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Artigo

A Compendium of Tyrosine-kinase Inhibitors: Powerful and Efficient Drugs against Cancer

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Um Compêndio de Inibidores de Tirosina Quinase: Fármacos Poderosos e Eficientes contra o Câncer

Resumo: Os inibidores das enzimas tirosina quinases (ITQs), também conhecidos como "tinibs", têm sido usados como fármacos mais modernos e eficazes no tratamento de diversos tipos de câncer. Este artigo é um compêndio de uma grande série de inibidores de tirosina quinase, recentemente aprovados ou que estão em fase de análise pelo FDA, contendo em cada um deles, relatos como: a primeira síntese química, linha de ação contra o câncer, fase clínica em que se encontram e o preço no mercado.

Palavras-chave: Tinibs; tirosina-quinase; quimioterapia; testes clínicos; câncer.

Abstract

The inhibitors of the enzymes tyrosine kinase (ITKs), also known by "tinibs", have been used as the most modern and effective tools in the treatment of several types of cancer. This article is a compilation of a huge series of tyrosine kinase inhibitors, recently approved or under clinical trials, containing in each of them information such as: the first chemical synthesis, the mechanism of action against cancer, clinical trials stage and price in the market.

Keywords: Tinibs; Tyrosine-kinase; chemotherapy; clinical trials; cancer.

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A Compendium of Tyrosine-kinase Inhibitors: Powerful and Efficient Drugs against Cancer

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1. Introduction

The synthesis of new drug is an important subject of organic chemistry since it allows the construction of molecules with various levels of complexity.[1] In order to obtain new prototypes or drug candidates to be introduced in the pharmaceutical market it is necessary to accomplish several steps to get to target compound. Initially, there is a literature search to find the biological target, which allows us to promote rational design, perform the synthesis and find promising new prototype compounds. Afterward, is necessary to carry out studies to know the proper interactions with biological receptors and other active sites, as well as the elucidation of the relationships between their chemical structures and the biological activities.[2]

It is critical that these drug candidates have their mechanisms of action elucidated by experiments in cell cultures, enzymatic tests and human models. The main objective of this phase is to verify how this substance behaves in an organism. In this phase, several protocols are followed in experimental animals and frequently some of them are canceled because they are unsatisfactory.[3]

When these results are shown to be promising, it is therefore necessary to proceed the clinical trials in humans. This stage is composed of three successive phases. Only after all those phases are completed the drug may be released to the market.

The phase 1 is based on testing the safety of the drug for the first time, especially in order to define dosage and side-effects. At this stage, small groups of 20 to 30 healthy volunteers are involved for a minimum of six

months of testing. After ensuring the safety of the drug candidate, it goes to Phase 2, where the objective is to evaluate the efficacy and safety of the dosage established in the previous phase in a larger number of people, from 70 to 100 volunteers, for a period of testing of nearly one year.[3]

When the drug enters Stage 3, with evidence of drug efficacy, the drug candidate is compared to the best therapy available on the market for the target disease. Usually 100 to 1,000 volunteers are involved, and last phase lasts approximately three years. Generally, the studies of this phase are randomized, that is, the patients are divided into two groups: the control group, which receives the standard treatment and the investigational group, which receives the new treatment. The division between the groups is done in the form of a lottery performed in double or triple blind.[3]

Cancer is the generic name for defining a group of diseases that have in common the disordered growth of abnormal cells that invade tissues and organs and can spread to other parts of the body.

The cancer disease in all of its forms has been poorly understood. It is feared by the population since it can be fatal in most of the cases. The causes of this pathology are varied, however, it is estimated that 80-90% of cancers are related to the continuous exposure to environmental risk factors such as: infectious organisms, smoking, alcoholism, eating habits, medications, occupational factors, chemical agents and radiation.

Treatment varies according to the type of cancer, and, in many cases, requires the association between different therapeutic resources such as radiation therapy, chemotherapy, surgery or even transplantation. The development of new chemotherapeutics has improved the survival of patients, but there is still a need for the development of new drugs that are more specific, efficient and with fewer side effects.

This disease represents a public health concern due to the high incidence and mortality rate worldwide. According to the World Health Organization (WHO) it is estimated that by 2030, 21.4 million new cases of cancer will occur.

The protein tyrosine-kinases (PTK's) are responsible for the phosphorylation and modulation of the enzymatic activity being related to fundamental processes, such as the cell cycle, proliferation, differentiation, mobility and cell survival or death. [4]

PTK's are classified into protein kinase receptors (RTKs), such as insulin for example, and non-receptors (NRTKs) which are intracellular components, are Src, Jak, Abl, Fak, Fps, Csk, Syk, Pyk2, and Btk. RTKs play an important role not only as key regulators of normal cellular processes, but also in the development and progression of various types of cancer.[4]

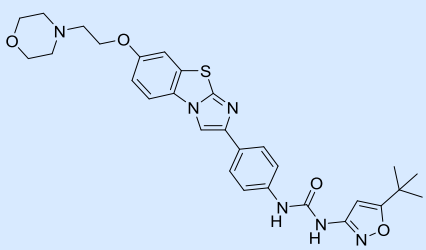
Generally, the inhibitors of the enzymes tyrosine kinase (ITK's), also known by "tinibs", compete for the ATP binding site at the catalytic site of various oncogenic tyrosine kinases, have a safe therapeutic profile, and can be combined with other chemotherapies or radiation.[4]

There are currently no fully efficient therapies, but research regarding tyrosine kinase inhibitors (ITK's), targeting the neoangiogenesis of cancer, has shown good results, especially for progression-free survival.[5]

This paper shows a compilation, up to 2016, of a huge series of tyrosine-kinase inhibitors, recently (or nearly) approved, containing in each of them reports such as: reference to the first chemical synthesis, the mode of action against cancer, the stage of the clinical trials and price in the market.

2. Tinibs Abstracts

AC220 (Quizartinib)



IUPAC Name: 1-(5-tert-butyl-1,2-oxazol-3-yl)-3-[4-[6-(2-morpholin-4-ylethoxy)imidazo[2,1-*b*][1,3]benzothiazol-2-yl]phenyl]urea.

CAS: 950769-58-1.

First Report: Bhagwat *et al.* from Ambit Biosciences Corporation, in 2007.[6]

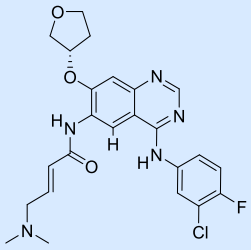
Activity: Quizartinib (AC220) is a small molecule receptor tyrosine kinase inhibitor FLT3, also known as CD135 which it has an half maximal inhibitory concentration (IC_{50}) of 0.56 nM, that is currently under development for the treatment of acute myeloid leukaemia.[7,8]

Clinical Trials: Stage 3.[9]

Storage / Stability: Stable if stored at -20°C.[10]

Prices: 5 mg - 230 EUR, 25 mg - 920 EUR, 100 mg - 2760 EUR.[11]

Afatinib



IUPAC Name: (*E*)-*N*-[4-(3-chloro-4-fluoroanilino)-7-[(3*S*)-oxolan-3-yl]oxyquinazolin-6-yl]-4-(dimethylamino)but-2-enamide.

CAS: 850140-72-6.

First Report: Soyka *et al.* from Boehringer Ingelheim International GmbH, in 2005.[12]

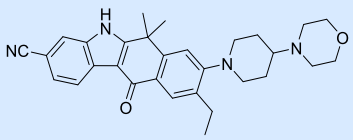
Activity: Afatinib is a tyrosine kinase inhibitor that irreversibly inhibits the activity of human epidermal growth factor receptor 2 (Her2) and epidermal growth factor receptor (EGFR) kinases. It is a candidate drug against non-small cell lung (NSCL) carcinoma, glioma, and cancers of the breast, prostate, head and neck.[13-15]

Clinical Trials: Stage 4.[16]

Storage / Stability: Stable if stored Store at -20 °C, keeping the container tightly closed.[17]

Prices: 5 mg - 85 EUR, 25 mg - 340 EUR, 100 mg - 1020 EUR.[18]

Alectinib



IUPAC Name: 9-ethyl-6,6-dimethyl-8-(4-morpholin-4-ylpiperidin-1-yl)-11-oxo-5*H*-benzo[*b*]carbazole-3-carbonitrile.

CAS: 1256589-74-8.

First Report: Kinoshita *et al.* from Chugai Pharmaceutical Co., Ltd., in 2010.[19]

Activity: Alectinib is potent, selective, and orally available ALK inhibitor (IC_{50} value of 1.9 nM) showing preferential antitumour activity against cancers with gene alterations of ALK, such as nonsmall cell lung cancer (NSCLC) cells expressing EML4-ALK fusion and anaplastic large-cell

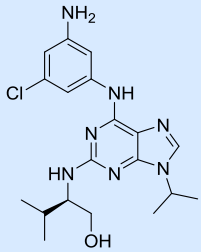
lymphoma (ALCL) cells expressing NPM-ALK fusion *in vitro* and *in vivo*. It inhibited ALK L1196M, which corresponds to the gatekeeper mutation conferring common resistance to kinase inhibitors and blocked EML4-ALK L1196M-driven cell growth.[20,21]

Clinical Trials: Stage 3.[22]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[23]

Prices: 5 mg - 120 EUR, 25 mg - 480 EUR, 100 mg - 1440 EUR.[24]

Aminopurvalanol



IUPAC Name: (2*R*)-2-[[6-(3-amino-5-chloroanilino)-9-propan-2-ylpurin-2-yl]amino]-3-methylbutan-1-ol.

CAS: 220792-57-4.

First Report: Rosania *et al.* in 1999.[25]

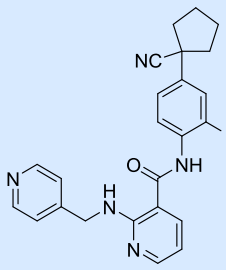
Activity: Aminopurvalanol is a potent cyclin-dependent kinase inhibitor; it has IC_{50} values of 33 nM for CDK1/cyclin B, 28 nM for CDK2/cyclin E, and 20 nM for CDK5/p35. Aminopurvalanol-treated cells acquired phenotypic characteristics of differentiated macrophages and underwent cell cycle with 4N DNA content. Affinity chromatography and biochemical reconstitution experiments indicated that it targets cyclin-dependent kinase 1 (CDK1). This compound showed to be capable of the decreasing of the basal LNCaP human prostate cancer cell proliferation at 3 nM.[26-28]

Clinical Trials: No studies in the moment.[29]

Storage / Stability: Stable if stored at -20 °C, Keeping the container tightly closed in a dry and well-ventilated place.[30]

Prices: 5 mg - 98 EUR, 25 mg - 392 EUR, 100 mg - 1176 EUR.[31]

Apatinib



IUPAC Name: *N*-[4-(1-cyanocyclopentyl)phenyl]-2-(pyridin-4-ylmethylamino)pyridine-3-carboxamide.

CAS: 1218779-75-9.

First Report: Yuan *et al.* from Jiangsu Hengrui Medicine, in 2004.[32]

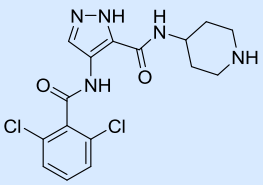
Activity: Apatinib is an orally bioavailable tyrosine kinase inhibitor that selectively inhibits the vascular endothelial growth factor receptor-2 (VEGFR2/KDR) with IC_{50} value of 2.4 nM. Inhibition of this important pro-angiogenic receptor blocks VEGF-mediated endothelial cell migration and proliferation that in turn reduces new blood vessel formation in tumour tissue. It is being developed as a potential targeted treatment for metastatic gastric carcinoma, metastatic breast cancer and advanced hepatocellular carcinoma.[33,34]

Clinical Trials: Stage 4.[35]

Storage / Stability: Stable up to one week if stored at 4°C or six months if stored at -20°C.[36]

Prices: 5 mg - 165 EUR, 25 mg - 660 EUR, 100 mg - 1980 EUR.[37]

AT7519



IUPAC Name: 4-[(2,6-dichlorobenzoyl)amino]-*N*-piperidin-4-yl-1*H*-pyrazole-5-carboxamide.

CAS: 844442-38-2.

First Report: Astex Technology Ltd., in 2005.[38]

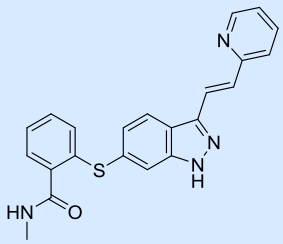
Activity: AT7519 is a potent inhibitor of several cyclin-dependent kinases (CDKs) that showed potent antiproliferative activity (40-940 nmol/L) in a panel of human tumour cell lines. Short-term treatments inhibited phosphorylation of the transcriptional marker RNA polymerase II and caused downregulation of the antiapoptotic protein MCL-1, without affecting the abundance of XIAP or BCL-2. The reduced abundance of the MCL-1 protein level was linked to an increase in cleaved poly(ADP-ribose) polymerase. The mechanism of action was shown to be consistent with the inhibition of CDK1, CDK2 and CDK9 in tumour cell lines.[39-42] It is now under clinical trials as a potential targeted treatment for metastatic solid neoplasm, lymphoma and chronic lymphocytic leukaemia.[43]

Clinical Trials: Stage 2 completed.[44]

Storage / Stability: Stable if stored Store at -20°C.[45]

Prices: 5 mg - 140 EUR, 25 mg - 560 EUR, 100 mg - 1680 EUR.[46]

Axitinib



IUPAC Name: *N*-methyl-2-[[3-[(*E*)-2-pyridin-2-ylethenyl]-1*H*-indazol-6-yl]sulfanyl]benzamide.

