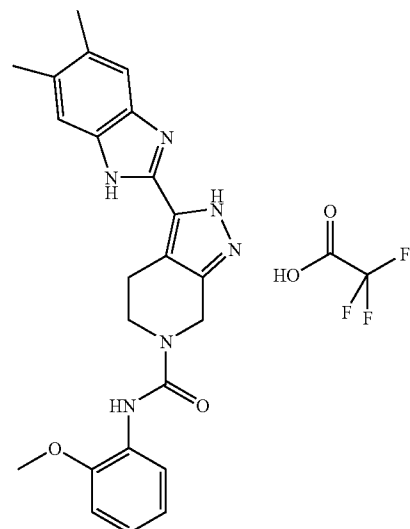
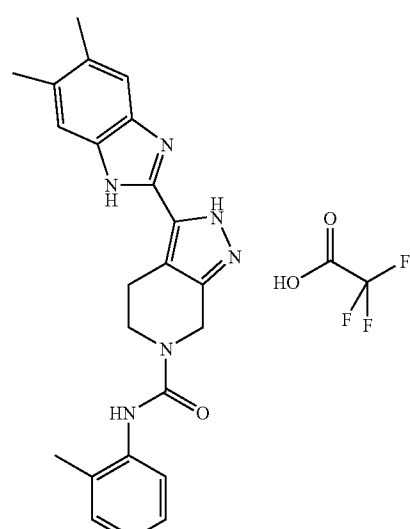
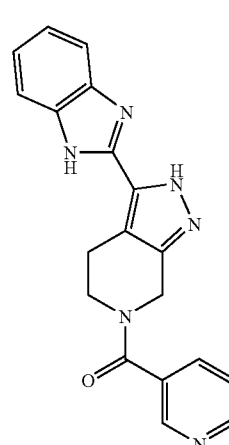
	18	38.5
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Chemistry 64

	63.3	85.9
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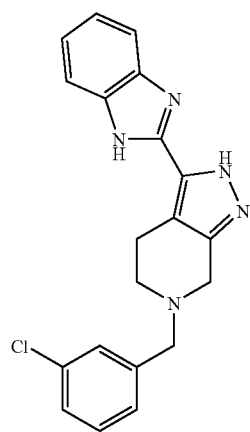
Chemistry 65

-continued

Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
	8.1	18.05
Chemistry 67		
	19.5	19.1
Chemistry 68		
	18.55	59.3
Chemistry 69		

-continued

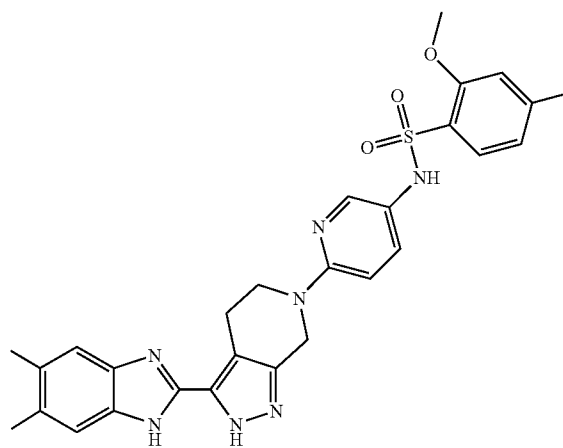
Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
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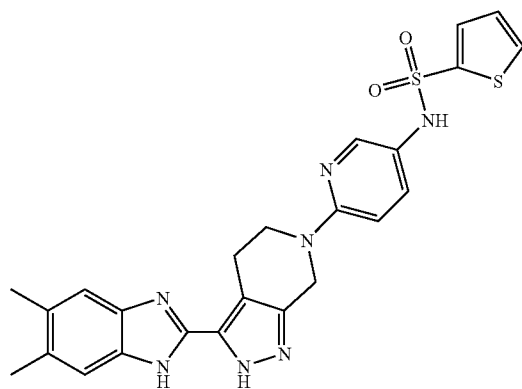
92.1

65.5

Chemistry 70

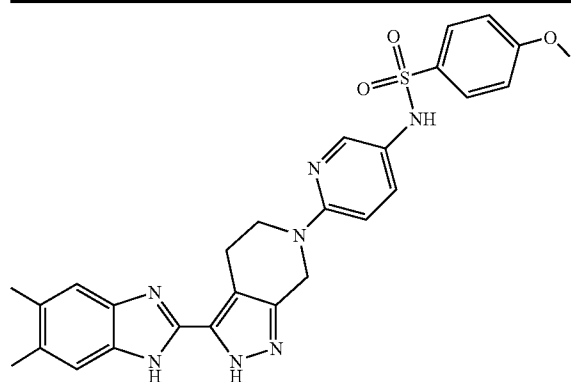
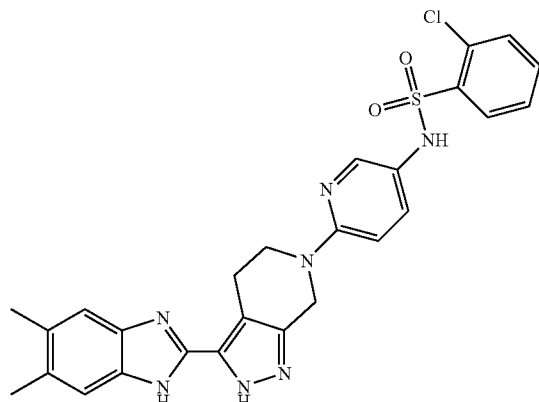