CAS: 319460-85-0.

First Report: Kania *et al*. from Agouron Pharmaceuticals Inc., in 2001.[47]

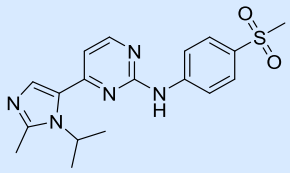
Activity: Axitinib is a potent and selective oral inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3. It inhibits cellular autophosphorylation of VEGF receptors (VEGFR) with 100-300 picomolar IC_{50} values. Counterscreening across multiple kinase and protein panels showed that it is selective for VEGFRs. Axitinib blocks VEGF-mediated endothelial cell survival, tube formation, and downstream signaling through endothelial nitric oxide synthase, AKT and extracellular signal-regulated kinase. It was approved for use in patients with renal cell carcinoma that had failed to respond to a previous treatment.[48,49]

Clinical Trials: Stage 4.[50]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[51]

Prices: 25 mg - 52 EUR, 100 mg - 156 EUR, 250 mg - 312 EUR.[52]

AZD5438



IUPAC Name: 4-(2-methyl-3-propan-2-ylimidazol-4-yl)-*N*-(4-methylsulfonylphenyl)pyrimidin-2-amine.

CAS: 602306-29-6.

First Report: Wheeler *et al*. in 2003.[53]

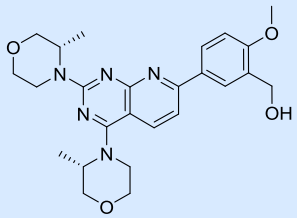
Activity: AZD5438 is a potent inhibitor of cyclin-dependent kinases (CDKs) 1, 2 and 9 (IC_{50}, 16. 6, and 20 nmol/L, respectively). It exhibits significant *in vitro* antiproliferative activity in human tumour cell lines (with IC_{50} values ranging from 0.2-1.7 micromol/L), inhibiting the phosphorylation of CDK substrates including pRb, nucleolin, protein phosphatase 1a, and the carboxy-termiinal domain of RNA polymerase II. n this way, it blocks cell cycle progression in the G(2)-M, S and G(1) phases. It is currently undergoing clinical trials as an anticancer drug, namely, advanced solid malignancies like as lung, colorectal, breast, prostate, and hematologic tumours.[54]

Clinical Trials: Stage 1 completed.[55]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[56]

Prices: 5 mg - 88 EUR, 25 mg - 352 EUR, 100 mg - 1056 EUR.[57]

AZD8055



IUPAC Name: [5-[2,4-bis[(3*S*)-3-methylmorpholin-4-yl]pyrido[2,3-*d*]pyrimidin-7-yl]-2-methoxyphenyl]methanol.

CAS: 1009298-09-2.

First Report: Chresta *et al*. in 2010.[58]

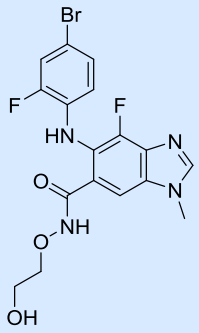
Activity: AZD8055 is a potent, selective, and orally bioavailable mammalian target of rapamycin kinase inhibitor with *in vitro* and *in vivo* antitumour activity. It is an ATP-competitive inhibitor of mTOR kinase activity with an IC_{50} of 0.8 nmol/L. AZD8055 showed excellent selectivity (approximately 1,000-fold) against all class I phosphatidylinositol 3-kinase (PI3K) isoforms and other members of the PI3K-like kinase family. Moreover, it exhibited no significant activity against a panel of 260 kinases at concentrations of up to 10 micromol/L. AZD8055 inhibits the phosphorylation of mTORC1 substrates p70S6K and 4E-BP1 as well as that of the mTORC2 substrate AKT and downstream proteins.[58]

Clinical Trials: Stage 1 completed.[59]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[60]

Prices: 5 mg - 74 EUR, 25 mg - 296 EUR, 100 mg - 888 EUR.[61]

Binimetinib



IUPAC Name: 6-(4-bromo-2-fluoroanilino)-7-fluoro-*N*-(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide.

CAS: 606143-89-9.

First Report: Wallace *et al*. from Array BioPharma, Inc, in 2003.[62]

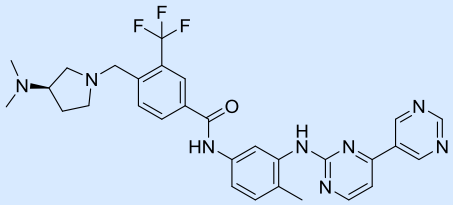
Activity: Binimetinib is a second generation MEK1/2 inhibitor with demonstrated efficacy against BRAF- and RAS-mutant tumours. Binimetinib is an ATP-uncompetitive inhibitor of MEK1/2, with nanomolar activity against purified MEK enzyme (IC_{50} = 12 nM), but without any activity on a kinase panel of 220 enzymes at a dose of 10 µM. It inhibits both basal and induced levels of ERK phosphorylation in numerous cancer cell lines with IC_{50}'s as low as 5 nM. Binimetinib is especially potent at inhibiting the cell proliferation of mutant B-Raf and Ras cell lines such as HT29, Malme-3M, SK-MEL-2, COLO 205, SK-MEL-28 and A375 (IC_{50}s from 30-250 nM).[63,64]

Clinical Trials: Stage 3.[65]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[66]

Prices: 5 mg - 65 EUR, 25 mg - 195 EUR, 100 mg - 585 EUR.[67]

Bafetinib



IUPAC Name: 4-[[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]methyl]-*N*-[4-methyl-3-[(4-pyrimidin-5-ylpyrimidin-2-yl)amino]phenyl]-3-(trifluoromethyl)benzamide.

CAS: 859212-16-1.

First Report: Asaki *et al*. from Nippon Shinyaku Co., Ltd., in 2005.[68]

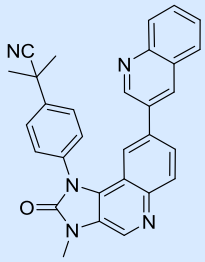
Activity: Bafetinib is an orally available, dual BCR/ABL and Lyn kinase inhibitor that was developed to treat BCR/ABL positive leukaemias such as chronic myelogenous leukaemia (CML) and Philadelphia-positive acute lymphoblastic leukaemia (AML). It is 25- to 55-fold more potent than imatinib *in vitro* and at least 10-fold more potent *in vivo*. Bafetinib inhibits 12 of the 13 most frequent imatinib-resistant BCR-ABL isoforms originating from point mutations, but not that bearing the Thr315Ile mutation.[69,70]

Clinical Trials: Stage 2 completed.[71]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[72]

Prices: 5 mg - 194 EUR, 25 mg - 776 EUR, 100 mg - 2328 EUR.[73]

BEZ235



IUPAC Name: 2-methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-ylimidazo[4,5-c]quinolin-1-yl)phenyl]propanenitrile.

CAS: 915019-65-7.

First Report: Garcia-Echeverria *et al*. from Novartis Ag, in 2006.[74]

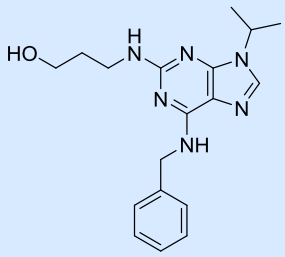
Activity: BEZ235 is an imidazo[4,5-c]quinoline derivative that competitively inhibits the PI3K and mTOR kinases, efficiently and selectively preventing dysfunctional activation of the PI3K pathway and thereby inducing G(1) arrest. It has an IC_{50} value of 4 nM against the p110a isoform of PI3K, 75 nM against the p110b isoform, 7 nM against the p110d isoform and 5 nM against the p110g isoform.[75-77] Currently it is under clinical trials for treatment of castration-resistant prostate cancer, inoperable locally advanced breast cancer and also metastatic breast cancer (MBC).[78]

Clinical Trials: Stage 2 completed.[79]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[80]

Prices: 25 mg - 70 EUR, 100 mg - 210 EUR, 250 mg - 420 EUR.[81]

Bohemine



IUPAC Name: 3-[[6-(benzylamino)-9-propan-2-ylpurin-2-yl]amino]propan-1-ol.

CAS: 189232-42-6.

First Report: Havlicek *et al*. in 1997.[82]

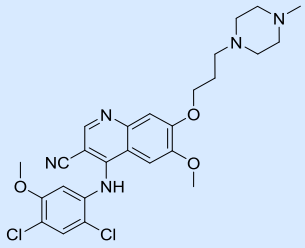
Activity: The 2,6,9-trisubstituted purine derivative bohemine is a synthetic inhibitor of cyclin-dependent kinases that was developed from the original hit olomoucine. Bohemine inhibits CDK1 and CDK2 with IC_{50} values of around 1 microM. It also exhibits antitumour activity *in vitro*, with a mean IC_{50} value of 27 microM, for CEM T-lymphoblastic leukaemia cell line.[83-85]

Clinical Trials: No studies in the moment.[86]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[87]

Prices: 5 mg - 41 EUR, 25 mg - 164 EUR, 100 mg - 492 EUR.[88]

Bosutinib



IUPAC Name: 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile.

CAS: 380843-75-4.

First Report: Boschelli *et al*. from Wyeth Holdings Corporation, in 2003.[89]

Activity: Bosutinib is a dual inhibitor of the SRC and ABL kinases. It inhibits the activating autophosphorylation of BCR-ABL in CML cells and of v-ABL in fibroblasts. At concentrations that inhibit proliferation in CML cells, this inhibits the phosphorylation of

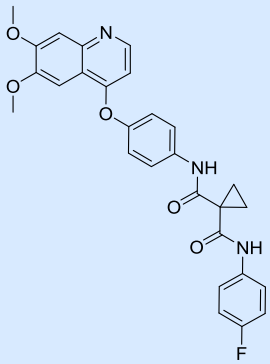
cellular proteins such as STAT5. Preclinical studies demonstrated bosutinib to have strong antiproliferative activity in human and murine CML cell lines. It also performed well in clinical trials, exhibiting high clinical efficacy, good tolerability and low toxicity in imatinib-resistant or -intolerant CML patients.[90-92]

Clinical Trials: Stage 4.[93]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[94]

Prices: 5 mg - 52 EUR, 25 mg - 208 EUR, 100 mg - 624 EUR.[95]

Cabozantinib



IUPAC Name: 1-*N*-[4-(6,7-dimethoxyquinolin-4-yl)oxyphenyl]-1-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

CAS: 849217-68-1.

First Report: Bannen *et al*. from Exelixis, Inc., in 2005.[96]

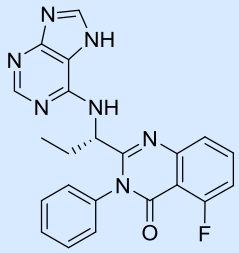
Activity: Cabozantinib is a small molecule kinase inhibitor of MET and VEGFR2, as well as a number of other receptor tyrosine kinases that have also been implicated in tumour pathobiology, including RET, KIT, AXL. Treatment with cabozantinib inhibited MET and VEGFR2 phosphorylation and led to significant reductions in cell invasion.[97,98] It is currently under clinical trials for medullary thyroid cancer, melanoma, prostate cancer, breast cancer, metastatic brain tumour and, also, non-small cell lung cancer treament.[99]

Clinical Trials: Stage 4.[100]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[101]

Prices: 5 mg - 140 EUR, 25 mg - 560 EUR, 100 mg - 1680 EUR.[102]

CAL-101 (Idelalisib)



IUPAC Name: 5-fluoro-3-phenyl-2-[(1*S*)-1-(7*H*-purin-6-ylamino)propyl]quinazolin-4-one.

CAS: 870281-82-6.

First Report: Fowler *et al*. from Icos Corporation, in 2005.[103]

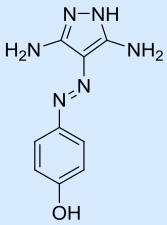
Activity: CAL-101 is a potent inhibitor of PI3 kinase with an IC_{50} of 65 nM for the p110d isoform. It blocks constitutive PI3K signaling which disfavours AKT phosphorylation and promotes apoptosis in primary CLL cells *ex vivo* in a dose- and time-dependent fashion.[104]

Clinical Trials: Stage 4.[105]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[106]

Prices: 5 mg - 74 EUR, 25 mg - 296 EUR, 100 mg - 888 EUR.[107]

CAN508



IUPAC Name: 4-[(3,5-diamino-1*H*-pyrazol-4-yl)hydrazinylidene]cyclohexa-2,5-dien-1-one.

CAS: 140651-18-9.

First Report: Krystof *et al*. in 2006.[108]

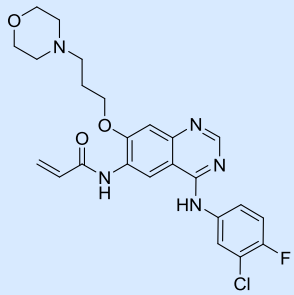
Activity: CAN508 was described as a selective inhibitor of transcriptional cyclin-dependent kinase 9. Its cellular effects include decreased phosphorylation of the C-terminal domain of RNA polymerase II, inhibition of mRNA synthesis, and induction of the tumour suppressor protein p53, all of which are consistent with inhibition of CDK9.[108-112]

Clinical Trials: No studies in the moment.[113]

Storage / Stability: Stable if stored at 4 ºC.[114]

Prices: 5 mg - 52 EUR, 25 mg - 208 EUR, 100 mg - 624 EUR.[115]

Canertinib



IUPAC Name: *N*-[4-(3-chloro-4-fluoroanilino)-7-(3-morpholin-4-ylpropoxy)quinazolin-6-yl]prop-2-enamide.

CAS: 267243-28-7.

First Report: Smaill *et al*. in 2000.[116]

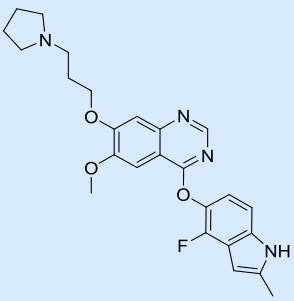
Activity: Canertinib is an orally available irreversible inhibitor of receptor tyrosine kinases that targets EGFRs. It has IC_{50} values of 0.8, 19 and 7 nM for EGFR, HER-2 and ErbB-4, respectively. Canertinib was beány developed as an anticancer drug, but its development was discontinued.[117] Now, it is under clinical evaluation for breast and and NSCL carcinoma treatment.[118]

Clinical Trials: Stage 2 completed.[119]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[120]

Prices: 5 mg - 52 EUR, 25 mg - 208 EUR, 100 mg - 624 EUR.[121]

Cediranib



IUPAC Name: 4-[(4-fluoro-2-methyl-1*H*-indol-5-yl)oxy]-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline.

CAS: 288383-20-0.

First Report: Wheeler *et al*. in 2003.[53]

Activity: Cediranib is a highly potent (IC_{50} < 1 nmol/L) ATP-competitive inhibitor of KDR tyrosine kinase. Concordant with this activity it inhibits VEGF-stimulated proliferation and KDR phosphorylation in human umbilical vein endothelial cells with IC_{50} values of 0.4 and 0.5 nmol/L, respectively. In a fibroblast/endothelial cell co-culture model for vessel sprouting, Cediranib also reduced vessel area, length, and branching at subnanomolar

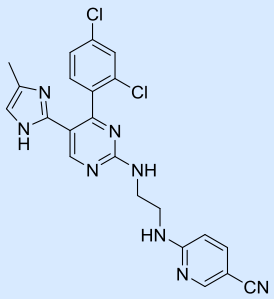
concentrations.[122]

Clinical Trials: Stage 3 completed.[123]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[124]

Prices: 5 mg - 140 EUR, 25 mg - 560 EUR, 100 mg - 1680 EUR.[125]

CHIR-99021



IUPAC Name: 6-[2-[[4-(2,4-dichlorophenyl)-5-(5-methyl-1*H*-imidazol-2-yl)pyrimidin-2-yl]amino]ethylamino]pyridine-3-carbonitrile.

CAS: 252917-06-9.

First Report: MacDougald *et al.* fromChiron Corporation, in 2002.[126]

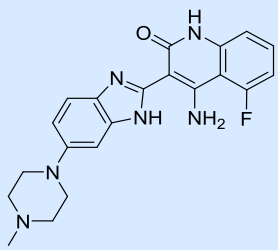
Activity: CHIR-99021 is a glycogen synthase kinase 3b (GSK3b) inhibitor with an IC_{50} value of 7 nM. It does not exhibit cross-reactivity against CDKs and is reported to have a 350-fold selectivity toward GSK3b. CHIR-99021 inhibits cellular proliferation with an IC_{50} value of about 10 microM.[127] It is most effective in solid tumours, such as, pancreatic tumors.[128]

Clinical Trials: No studies in the moment.[129]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[130]

Prices: 5 mg - 194 EUR, 25 mg - 776 EUR, 100 mg - 2328 EUR.[131]

CHIR-258



IUPAC Name: (3*E*)-4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1,3-dihydrobenzimidazol-2-ylidene]quinolin-2-one.

CAS: 915769-50-5.

First Report: Renhowe *et al*. from Chiron Corporation, in 2002.[132]

Activity: CHIR-258 is an orally bioavailable, inhibitor of VEGFR-2, FGFR-1, and PDGFRbeta, with IC_{50} values of <0.1 microM against these kinases. It is in phase III development for the treatment of renal cell carcinoma, and in phase II development as a treatment for advanced breast cancer, relapsed multiple myeloma and urothelial cancer.[133,134]

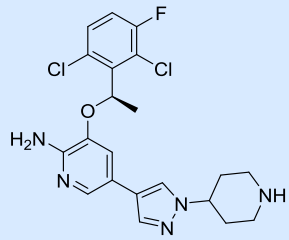
Clinical Trials: Stage 3 completed.[135]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[136]

Prices: 5 mg - 53 EUR, 25 mg - 220 EUR, 100 mg - 660 EUR.[137]

Crizotinib

IUPAC Name: 3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4-yl)pyridin-2-amine.



CAS: 877399-52-5.

First Report: Cui *et al.* from Pfizer Inc., in 2006.[138]

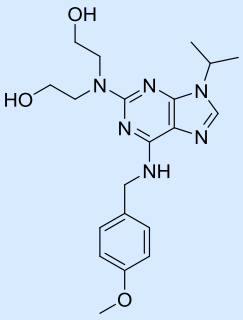
Activity: Crizotinib is an orally bioavailable, ATP-competitive, potent and selective dual inhibitor of the c-MET and ALK kinases. It has been particularly effective against anaplastic large cell lymphoma and non-small cell lung cancer (NSCLC) cell lines harboring ALK translocations that cause the expression of oncogenic ALK fusion proteins.[139-142]

Clinical Trials: Stage 4.[143]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[144]

Prices: 5 mg - 85 EUR, 25 mg - 340 EUR, 100 mg - 1020 EUR.[145]

CVT313



IUPAC Name: 2-[2-hydroxyethyl-[6-[(4-methoxyphenyl)methylamino]-9-propan-2-ylpurin-2-yl]amino]ethanol.

CAS: 199986-75-9.

First Report: Brooks *et al*. in 1997.[146]

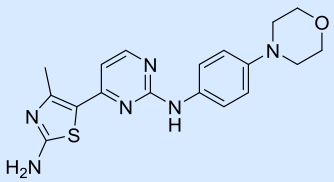
Activity: CVT-313 is a potent and selective CDK2 inhibitor with an IC_{50} of 0.5 microM *in vitro*. Its IC_{50} against CDK4 is 215 microM while those against MAPK, PKA, and PKC are > 1.25 mM; it has no effect on other, non-related ATP-dependent serine/threonine kinases. In cells exposed to CVT-313, hyperphosphorylation of the retinoblastoma gene product was inhibited, and progression through the cell cycle was arrested at the G1/S boundary. CVT-313 also inhibits CDC5L.[147,148]

Clinical Trials: No studies in the moment.[149]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[150]

Prices: 5 mg - 98 EUR, 25 mg - 392 EUR, 100 mg - 1176 EUR.[151]

CYC116



IUPAC Name: 4-methyl-5-[2-(4-morpholin-4-ylanilino)pyrimidin-4-yl]-1,3-thiazol-2-amine.

CAS: 693228-63-6.

First Report: Wang *et al*. in 2010.[152]

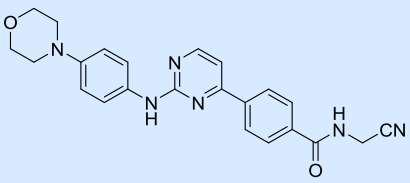
Activity: CYC116 is a small molecule inhibitor of aurora kinases A and B with K(i) values of 8.0 and 9.2 nM, respectively, in myelogenous leukaemia cell line MV4-11. Its anticancer effects were shown to emanate from cell death following mitotic failure and increased polyploidy due to cellular inhibition of the aurora kinases.[152]

Clinical Trials: Stage 1.[153]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[154]

Prices: 5 mg - 74 EUR, 25 mg - 296 EUR, 100 mg - 888 EUR.[155]

CYT387



IUPAC Name: *N*-(cyanomethyl)-4-[2-(4-morpholin-4-ylanilino)pyrimidin-4-yl]benzamide.

CAS: 1056634-68-4.

First Report: Burns *et al*. from Cytopia Research, in 2008.[156]

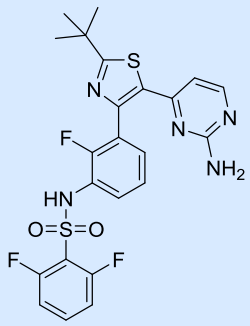
Activity: CYT387 is a potent inhibitor of the JAK1 and JAK2 kinases (IC_{50} = 11 and 18 nM, respectively) that is significantly less active against other kinases, including JAK3 (IC_{50} = 155 nM). CYT387 caused growth suppression and apoptosis in JAK2-dependent hematopoietic cell lines, while nonhematopoietic cell lines were unaffected. It is being developed to treat myeloproliferative neoplasms/disorders.[157-159]

Clinical Trials: Stage 3.[160]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[161]

Prices: 5 mg - 97 EUR, 25 mg - 388 EUR, 100 mg - 1164 EUR.[162]

Dabrafenib



IUPAC Name: *N*-[3-[5-(2-aminopyrimidin-4-yl)-2-tert-butyl-1,3-thiazol-4-yl]-2-fluorophenyl]-2,6-difluorobenzenesulfonamide.

CAS: 1195765-45-7.

First Report: Adams *et al*. from SmithKline Beecham Corporation, in 2009.[163]

Activity: Dabrafenib is the second selective BRAF inhibitor approved for treatment of BRAF-mutated metastatic melanoma. It is a highly potent ATP-competitive inhibitor of BRAF (V600E) and BRAF (V600K) kinases, with IC_{50} values of 0.6 and 0.5 nM, respectively. In contrast, B-Raf and c-Raf display 4- and 6-fold weaker sensitivity, respectively. Dabrafenib has been shown to reduce MEK and ERK phosphorylation, induce G1 cell cycle arrest, followed by cell death. In a xenograft model of human melanoma expressing oncogenic BRAF (V600E), it inhibited ERK activation and tumor growth.[164-166]

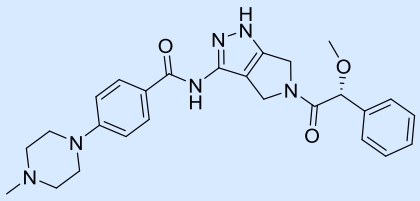
Clinical Trials: Stage 3.[167]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[168]

Prices: 5 mg - 80 EUR, 25 mg - 320 EUR, 100 mg - 660 EUR[169]

Danusertib

IUPAC Name: *N*-[5-[(2*R*)-2-methoxy-2-phenylacetyl]-4,6-dihydro-1*H*-pyrrolo[3,4-*c*]pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide.



CAS: 827318-97-8.

First Report: Fancelli *et al*. in 2006.[170]

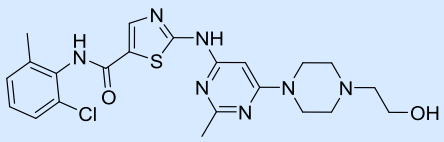
Activity: Danusertib (PHA-739358) is a small-molecule pan-aurora kinase inhibitor. It also inhibits the kinase activity of wild-type ABL and of several mutants (including T315I) *in vitro*.[171,172] It is under clinical trials for treatment of metastatic hormone refractory prostate cancer and multiple myeloma.[173]

Clinical Trials: Stage 2 completed.[174]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[175]

Prices: 5 mg - 195 EUR, 25 mg - 780 EUR, 100 mg - 2340 EUR.[176]

Dasatinib



IUPAC Name: *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-yl]amino]-1,3-thiazole-5-carboxamide.

CAS: 302962-49-8.