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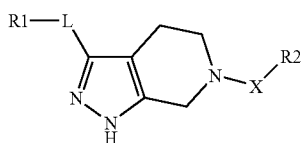
100

-continued

Chemistry	KDR % Inhib. 10 μ M	Tie2 % Inhib. 10 μ M
		99
		100

What is claimed is:

1. A compound of formula (I), including its tautomers:



wherein:

L is chosen from CH₂, CO, SO₂, COO, NHCO, NHSO₂, and NHCH₂;X is chosen from a bond, CH₂, CO, SO₂, CONH and COO;

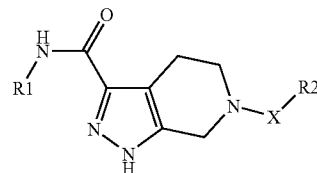
R1 is OH or H, or is chosen from alkyl, cycloalkyl, heterocycle, aryl, heteroaryl, all of which is optionally substituted, and, when X is a bond, then R1 may also be halogen;

R2 is H or is chosen from alkyl, alkylene, cycloalkyl, heterocycle, aryl, heteroaryl, all of which is optionally substituted;

and in that the optional substituents are chosen independently from R3, O—R3, halogen, NO₂, SO₂—R3, CO—R3, SO₂NH—R3, CONH—R3, N—(R3)₂, NHCO—R3, NHSO₂—R3, NHCONH—R3, NHSO₂NH—R3, OCO—R3, COO—R3, OSO₂—R3, SO₂O—R3, OCONH—R3 and OSO₂NH—R3,wherein R3 is H or is chosen independently from alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, heterocycle, all of which is optionally substituted with halogen, aryl, heteroaryl, R4, OR4 or N(R4)₂, wherein each R4 is chosen independently from H, C₁-C₄ alkyl and halogenated C₁-C₄ alkyl, or

a racemate, a stereoisomer, an enantiomer, or a mixture in any combination thereof, or a pharmaceutically acceptable salt thereof.

2. The compound as set forth in claim 1, which is of the formula (III):



and its tautomers, wherein:

X is chosen from a bond, CH₂, CO, SO₂, CONH and COO;

R1 is chosen from alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, all of which is optionally substituted;

R2 is H or is chosen from alkyl, alkylene, cycloalkyl, heterocycle, aryl, heteroaryl, all of which is optionally substituted;

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and in that the optional substituents are chosen independently from R3, O—R3, halogen, NO₂, SO₂—R3, CO—R3, SO₂NH—R3, CONH—R3, N—(R3)₂, NH—CO—R3, NH—SO₂—R3, NHCONH—R3, NHSO₂NH—R3, OCO—R3, COO—R3, OSO₂—R3, SO₂O—R3, OCONH—R3 and OSO₂NH—R3, wherein each R3 is H or is chosen independently from alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, heterocycle, all of which is optionally substituted with halogen, aryl, heteroaryl, OR4 or N(R4)₂, and wherein each R4 is chosen independently from H and C₁-C₄ alkyl, or

a racemate, a stereoisomer, an enantiomer, or a mixture in any combination thereof, or a pharmaceutically acceptable salt thereof.

3. The compound as set forth in claim 2, wherein R1 is heteroaryl, which is optionally substituted.

4. The compound as set forth in claim 1, wherein R1-L is R1-NH—CO.

5. The compound as set forth in claim 4, wherein R1 is H.

6. The compound as set forth in claim 4, wherein X is a bond, and R2 is chosen from substituted aryl and substituted heteroaryl.

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7. The compound as set forth in claim 5, wherein X is a bond, and R2 is chosen from substituted aryl and substituted heteroaryl.

8. The compound as set forth in claim 7, wherein R2 is chosen from:

aryl substituted with NHSO₂—R3 or NHCONH—R3, and heteroaryl substituted with NHSO₂—R3 or NHCONH—R3,

wherein each R3 is H or is chosen independently from alkyl, cycloalkyl, alkenyl, aryl, heteroaryl, heterocycle, all of which is optionally substituted with halogen, aryl, heteroaryl, OR4 or N(R4)₂, and wherein each R4 is chosen independently from H, C₁-C₄ alkyl and halogenated C₁-C₄ alkyl.

9. The compound as set forth in claim 8, wherein aryl is phenyl, and heteroaryl is chosen from pyridyl and pyrimidyl.

10. The compound as set forth in claim 8, wherein R3 is chosen from substituted aryl and substituted heteroaryl.

11. The compound as set forth in claim 10, wherein R3 is substituted with a substituent selected from the group consisting of halogen, R4, OR4 and N(R4)₂, wherein each R4 is chosen independently from H, C₁-C₄ alkyl and halogenated C₁-C₄ alkyl.

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