First Report: Das *et al.* from Bristol-Myers Squibb Co., in 2000.[177]

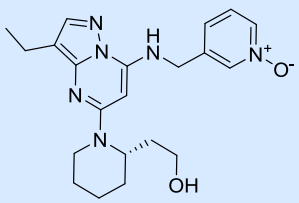
Activity: Dasatinib is a dual SRC/ABL kinase inhibitor with potent antitumor activity, such as, chronic myeloid leukaemia and melanoma.[178] In addition to inhibiting the wild-type BCR-ABL, dasatinib inhibited 14 of 15 BCR-ABL mutants. It is a potent inhibitor of all members of the SRC family, including c-SRC, LCK, FYN and YES (IC_{50} < 1.1 nmol/L).[179-182]

Clinical Trials: Stage 4 completed.[183]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[184]

Prices: 25 mg - 103 EUR, 100 mg - 309 EUR, 250 mg - 618 EUR.[185]

Dinaciclib



IUPAC Name: 2-[(2*S*)-1-[3-ethyl-7-[(1-oxidopyridin-1-ium-3-yl)methylamino]pyrazolo[1,5-a]pyrimidin-5-yl]piperidin-2-yl]ethanol.

CAS: 779353-01-4.

First Report: Paruch *et al*. in 2010.[186]

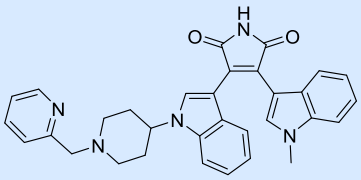
Activity: Dinaciclib inhibits CDK2, CDK5, CDK1, and CDK9 activity *in vitro* with IC_{50} values of 1, 1, 3, and 4 nmol/L, respectively. In cell-based assays, it completely suppressed pRB phosphorylation, blocked cellular replication and induced apoptosis. Dinaciclib induced regression of established solid tumors in a range of mouse models following intermittent scheduling of doses below the maximally tolerated level.[187,188] IT is currently under clinical trials for treatment of chronic lymphocytic leukaemia, advanced or metastatic breast cancer and lymphoma.[189]

Clinical Trials: Stage 3 completed.[190]

Storage / Stability: Stable if stored at -4 °C for short term (days to weeks) or for long term (months to years) if stored at -20 °C.[191]

Prices: 5 mg - 130 EUR, 25 mg - 520 EUR.[192]

Enzastaurin



IUPAC Name: 3-(1-methyl-1*H*-indol-3-yl)-4-(1-(1-(2-pyridinyl methyl)-4-piperidinyl)-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione.

CAS: 170364-57-5.

First Report: Teicher *et al.* in 2002.[193]

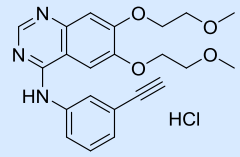
Activity: Enzastaurin is an inhibitor of several isoforms of protein kinase C, including beta, alpha, gamma and epsilon, with IC_{50} values of 6, 39, 83 and 110 nM, respectively. Enzastaurin inhibits tumor growth through several mechanisms: block of tumor cell proliferation, induction of tumor cell apoptosis and inhibition of tumor-induced angiogenesis.[194,195] It is, at the present, under clinical studies for non Hodgkin lymphoma, glioblastoma, NSCL cancer, breast cancer and prostate cancer treatment.[196]

Clinical Trials: Stage 3 completed.[197]

Storage / Stability: Storage temperature: 2-4 °C and keep container tightly closed in a dry and well-ventilated place. This product is relatively unstable under normal temperature.[198]

Prices: 5 mg - 62 EUR, 25 mg - 248 EUR, 100 mg - 744 EUR.[194]

Erlotinib Hydrochloride



IUPAC Name: *N*-(3-ethynylphenyl)-(6,7-bis(2-methoxyethoxy)quinazolin-4-yl)-amine hydrochloride.

CAS: 183319-69-9.

First Report: Moyer *et al.* in 1997.[199]

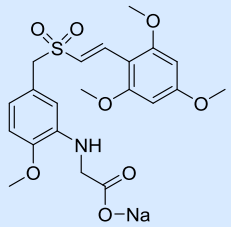
Activity: Erlotinib is a low molecular weight, orally active, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (IC_{50} = 2 nmol/L). Inhibition of the EGFR tyrosine kinase disrupts of processes involved in cancer growth and development, including cell migration, proliferation, angiogenesis, and apoptosis. Erlotinib is used clinically for the treatment of non-small-cell lung cancer (NSCLC).[200-202]

Clinical Trials: Stage 4 completed.[203]

Storage / Stability: Stable store in a cool, dry, well-ventilated area away from incompatible. Stable under normal temperatures and pressures.[204]

Prices: 25 mg - 35 EUR, 100 mg - 103 EUR, 250 mg - 206 EUR.

Estybon (Rigosertib)



IUPAC Name: *N*-(2-methoxy-5-(((2-(2,4,6-trimethoxyphenyl)ethenyl) sulfonyl)methyl)phenyl)glycine sodium salt.

CAS: 1225497-78-8.

First Report: Premkumar Reddy *et al.* in 2005.[205]

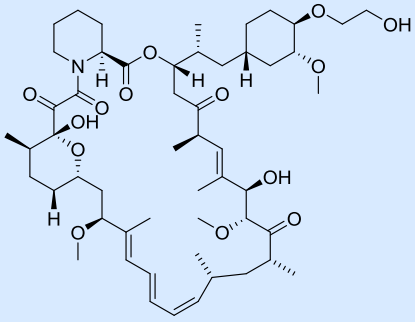
Activity: Estybon is a non-ATP-competitive inhibitor of protein kinase PLK1 with an IC_{50} of 9 nM.[206,207] This TKI is, currently, under clinical trials for the treatment of several cancer types, such as, metastatic pancreatic adenocarcinoma, head and neck neoplasms, acute myelocytic Leukaemia, ovarian cancer and also, acute lymphocytic Leukaemia.[208]

Clinical Trials: Stage 2 completed.[209]

Storage/Stability: Keep container tightly closed in a dry and well-ventilated place. Recommended storage temperature: Store at -20°C. Keep in a dry place.[210]

Prices: 5 mg - 194 EUR; 25 mg - 776 EUR; 100 mg - 2328 EUR.[207]

Everolimus



IUPAC Name: Dihydroxy-12-[(2*R*)-1-[(1*S*,3*R*,4*R*)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]propan-2-yl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.0-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone.

CAS: 159351-69-6.

First Report: Reported in 1966.[211]

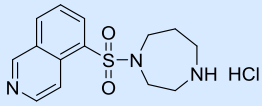
Activity: Everolimus is a derivative of rapamycin, a drug with immunosuppressant and anti-angiogenic properties. compared to rapamycin, it has structural modifications that confer improved aqueous solubility. Everolimus inhibits the activity of mTOR, an intracellular serine-threonine kinase from phosphatidylinositol 3 kinase/protein kinase B signaling pathway, whose dysregulation leads to increased tumor growth. The inhibition of mTORresults in decreased protein synthesis as well as cell cycle arrest, leading to reduced cell proliferation.[211,212] And also, it is under clinical trials for the treatment of breast cancer, pancreatic neuroendocrine tumours, hepatocellular carcinoma, metastatic renal cell carcinoma, angiomyolipoma and melanoma.[213]

Clinical Trials: Stage 4 completed.[214]

Storage/Stability: Keep container tightly closed in a dry and well-ventilated place. Recommended storage temperature: -20 °C. Store under inert gas.[215]

Prices: 5 mg - 70 EUR, 25 mg - 280 EUR, 100 mg - 840 EUR.[212]

Fasudil



IUPAC Name: 1-(5-isoquinolinesulfonyl)-homopiperazine hydrochloride; hexahydro-1-(5-isoquinolinylsulfonyl)-1*H*-1,4-diazepine monohydrochloride.

CAS: 105628-07-7.

First Report: Uehata *et al.* in 1997.[216]

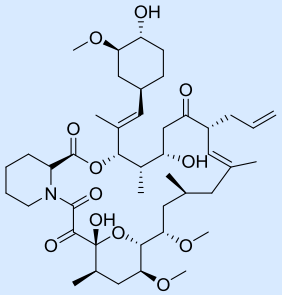
Activity: Fasudil is an inhibitor of Rho-associated kinase II with an IC_{50} value of 1.9 µM. This drug is marketed in Japan to treat cerebral vasospasm following surgery for subarachnoid hemorrhage and associated cerebral ischemic symptoms. [217-219]

Clinical Trials: Stage 4.[220]

Storage/Stability: Stable store in a cool, dry, well-ventilated area awayfrom incompatible. Stable under normal temperatures and pressures.[221]

Prices: 25 mg - 22 EUR, 100 mg - 65 EUR, 250 mg - 130 EUR.[217]

FK-506



IUPAC Name: 3S-[3*R*[E(1*S*,3*S*,4S)] ,4*S*,5*R*,8*S*,9*E*,12*R*,14*R*,15*S*,16*R*,18*S*,19*S*,26a*R*-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c] [1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone

CAS: 104987-11-3

First Report: Toru Kino *et al.* in 1987.[222]

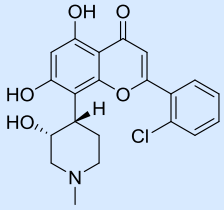
Activity: FK-506 is a potent immunosuppressant that is used after allogeneic organ transplantation to reduce the risk of organ rejection. It disrupts signaling events mediated by calcineurin (Ca-dependent phosphatase) in T lymphocytes. Its mechanism of action involves the formation of a molecular complex with the intracellular FK506-binding protein-12 (FKBP12), thereby acquiring the ability to interact with calcineurin and to interfere with its access to and dephosphorylation of various substrates. The knows substrates of calcineurin involved in induced immunosuppression include the nuclear factors of activated T cells (NFAT). [223,224] It is also under clinical evaluation for de treatment for prostate cancer, hepatocellular carcinoma and acute leukaemia.[225]

Clinical Trials: Stage 4 completed.[226]

Storage / Stability: Keep container tightly closed. Keep container in a cool, well-ventilated area. The product is stable.[227]

Prices: 25 mg - 52 EUR, 100 mg - 156 EUR, 250 mg - 312 EUR.[223]

Flavopiridol



IUPAC Name: 2-(2-chlorophenyl)-5,7-dihydroxy-8-((3*S*,4*R*)-3-hydroxy-1-methyl-4-piperidyl)chromen-4-one.

CAS: 146426-40-6.

First Report: Kattige *et al.* in 1986.[228]

Activity: Flavopiridol was initially identified as an inhibitor of cyclin-dependent kinases 1 and 2. However, its primary target is CDK9, the catalytic component of positive transcription elongation factor b (P-TEFb). It is currently being tested as an anticancer drug in numerous

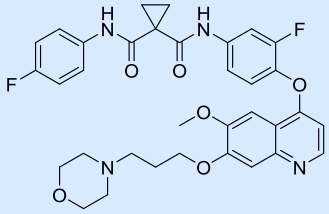
clinical trials, such as prostate cancer, breast cancer, kidney cancer, esophageal cancer, adenocarcinoma of the pancreas, recurrent pancreatic cancer, stage IV pancreatic cancer, liver cancer, lymphoma, leukaemia, ovarian epithelial cancer, sarcoma, melanoma and lymphoma.[229-232]

Clinical Trials: Stage 2 completed.[233]

Storage / Stability: Store in cool place. Keep container tightly closed in a dry, well-ventilated place. Recommended storage temperature 2-8 ° C. Store with desiccant.[234]

Prices: 5 mg - 85 EUR, 25 mg - 340 EUR, 100 mg - 1020 EUR.[229]

Foretinib



IUPAC Name: *N*-(3-fluoro-4-((6-methoxy-7-(3-(4-morpholinyl) propoxy)-4-quinolinyl)oxy)phenyl)-*N*'-(4 fluorophenyl)-1,1-cyclo propanedicarboxamide.

CAS: 849217-64-7.

First Report: Bannen *et al.* in 2003.[235]

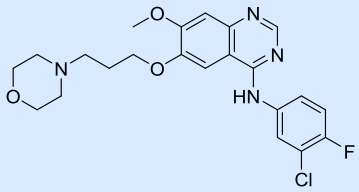
Activity: Foretinib is a small-molecule inhibitor of the hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) receptor tyrosine kinases with single-digit nanomolar IC_{50} values. It also inhibits KIT, FLT-3, PDGFR-beta and TIE-2. Foretinib exerted cytotoxicity against a broad panel of cancer cell lines. It also reduced tumor cell migration, invasion and tumor-induced angiogenesis. Because of these facts, this TKI is under several clinical evaluations, such as, breast cancer, lung cancer, head and neck cancer (HNC), hepatocellular and renal carcinoma [236-238]

Clinical Trials: Stage 2 completed.[239]

Storage / Stability: Storage temperature: 2-4 °C and keep container tightly closed in a dry and well-ventilated place. This product is relatively unstable under normal temperature.[240]

Prices: 5 mg - 80 EUR, 25 mg - 320 EUR, 100 mg - 960 EUR.[236]

Gefitinib



IUPAC Name: *N*-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine.

CAS: 184475-35-2.

First Report: Lemmon *et al.* in 1994.[241]

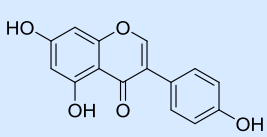
Activity: Gefitinib is a selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase domain, which is sometimes referred to as HER1 or ERBB-1. Gefitinib blocks signal transduction pathways implicated in the proliferation and survival of cancer cells and other host-dependent processes that promote cancer growth.[242,243] It is, currently, under advanced clinical trials stage for NSCL Cancer, cancer of the head and neck and melanoma.[244]

Clinical Trials: Stage 4 completed.[245]

Storage / Stability: Store in closed vessels, under -20◦C. Heat, flames and sparks.[246]

Prices: 5 mg - 52 EUR, 25 mg - 208 EUR, 100 mg - 624 EUR.[242]

Genistein



IUPAC Name: 4',5,7-trihydroxyisoflavone.

CAS: 446-72-0.

First Report: Akiyama *et al.* in 1987.[247]

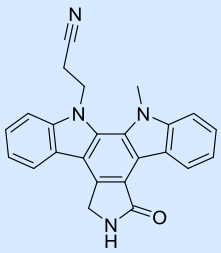
Activity: Genistein is an isoflavone-related natural product. It influences multiple biochemical pathways in cells, including those involved in PPAR activation, the activation of estrogen receptors and topoisomerase activity. In addition, it displays direct antioxidative activity. The molecular mechanism of its anticancer activity is probably related to its ability to inhibit several tyrosine kinases. Genistein treatment inhibited MEKK1 kinase activity when tested by a kinase assay, which demonstrates that genistein inhibits MEKK1 activity, which may be responsible for the decreased phosphorylation of IjB, thereby, resulting in the inactivation of NF-jB.[248,249] It is, currently, under clinical trials for the treatment of prostate cancer, breast cancer, NSCL Cancer, colorectal cancer, pancreatic cancer, bladder cancer and leukaemia.[250]

Clinical Trials: Stage 3 completed.[251]

Storage / Stability: Keep container dry. Keep in a cool place. Ground all equipment containing material. Carcinogenic, teratogenic or mutagenic materials should be stored in a separate locked safety storage cabinet or room. The product is stable.[252]

Prices: 25 mg - 103EUR, 100 mg - 309 EUR, 250 mg - 618 EUR.[248]

GÖ 6976



IUPAC Name: 5,6,7,13-tetrahydro-13-methyl-5-oxo-12*H*-indolo(2,3-a)pyrrolo(3,4-c)carbazole-12-propanenitrile.

CAS: 136194-77-9.

First Report: Hartenstein *et al.* in 1993.[253]

Activity: Gö 6976 inhibits the Ca($^{2+}$)-dependent isozymes protein kinase C (PKC) alpha and beta 1 at nanomolar concentrations, using rat brain cells. Kinetic analysis revealed that PKC inhibition by Gö 6976 is competitive with respect to ATP, non-competitive with respect to the protein substrate and mixed type with respect to phosphatidylserine.[254,255] GÖ 6976 swowed to be capacle of to restore hyperphosphorylated and therefore inactive Rb function in cancer cells, such as T24 urinary bladder carcinoma cells.[256]

Clinical Trials: No studies in the moment.[257]

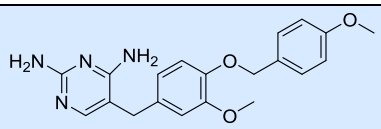
Storage / Stability: Store in a well closed container. Stable under normal temperatures and pressures.[258]

Prices: 5 mg - 550 EUR, 25 mg - 2200 EUR.[254]

GW2580

IUPAC Name: 5-((3-methoxy-4-((4-methoxyphenyl)methoxy) phenyl) methyl) -2,4-pyrimidinediamine.

CAS: 870483-87-7.



First Report: Conway *et al.* in 2005.[259]

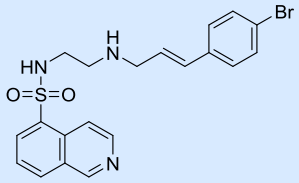
Activity: GW2580 is an orally bioavailable inhibitor of cFMS receptor kinase. It completely inhibited human cFMS kinase *in vitro* at 0.06 microM. GW2580 selectively inhibited cFMS kinase compared with 186 other kinases *in vitro* and completely inhibited CSF-1-induced growth of rat monocytes, with an IC_{50} value of 0.2 µM. GW2580 at 1 µM completely inhibited CSF-1-induced growth of mouse myeloid cells and human monocytes and completely inhibited bone degradation in cultures of human osteoclasts, rat calvaria and rat fetal long bone.[259-261]

Clinical Trials: No studies in the moment.[262]

Storage / Stability: Store in cool place. Keep container tightly closed in a dry, well-ventilated place. Recommended storage temperature: -20 ° C.[263]

Prices: 25 mg - 72 EUR, 100 mg - 216 EUR, 250 mg - 432 EUR.[260]

H-89



IUPAC Name: *N*-(2-((3-(4-bromophenyl)-2-propen-1-yl)amino)ethyl)-5-isoquinolinesulfonamide.

CAS: 127243-85-0.

First Report: Chijiwa *et al.* in 1990.[264]

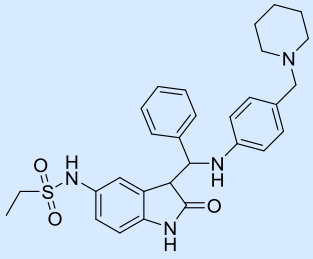
Activity: H-89 is known as a selective and potent inhibitor of protein kinase A (PKA). However, H89 is able to inhibit at least eight additional protein kinases at 1 µM (PRKG1, PRKG2, PRKX, ROCK1, ROCK2, MSK1, MSK2, S6K1). IC_{50} values determined for the compound proved that three kinases (MSK1, S6K1 and ROCK2) were inhibited with a potency similar to or greater than that for PKA.[265,266]

Clinical Trials: No studies in the moment.[267]

Storage / Stability: Keep refrigerated (Store below 4 °C). Keep container tightly closed. Stable under normal temperatures and pressures.[268]

Prices: 5 mg - 64 EUR, 25 mg - 192 EUR, 100 mg - 576 EUR.[265]

Hesperadin



IUPAC Name: *N*-(2,3-dihydro-2-oxo-3-((3*Z*)-phenyl((4-(1-piperidinylmethyl)-phenyl)-amino)methylene)-1*H*-indol-5-yl)-methanesulfona mide.

CAS: 422513-13-1.

First Report: Walter *et al.* in 2002.[269]

Activity: Hesperadin is an inhibitor of the Aurora B protein kinase, against which it has an IC_{50} of 40 nM. Mammalian cells treated with Hesperadin enter anaphase with numerous monooriented chromosomes, many of which may have both sister kinetochores attached to one spindle pole (syntelic attachment). Hesperadin causes cells arrested by taxol or monastrol to enter anaphase within <1 h, whereas cells treated with nocodazole remain arrested for 3-5 h.[270,271]

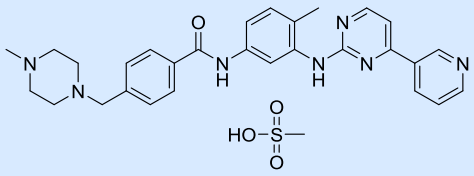
Clinical Trials: Stage 4 completed.[272]

Storage / Stability: Store in a well closed container. Stable under normal temperatures and

pressures.[273]

Prices: 5 mg - 194 EUR, 25 mg - 776 EUR, 100 mg - 2328 EUR.[270]

Imatinib



IUPAC Name: 4-((4-methyl-1-piperazinyl)methyl)-*N*-(4-methyl-3-((4-(3-pyridinyl)-2pyrimidinyl)amino)-phenyl)-benzamidemonomethane sulfonate.

CAS: 220127-57-1.

First Report: Zimmermann *et al.* in 1996.[274]

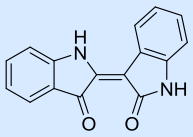
Activity: Imatinib is an inhibitor of several tyrosine kinases that is selective for the oncoproteins BCR/ABL, c-Kit and PDGFR. It is used in treating chronic myelogenous leukaemia (CML), gastrointestinal stromal tumors (GISTs) and some other diseases in which these kinases are strongly expressed or unusually active. As one of the first cancer drugs developed using the principles of rational drug design based on an understanding of how cancer cells work, Imatinib is a ground-breaking compound. It was approved in the U.S. in 2001 for the treatment of Philadelphia-chromosome positive (Ph+) CML and in 2002 for the treatment of patients with KIT (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).[275,276]

Clinical Trials: Stage 4 completed.[277]

Storage / Stability: Stable Store in a cool, dry, well-ventilated area away from incompatible. Stable under normal temperatures and pressures.[278]

Prices: 25 mg - 25 EUR, 100 mg - 75 EUR, 250 mg - 150 EUR.[275]

Indirubin



IUPAC Name: 2-(2-oxo-1*H*-indol-3-ylidene)-1*H*-indol-3-one.

CAS: 479-41-4.

First Report: Zheng *et al.* in 1979.[279]

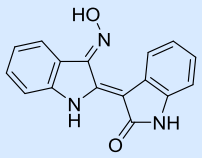
Activity: Indirubin is an inhibitor of cyclin-dependent kinases and GSK3b inhibitor with IC_{50} values against the two kinase classes of approximately 75 nM and 190 nM, respectively. Indirubin was identified as the active ingredient of Danggui Longhui Wan, a mixture of plants that is used in traditional Chinese medicine to treat chronic diseases.[280,281] It is currently under clinical trials for treatment of childhood acute promyelocytic leukaemia.[282]

Clinical Trials: Stage 4 completed.[282]

Storage / Stability: Keep container tightly closed in a dry and well-ventilated place. Store in refrigerator. Store away from oxidizing agents. Stable under recommended storage conditions.[283]

Prices: 5 mg - 41 EUR, 25 mg - 164 EUR, 100 mg - 492 EUR.[280]

Indirubin-3'-monooxime



IUPAC Name: 3-(1,3-dihydro-3-(hydroxyimino)-2*H*-indol-2-ylidene)-1,3-dihydro-2*H*-indol-2-one.

CAS: 160807-49-8.

First Report: Zheng *et al.* in 1979.[279]

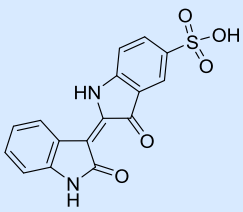
Activity: Indirubin-3'-monooxime is an inhibitor of GSK3b (IC_{50}=22 nM), CDK1 (IC_{50}=180 nM) and CDK5 (IC_{50}=100 nM). Treatment with indirubin-3-monooxime caused time-dependent inhibition of cell growth, with the treated cells exhibiting many hallmark features of apoptosis. It has been proved that the treatment with this drug induces cell death and apoptosis in human laryngeal carcinoma cells.[284-286]

Clinical Trials: No studies in the moment.[287]

Storage / Stability: Keep tightly closed. Store at correct temperature. Stable.[288]

Prices: 5 mg - 98 EUR, 25 mg - 392 EUR, 100 mg - 1176 EUR.[284]

Indirubin-5-sulfonic Acid



IUPAC Name: 2-(1,2-dihydro-2-oxo-*3H*-indol-3-ylidene)-2,3-dihydro-3-oxo-1*H*-indole-5-sulfonic acid.

CAS: 864131-82-8.

First Report: Zheng *et al.* in 1979.[279]

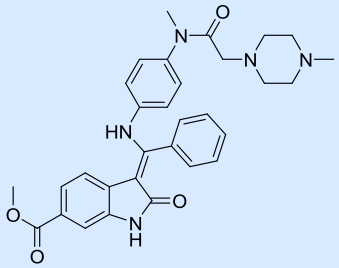
Activity: Indirubin-5-sulfonic acid is an indigoid inhibitor of CDK1/cyclin B (IC_{50}= 55 nM), CDK2/cyclin A (IC_{50}=35 nM), CDK2/cyclin E (IC_{50}=150 nM), CDK4/cyclin D1 (IC_{50}=300 nM), CDK5/p35 (IC_{50}=65 nM) and GSK3b (IC_{50}=280 nM).[289,290]

Clinical Trials: No studies in the moment.[291]

Storage / Stability: Keep containers tightly closed in a dry, cool, well ventilated. Stable under normal conditions.[292]

Prices: 5 mg - 98 EUR, 25 mg - 392 EUR, 100 mg - 1176 EUR.[289]

Indetanib



IUPAC Name: Methyl (3*Z*)-3-{[(4-{methyl[(4-methylpiperazin-1-yl)acetyl]amino}phenyl)amino](phenyl)methylidene}-2-oxo-2,3-dihydro-1*H*-indole-6-carboxylate.

CAS: 656247-17-5.

First Report: Hilberg *et al.* in 2008.[293]

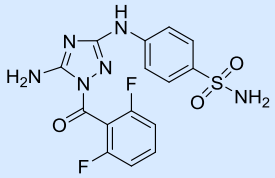
Activity: Intedanib is a kinase inhibitor blocking VEGFR, PDGFR and FGFR receptors, developed for the treatment of several malignancies and idiopathic pulmonary fibrosis. Intedanib also significantly decreased blood vessel area in treated tumours. The sustained inhibition of VEGFR phosphorylation, the fast *in vivo* clearance and clinical efficacy against a broad range of malignancies appear to be the major advantages of intedanib. Furthermore, the existing data suggest an excellent safety profile. As of 2012, intedanib undergoes several phase III trials for the treatment of NSCLC and ovarian cancer.[294,295]

Clinical Trials: Stage 3 completed.[296]

Storage / Stability: Store in a well closed container. Stable under normal temperatures and pressures.[297]

Prices: 5 mg - 80 EUR, 25 mg - 320 EUR, 100 mg - 960 EUR.[294]

JNJ-7706621



IUPAC Name: 4-((5-amino-1-(2,6-difluorobenzoyl)-1*H*-1,2,4-triazol-3-yl)amino)benzenesulfonamide.

CAS: 443797-96-4.

First Report: Emanuel *et al.* in 2005.[298]

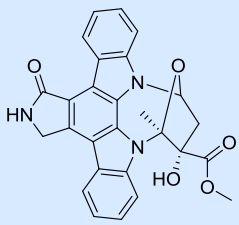
Activity: JNJ-7706621 is a potent cell cycle inhibitor that targets several cyclin-dependent kinases (CDK) and Aurora kinases. It has IC_{50} values of 9 and 11 nM for CDK1/Cyclin B and aurora A, respectively, and blocked the growth of several different types of tumour cell *in vitro* (such as HeLa cells, A375 melanoma human tumour and retinoblastom*a cells)* ten times more effectively than it inhibited the growth of normal human cells. At low concentrations, JNJ-7706621 slowed cell growth; at high concentrations, it was cytotoxic. Flow cytometric analysis of cellular DNA content showed that JNJ-7706621 delayed progression through G1 and arrested the cell cycle in the G2-M phase. Additional cellular effects due to Aurora kinase inhibition included endoreduplication and inhibition of histone H3 phosphorylation.[298-300]

Clinical Trials: No studies in the moment.[301]

Storage / Stability: Storage temperature: 2-4 °C and keep container tightly closed in a dry and well-ventilated place. This product is relatively unstable under normal temperature.[302]

Prices: 5 mg - 230 EUR, 25 mg - 920 EUR, 100 mg - 2760 EUR.[299]

K252a



IUPAC Name: (9*S*-(9α,10β,12α))-2,3,9,10,11,12-hexahydro-10-hydroxy-10-(methoxycarbonyl)-9-methyl-9,12-epoxy-1*H*-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one.

CAS: 99533-80-9.

First Report: Kase *et al.* in 1986.[303]

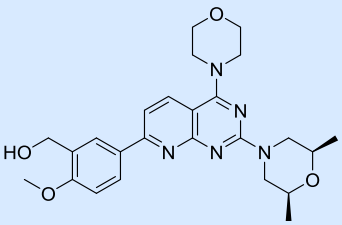
Activity: K252a is an alkaloid related to staurosporin, but isolated from *Nocardiopisis sp*. soil fungi. It is potent inhibitor of multiple serine/threonine protein kinases (IC_{50}'s of 10 to 30 nM), including Ca2+/calmodulin-dependent protein kinase II, protein kinase A, protein kinase C and protein kinase G.[304,305] This inhibitor is associated to the reducing of the proliferation of in GTL-16 gastric carcinoma cells (100 nM), and cause reversion in NIH3T3 fibroblasts transformed by the oncogenic form of the receptor, TprMet (75 nM). K252a inhibits Met autophosphorylation in cultured cells and in immunoprecipitates and prevents activation of its downstream effectors MAPKinase and Akt. Interestingly, K252a seems to be more effective at inhibiting the mutated form of Met (M1268T) found in papillary carcinoma of the kidney than the wild type receptor. Pretreatment of both Tpr-Met-transformed NIH3T3 fibroblasts and of GTL-16 gastric carcinoma cells with K252a results in loss of their ability to form lung metastases in nude mice upon injection into the caudal vein.[306]

Clinical Trials: No studies in the moment.[307]

Storage / Stability: Keep container tightlyclosed. Stable.[308]

Prices: 5 mg - 208 EUR, 25 mg - 832 EUR, 100 mg - 2496 EUR.[304]

KU0063794



IUPAC Name: 5-(2-((2*R*,6*S*)-2,6-dimethyl-4-morpholinyl)-4-(4-morpholinyl)pyrido(2,3-d)pyrimidin-7-yl)-2-methoxybenzenemethanol.

CAS: 938440-64-3.

First Report: García-Martínez *et al.* in 2009.[309]

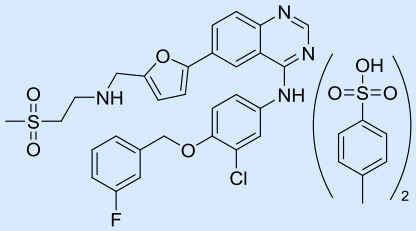
Activity: KU0063794 is selective inhibitor of mammalian target of rapamycin (mTOR) with an IC_{50} value of 10 nM. It displays no activity against PI3-kinase or 76 other kinases tested. It inhibits the activation of AKT, S6K and SGK, but not RSK. Treatment of cells suppresses their growth and induces G1 cell cycle arrest *in vitro*.[309,310]

Clinical Trials: No studies in the moment.[311]

Storage / Stability: Store in a well closed container. Stable under normal temperatures and pressures.[312]

Prices: 5 mg - 121 EUR, 25 mg - 484 EUR, 100 mg - 1452 EUR.[310]

Lapatinib Ditosylate



IUPAC Name: *N*-(3-chloro-4-((3-fluorophenyl)methoxy) phenyl)-6-(5-(((2-(methylsulfonyl) ethyl)amino)methyl)-2-furanyl)-4-quinazolinamine bis(4-methylbenzenesulfonate) monohydrate.

CAS: 388082-78-8.

First Report: Carter *et al.* in 1999.[313]

Activity: Lapatinib is an orally available small molecule that targets the tyrosine activity of the erbB1 and erbB2 (Her2) receptors. It is used to treat breast cancers and other solid tumours.[314,315]

Clinical Trials: Stage 4 completed.[316]

Storage / Stability: Storage temperature: 2-4 °C and keep container tightly closed in a dry and well-ventilated place. This product is relatively unstable under normal temperature.[317]

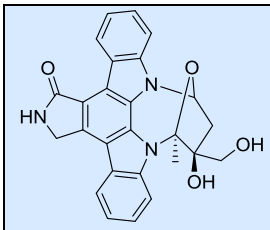
Prices: 25 mg - 103 EUR, 100 mg - 309 EUR, 250 mg - 618 EUR.[314]

Lestaurtinib

IUPAC Name: (5*S*,6*S*,8*R*)-6-hydroxy-6-(hydroxymethyl)-5-methyl-7,8,14,15-tetrahydro-5*H*-16-oxa-4b,8a,14-triaza-5,8-methanodibenzo[b,h] cycloocta[jkl]cyclopenta[e]-as-indacen-13(6*H*)-one.

CAS: 111358-88-4.

First Report: George *et al.* in 1999.[318]



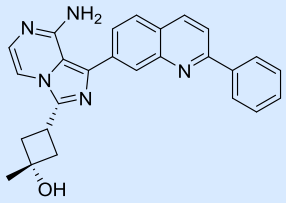
Activity: Lestaurtinib is a multi-targeted tyrosine kinase inhibitor. In preclinical studies, it was shown to inhibit FLT3 at nanomolar concentrations, prompting its rapid development as a potential agent for treating AML. Phase I studies have shown it to be an active agent, particularly when used in combination with cytotoxic drugs. It is currently undergoing Phase II and Phase III studies in patients with FLT3-ITD AML.[319,320]

Clinical Trials: Stage 2 completed.[321]

Storage / Stability: Keep container tightly closed in a dry and well-ventilated place. Recommended storage temperature: -20 °C. Keep in a dry place. Stable under recommended storage conditions.[322]

Prices: 5 mg - 220 EUR, 25 mg - 880 EUR, 100 mg - 2640 EUR.[319]

Linsitinib



IUPAC Name: cis-3-(8-amino-1-(2-phenyl-7-quinolinyl)imidazo (1,5-a)pyrazin-3-yl)-1-methylcyclobutanol.

CAS: 867160-71-2.

First Report: Arnold *et al.* in 2005.[323]

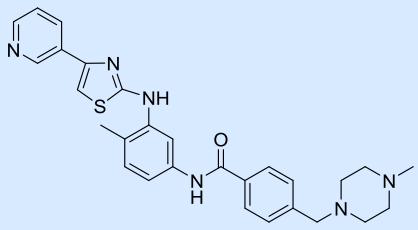
Activity: Linsitinib has been developed as a small-molecule inhibitor of IGF-1R and IR kinases, with IC_50 values of 35 nM and 75 nM, respectively. Linsitinib potently and selectively inhibits autophosphorylation of both human IGF-1R and IR in cells, displays *in vitro* antiproliferative effects in a variety of tumour cell lines and robust *in vivo* anti-tumour efficacy in a xenograft model. It undergoes clinical trials as a drug against several cancer types including adrenocortical, lung and ovarian carcinomas.[324-326]

Clinical Trials: Stage 3 completed.[327]

Storage / Stability: Store in a well closed container. Stable under normal temperatures and pressures.[328]

Prices: 5 mg - 85 EUR, 25 mg - 340 EUR, 100 mg - 1020 EUR.[324]

MASITINIB



IUPAC Name: 4-((4-methyl-1-piperazinyl)methyl)-*N*-(4-methyl-3-((4-(3-pyridinyl)-2-thiazolyl)amino)phenyl)benzamide.

CAS: 790299-79-5.

First Report: Developed by AB Science, S.A. (France).[329]

Activity: Masitinib is a tyrosine kinase inhibitor that targets KIT with an IC_{50} value of 200 nM. Masitinib also potently inhibited recombinant PDGFR and the intracellular kinase Lyn. In contrast, it was a weak inhibitor of ABL and c-FMS and was inactive against a variety of other tyrosine and serine/threonine kinases. Kinetic analyses suggest that its mode of binding is different from that of imatinib; it also proved to be a stronger inhibitor of degranulation, cytokine production, and bone marrow mast cell migration than imatinib. It has been approved as a veterinary medicine for the treatment of mast cell

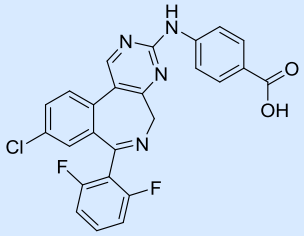
tumours in dogs.[329,330]

Clinical Trials: Stage 2 completed.[331]

Storage / Stability: Storage temperature: 2-4 °C and keep container tightly closed in a dry and well-ventilated place. This product is relatively unstable under normal temperature.[332]

Prices: 25 mg - 172 EUR, 100 mg - 516 EUR, 250 mg - 1032 EUR.[330]

MLN8054



IUPAC Name: 4-((9-chloro-7-(2,6-difluorophenyl)-5*H*-pyrimido (5,4-d)(2)benzazepin-2-yl)amino)benzoic acid.

CAS: 869363-13-3.

First Report: Manfredi *et al.* in 2007.[333]

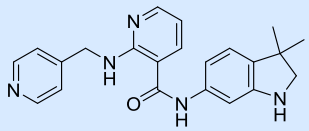
Activity: MLN8054 is an orally bioavailable, potent and selective inhibitor of the protein kinase Aurora A. MLN8054 inhibits AURKA activity with an IC_{50} of 4 nM (its IC_{50} for AURKB is 170 nM). MLN8054 treatment results in G2/M cell cycle arrest, spindle defects and cell death in many tumour cell lines.[334,335]

Clinical Trials: Stage 1 terminated.[336]

Storage / Stability: Store in a well closed container. Stable under normal temperatures and pressures.[337]

Prices: 5 mg - 194 EUR, 25 mg - 776 EUR, 100 mg - 2328 EUR.[334]

Motesanib



IUPAC Name: *N*-(2,3-dihydro-3,3-dimethyl-1*H*-indol-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide.

CAS: 857876-30-3.

First Report: Askew *et al.* in 2005.[338]

Activity: Motesanib is an oral multikinase inhibitor that selectively targets the vascular endothelial growth factor (VEGFR), platelet-derived growth factor (PDGFR) and kit receptors, potently inhibits angiogenesis and induces regression in tumour xenografts.[339,340]

Clinical Trials: Stage 3 terminated.[341]

Storage / Stability: Keep container tightly sealed in cool, well-ventilated area. Keep away from direct sunlight and sources of ignition. Recommended storage temperature: Store at -20°C. Stable under recommended storage conditions.[342]

Prices: 5 mg - 194 EUR, 25 mg - 776 EUR, 100 mg - 2328 EUR.[339]

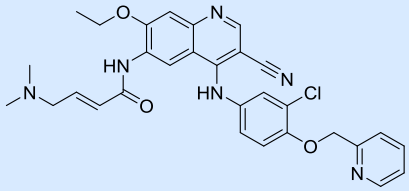
Neratinib

IUPAC Name: (2*E*)-*N*-[4-[[3-chloro-4-[(pyridin-2-yl)methoxy]phenyl]amino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide.

CAS: 698387-09-6.

First Report: Hilberg *et al.* in 2004.[343]

Activity: Neratinib is an orally available tyrosine kinase inhibitor with IC_{50} values of 59 nM and 92 nM for HER2 and EGFR, respectively. In contrast to other tyrosine kinase inhibitors that are ATP-competitors, Neratinib binds to the HER2 receptor irreversibly, forming a covalent bond with a cysteine residue in the ATP-binding pocket. Treatment of cells with neratinib inhibits mitogenic signal transduction events and induces arrest during the G1/S phase transition of the cell cycle.[344,345] This drug is under clinical trials to the treatment of bladder cancer, breast cancer, colorectal cancer, HER2-mutant NSCL cancer, lymphoma, leukaemia, and glioblastoma.[346]

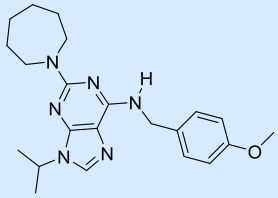


Storage / Stability: Stable if stored at -20 °C.[347]

Clinical Trials: Stage 3.[348]

Prices: 5 mg - 176 EUR; 25 mg - 704 EUR; 100 mg - 2112 EUR.[349]

NG38



IUPAC Name: 9-isopropyl-*N*-(4-methoxybenzyl)-2-(perhydroazepin-1-yl)-9*H*-purin-6-amine.

CAS: 244030-38-4.

First Report: Ann M. Lacy in 1965.[350]

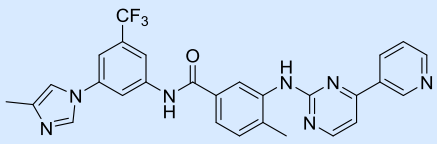
Activity: NG38 is an estrogen sulfotransferase (EST) inhibitor identified (wich function is related to kinase CDK2) from a trisubstituted purine library. It has an IC_{50} of 500 nM against the purified enzyme. EST catalyzes the transfer of a sulfuryl group to estrogens in the cytosol, solubilizing them to maintain hormone homeostasis. Unusually high levels of estrogen sulfate are found in breast tumour cells and EST is therefore considered to be a potential drug target.[351]

Storage / Stability: Stable if stored in original container and avoiding direct sunlight and water contact. Do not apply physical shock to container. Store in a secure, dry and temperate area. Keep the container closed when not in use.[352]

Clinical Trials: Stage 4 completed.[353]

Prices: 5 mg - 98 EUR; 25 mg - 392 EUR; 100 mg - 1176 EUR.[349]

Nilotinib



IUPAC Name: 4-methyl-3-[(4-(3-pyridinyl)-2-pyrimidinyl)amino]-*N*-[5-(4-methyl-1*H*-imidazol-1-yl)-3-(trifluoromethyl)phenyl]benzamide.

CAS: 641571-10-0.

First Report: Breitenstein *et al.* in 2004[354]

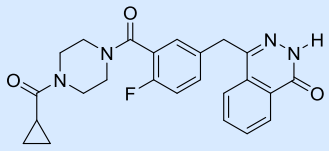
Activity: Nilotinib is a potent inhibitor of the BCR/ABL protein kinase that was developed as a drug against Philadelphia chromosome positive chronic myeloid and acute lymphoblastic leukaemias. Nilotinib is approximately 20 times more potent than imatinib, and this translates into improved inhibitory activity against most of the common BCR-ABL mutations.[355,356]

Storage / Stability: Stable if stored at -20 °C.[357]

Clinical Trials: Stage 4 completed[358]

Prices: 25 mg - 103 EUR; 100 mg - 309 EUR; 250 mg - 618 EUR.[349]

Olaparib



IUPAC Name: 1-(cyclopropylcarbonyl)-4-(5-((3,4-dihydro-4-oxo-1-phthalazinyl)methyl)-2-fluorobenzoyl)piperazine

CAS: 763113-22-0.

First Report: Martin *et al.* in 2004[359]

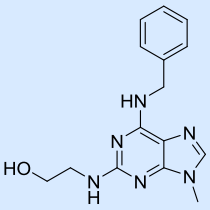
Activity: Olaparib is a single digit nanomolar inhibitor of poly(adenosine diphosphate-ribose) polymerase (PARP), an enzyme that is involved in DNA damage repair. It exhibits IC_{50} values of 5 and 1 nM for PARP-1 and PARP-2, respectively, and is being developed as a drug for BRCA1- and BRCA2-defective cancers.[360-362]

Storage / Stability: Stable if stored at -20 °C.[363]

Clinical Trials: Stage 4.[364]

Prices: 5 mg - 52 EUR; 25 mg - 208 EUR; 100 mg - 624 EUR.[349]

Olomoucine



IUPAC Name: 2-(2'-hydroxyethylamino)-9-methyl-6-(benzylamino)purine;6-(benzylamino)-2-(2-hydroxyethylamino)-9-methylpurine.

CAS: 101622-51-9.

First Report: Charles *et al.* in 1986.[365]

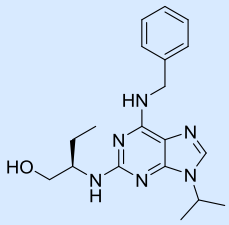
Activity: Olomoucine was one of the first selective inhibitors of cyclin-dependent kinases (CDKs) to be discovered. It competes with ATP for binding to the kinase active site, as demonstrated by the structure of a co-crystal with human CDK2. It was discovered by screening a library of 2,6,9-trisubstituted purines. Studies on olomoucine analogues resulted in the identification of the much more potent inhibitor roscovitine.[366,367] It inhibits the proliferation of human HL-60 leukaemia cells and HeLa cervical carcinoma.[368]

Storage / Stability: Stable if stored at -20 °C.[369]

Clinical Trials: No Studies in the moment.[370]

Prices: 5 mg - 41 EUR; 25 mg - 164 EUR; 100 mg - 492 EUR.[349]

Olomoucine II



IUPAC Name: 2-[[[2-[[(1*R*)-1-(hydroxymethyl)propyl]amino]-9-(1-methylethyl)-9*H*-purin-6-yl]amino]methyl]phenol.

CAS: 500735-47-7.

First Report: Vladimir *et al.* in 2002.[371]

Activity: Olomoucine II is potent inhibitor of several cyclin-dependent kinases (CDKs). It is an ATP-competitor that binds to the active site of

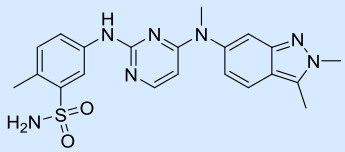
CDK2, as demonstrated by the analysis of co-crystal structures. In addition to its inhibition of the main cell cycle-regulating kinase CDK2, olomoucine II also binds to CDK7 and CDK9, which play important roles in regulating RNA transcription. It has been shown to have *in vitro* anticancer activity against a panel of tumour cell lines.[371,372]

Storage / Stability: Stable if stored at -20°C, under desiccating conditions. Under these conditions, the product can be stored for up to 12 months.[373]

Clinical Trials: No studies in the moment.[374]

Prices: 5 mg - 98 EUR; 25 mg - 392 EUR; 100 mg - 1176 EUR.[349]

Pazopanib



IUPAC Name: 5-[(4-((2,3-dimethyl-2*H*-indazol-6-yl)(methyl)amino)pyrimidin-2-yl)amino]-2-methylbenzenesulfonamide.

CAS: 444731-52-6.

First Report: Boloor *et al.* in 2002.[375]

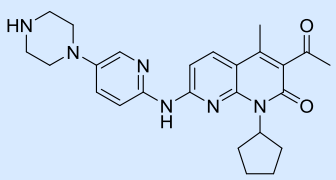
Activity: Pazopanib is a potent inhibitor of all three VEGFR receptors, with IC_{50} values of 10, 30, and 47 nM for VEGFR-1, -2, and -3, respectively. It also displays significant activity against closely related kinases (notably, PDGFRb, c-KIT, FGF-R1, c-FMS) with IC_{50} values in the submicromolar range. Pazopanib inhibits tumour vacsularization (angiogenesis) and thus blocks tumour growth.[376]

Storage / Stability: Stable if stored at -20 °C.[377]

Clinical Trials: Stage 4 completed.[378]

Prices: 5 mg - 52 EUR; 25 mg - 208 EUR; 100 mg - 624 EUR.[349]

PD-0332991



IUPAC Name: 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(1-piperazinyl)-2-pyridinyl]amino}pyrido(2,3-*d*)pyrimidin-7(8*H*)-one hydrochloride.

CAS: 827022-32-2.

First Report: Eck *et al*. in 2005[379]

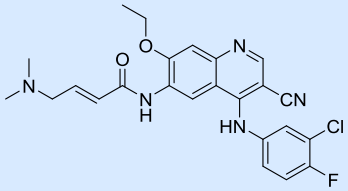
Activity: PD0332991 is a highly specific inhibitor of cyclin-dependent kinase 4 (CDK4, IC_{50} = 11 nM) and CDK6 (IC_{50}=16 nmol/L) that is inactive against other CDKs. It is a potent antiproliferative agent against retinoblastoma (Rb)-positive tumour cells *in vitro*, inducing G1 arrest with a concomitant reduction in the extent of phosphorylation of the pRb protein at Ser780 and Ser795.[380,381]

Storage / Stability: Stable if stored at -20 °C.[382]

Clinical Trials: Stage 4.[383]

Prices: 5 mg - 139 EUR; 25 mg - 556 EUR; 100 mg - 1668 EUR.[349]

Pelitinib



IUPAC Name: (2*E*)-*N*-{4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinolinyl-4-(dimethylamino)-2-butenamide}.

CAS: 257933-82-7.

First Report: Torrance *et al.* in 2000.[384]

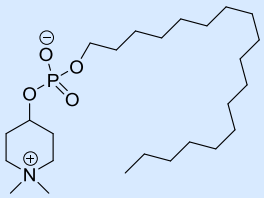
Activity: Pelitinib is an irreversible inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase in clinical trials. It inhibits EGF-induced phosphorylation of EGF-R and the growth of tumours that overexpress EGF-R in animal models.[385] It is now under clinical trials to the treatment of NSCL carcinoma and colorectal neoplasms.[386]

Storage / Stability: Stable if stored at -20 °C.[387]

Clinical Trials: Stage 2 completed.[388]

Prices: 5 mg - 176 EUR; 25 mg - 704 EUR; 100 mg - 2112 EUR.[349]

Perifosine



IUPAC Name: (1,1-dimethylpiperidin-1-ium-4-yl) octadecyl phosphate; 4-[(hydroxy(octadecyloxy)phosphinyl)oxy]-1,1-dimethylpiperidinium inner salt.

CAS: 157716-52-4.

First Report: Noessner *et al.* in 1994.[389]

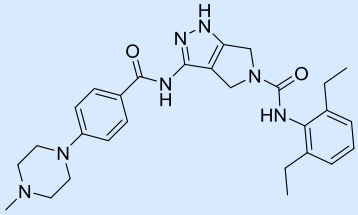
Activity: Perifosine is an oral AKT (protein kinase B, PKB) inhibitor that is currently being tested in clinical trials for the treatment of colon cancer, prostate cancer, renal cancer, ovarian cancer, breast cancer, pancreatic cancer, gastrointestinal stromal tumours, kidney cancer, leukaemia, lymphoma, brain tumour and melanoma. Unlike most kinase inhibitors, which target the adenosine triphosphate-binding region, perifosine targets the pleckstrin homology domain of AKT, thereby preventing its translocation to the plasma membrane. Perifosine exerts both AKT-dependent and AKT-independent effects.[390-392]

Storage / Stability: Stable if stored -20 °C.[393]

Clinical Trials: Stage 3 completed.[394]

Prices: 5 mg - 148 EUR; 25 mg - 592 EUR; 100 mg - 1776 EUR.[349]

PHA-680632



IUPAC Name: *N*-(2,6-diethylphenyl)-4,6-dihydro-3-((4-(4-methyl-1-piperazinyl)benzoyl)amino)pyrrolo(3,4-*c*)pyrazole-5(1*H*)-carboxamide.

CAS: 398493-79-3.

First Report: Fancelli *et al.* in 2005.[395]

Activity: PHA-680632 is a highly selective Aurora kinase inhibitor and an anticancer drug candidate. Its IC_{50} values against Aurora kinases A, B and C are 27, 135 and 120 nM, respectively, and it potently inhibits Histone H3 phosphorylation at Ser10. PHA-680632 is active against a wide range of cancer cell lines (HeLa cells, HL60 cells, HCT116

cells, U2OS cells) and shows significant tumour growth inhibition in different animal tumour models (HL60 human acute myelogenous leukaemia xenograft, A2780 human ovarian carcinoma model, HCT116 colon carcinoma xenograft).[396]

Storage / Stability: Stable if the container was kept tightly sealed in cool, well-ventilated area and away from direct sunlight or sources of ignition; at -20 °C.[397]

Clinical Trials: No studies in the moment.[398]

Prices: 5 mg - 194 EUR; 25 mg - 776 EUR; 100 mg - 2328 EUR.[349]

Pictilisib

IUPAC Name: 2-(1*H*-indazol-4-yl)-6-((4-(methylsulfonyl)-1-piperazinyl)methyl)-4-(4-morpholinyl)thieno(3,2-*d*)pyrimidine.

CAS: 957054-30-7.

First Report: Chuckowree *et al*. in 2007.[399]

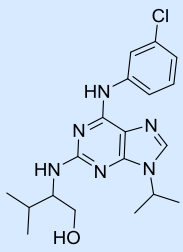
Activity: Pictilisib, formerly known as GDC-0941, is a potent, selective, orally bioavailable inhibitor of PI3K. It inhibits PI3K isoform p110 alpha with a single digit nanomolar IC_{50} value. The compound exhibits *in vitro* antiproliferative properties with submicromolar potency in PTEN-negative cells and clear PI3K pathway modulation. It is currently being evaluated in human clinical trials for the treatment of cancer, such as, breast cancer, NSCL cancer, non-Hodgkin's lymphoma and glioblastoma.[400,401]

Storage / Stability: Stable is stored at +4 °C, for up to 12 months.[402]

Clinical Trials: Stage 2 completed[403]

Prices: 5 mg - 52 EUR; 25 mg - 208 EUR; 100 mg - 624 EUR.[349]

Purvalanol A



IUPAC Name: (2*R)*-2-[[6-[(3-chlorophenyl)amino]-9-propan-2-ylpurin-2-yl]amino]-3-methylbutan-1-ol.

CAS: 212844-53-6.

First Report: Gray *et al.* in 1998.[404]

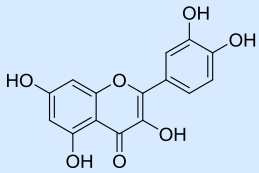
Activity: Purvalanol A is cyclin-dependent kinase inhibitor with IC_{50} values of 4, 70, 850 and 75 nM for CDK1, CDK2, CDK4 and CDK5, respectively. It is a strong inducer of cell cycle arrest during the G2-M phase, and a potent suppressor of the anchorage-independent growth of c-SRC-transformed cells. It also effectively suppressed the growth of human colon cancer HT29 and SW480 cells that express oncogenic SRC.[404,405]

Storage / Stability: Stable as a solid or solutions if stored at -20 °C.[406]

Clinical Trials: No studies in the moment.[407]

Prices: 5 mg - 98 EUR; 25 mg - 164 EUR; 100 mg - 492 EUR.[349]

Quercetin



IUPAC Name: 3,3',4',5,7-pentahydroxyflavone; 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one.

CAS: 117-39-5.

First Report: Fountain *et al.* in 1948.[408]

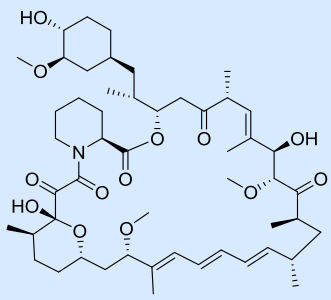
Activity: Quercetin is a natural compound with flavonoid structure. Quercetin appears to have many potential beneficial effects on human health, including antioxidant, anticancer, gastroprotective, antiinfective, antiinflammatory and many more. Quercetin is known PI3K and PKC inhibitor.[409] It is currently being evaluated in human clinical trials for the treatment of cancer, such as, colorectal cancer, kidney cancer, pancreatic ductal adenocarcinoma and follicular lymphoma.[410]

Storage / Stability: Stable if stored -20 °C.[411]

Clinical Trials: Stage 4 completed.[412]

Prices: 5 mg - 156 EUR; 25 mg - 624 EUR; 100 mg - 1872 EUR.[349]

Rapamycin



IUPAC Name: 23,27-epoxy-3*H*-pyrido(2,1-*c*)(1,4)oxaazacyclohentriacontine.

CAS: 53123-88-9.

First Report: Vezina *et al.* in 1975.[413]

Activity: Rapamycin is an immunosuppressant used to prevent rejection in organ transplantation. Due to its antiproliferative properties, it is also being tested as an anticancer drug. Rapamycin is a bacterial product that inhibits the mTOR kinase by associating with its intracellular receptor FKBP12; the FKBP12-rapamycin complex binds directly to mTOR.[414] It is currently being evaluated in human clinical trials for the treatment of several kinds of cancer such as, estrogen receptor positive advanced breast cancer, large cell carcinoma, skin cancer resulting of kidney transplantation, progressive gastrointestinal stromal tumour, non-Hodgkin's lymphoma, renal cell carcinoma and melanoma.[415]

Storage / Stability: Stable if stored -20 °C.[416]

Clinical Trials: Stage 4 completed.[417]

Prices: 5 mg - 103 EUR; 25 mg - 412 EUR; 100 mg - 1236 EUR.[349]

Regorafenib

IUPAC Name: 4-(4-({(4-chloro-3-(trifluoromethyl)phenyl)carbamoyl}amino)-3-fluorophenoxy)-*N*-methylpyridine-2-carboxamide.

CAS: 755037-03-7.

First Report: Wilhelm *et al.* in 2004.[418]

Activity: Regorafenib is an orally available multi-kinase inhibitor that targets several receptor tyrosine kinases, with IC_{50} values of 17, 40 and 69 nM for c-KIT, VEGFR2, B-RAF. It is currently

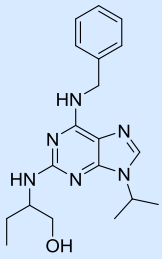
being studied in the treatment of multiple tumour types, such as, colorectal neoplasms, gastrointestinal stromal tumours, urothelial cancer and melanoma.[419,420]

Storage / Stability: Stable if stored -20 °C.[421]

Clinical Trials: Stage 4.[422]

Prices: 5 mg - 148 EUR; 25 mg - 592 EUR; 100 mg - 1776 EUR.[349]

(*R*/*S*)-Roscovitine



IUPAC Name: 2-[(9-(1-methylethyl)-6-[(phenylmethyl)amino]-9*H*-purin-2-yl)amino]-1-butanol.

CAS: 186692-44-4.

First Report: Meijer *et al.* in 1997.[423]

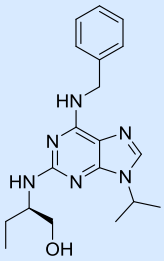
Activity: Roscovitine is a highly efficient and selective inhibitor of certain cyclin-dependent kinases, including CDK2, CDK5, CDK7 and CDK9. It reversibly halts the cell cycle and DNA synthesis in several model systems and inhibits proliferation in various mammalian cell lines with an average IC_{50} of 16 microM.[424]

Storage / Stability: Stable is kept in a well-closed container at -20 °C until 2 years.[425,426]

Clinical Trials: Stage 2.[427]

Prices: 5 mg - 41 EUR; 25 mg - 164 EUR; 100 mg - 492 EUR.[349]

(*R*)-Roscovitine



IUPAC Name: 2-(*R*)-[[9-(1-methylethyl)-6-[(phenylmethyl)amino]-9*H*-purin-2-yl]amino]-1-butanol.

CAS: 186692-46-6.

First Report: Meijer *et al*. in 1997.[423]

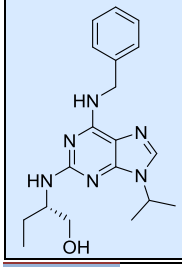
Activity: Roscovitine is a highly efficient and selective inhibitor of certain cyclin-dependent kinases, including CDK2, CDK5, CDK7 and CDK9. It reversibly halts the cell cycle and DNA synthesis in several model systems and inhibits proliferation in various mammalian cell lines with an average IC_{50} of 16 microM.[424]

Storage / Stability: Stable if stored at -20 °C. [428]

Clinical Trials: Stage 2.[429]

Prices: 5 mg - 41 EUR; 25 mg - 164 EUR; 100 mg - 492 EUR.[349]

(*S*)-roscovitine



IUPAC Name: (2*S*)-2-((9-(1-methylethyl)-6-((phenylmethyl)amino)-9*H*-purin-2-yl)amino)-1-butanol.

CAS: 186692-45-5.

First Report: Wang *et al.* in 2001.[430]

Activity: Roscovitine is a highly efficient and selective inhibitor of certain cyclin-

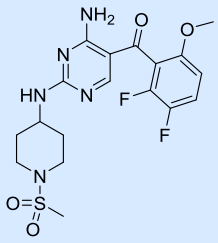
dependent kinases, including CDK2, CDK5, CDK7 and CDK9. In addition to its anticancer activities (and in contrast to the R isomer), S-roscovitine is being studied as a potential neuroprotectant for stroke because it can cross the blood brain barrier. In the brain, its inhibition of CDK5 blocks hypoxia-induced apoptosis in neurons.[424]

Storage / Stability: Stable for at least 2 years after receipt when stored at -20 °C.[431]

Clinical Trials: Stage 2.[432]

Prices: 5 mg - 41 EUR; 25 mg - 164 EUR; 100 mg - 492 EUR.[349]

R547



IUPAC Name: (4-amino-2-((1-methylsulfonylpiperidin-4-yl)amino)pyrimidin-5-yl)(2,3-difluoro-6-methoxyphenyl)methanone.

CAS: 741713-40-6.

First Report: DePinto *et al.* in 2006.[433]

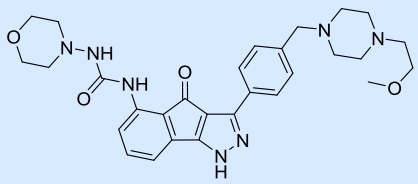
Activity: R547 is a CDK inhibitor (Ki = 1, 3, and 1 nM for CDK1, CDK2, and CDK4, respectively) with excellent *in vitro* cellular potency that inhibits the growth of various human tumour cell lines (HCT116 cells, H460a cells, MDA-MB-435 cells, DU145 cells, LOX cells and A549 cells). Its growth-inhibitory activity is characterized by cell cycle blockage in the G(1) and G(2) phases, reduced phosphorylation of the cellular retinoblastoma protein, and induction of apoptosis.[433]

Storage/Stability: Stable if the container was kept tightly closed in a dry and well-ventilated place, at -20 °C.[434]

Clinical Trials: Stage 1 completed.[435]

Prices: 5 mg - 647 EUR; 25 mg - 2558 EUR; 100 mg - 7764 EUR.[349]

RGB-286638



IUPAC Name: *N*-(1,4-dihydro-3-(4-((4-(2-methoxyethyl)-1-piperazinyl)methyl)phenyl)-4-oxoindeno(1,2-*c*)pyrazol-5-yl)-*N*'-4-morpholinylurea.

CAS: 784210-88-4.

First Report: Caligiuri *et al*. in 2006.[436]

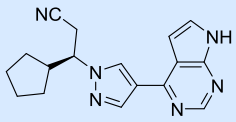
Activity: RGB-286638 is a cyclin-dependent kinase inhibitor with IC_{50} values of 1, 2, 3 and 44 nM for CDK9, CDK1, CDK2, and CDK4, respectively. It has been shown to inhibit cell cycle progression in cancer cells by targeting CDKs, and was found to induce apoptosis. In a range of pre-clinical models of solid and hematological tumours, RGB-286638 treatment resulted in tumour regression and increased survival.[437]

Storage / Stability: Stable if stored -20 C.[438]I

Clinical Trials: Stage 1.[439]

Prices: 5 mg - 185 EUR; 25 mg - 745 EUR; 100 mg - 2220 EUR.[349]

Ruxolitinib



IUPAC Name: (3*R*)-3-cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propanenitrilbeta.

CAS: 941678-49-5.

First Report: Rodgers *et al.* in 2007.[440]

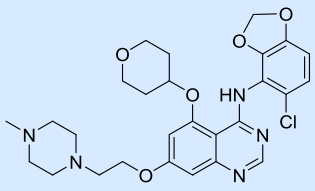
Activity: Ruxolitinib is a selective orally bioavailable JAK1/JAK2 inhibitor with nanomolar potency against JAK1 (5.9 nM) and JAK2 (5.7 nM). It inhibits the proliferation of JAK2V617F-positive cells. In a mouse model of JAK2V617F-positive MPN, it markedly reduced splenomegaly and circulating levels of inflammatory cytokines and preferentially eliminated neoplastic cells. This significantly increased survival without myelo- or immunosuppression.[441]

Storage / Stability: Stable if stored -20 °C.[442]

Clinical Trials: Stage 4.[443]

Prices: 5 mg - 185 EUR; 25 mg - 745 EUR; 100 mg - 2220 EUR.[349]

Saracatinib



IUPAC Name: *N*-(5-chloro-1,3-benzodioxol-4-yl)-7-(2-(4-methyl-1-piperazinyl)ethoxy)-5-((tetrahydro-2h-pyran-4-yl)oxy)-4-quinazolinamine.

CAS: 379231-04-6.

First Report: Hennequin *et al.* in 2001.[444]

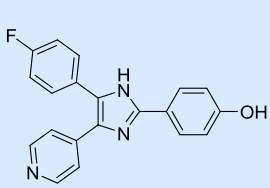
Activity: Saracatinib inhibits c-SRC and ABL at low nanomolar concentrations and exhibited high selectivity for these two enzymes against a range of kinases. It has excellent pharmacokinetic properties and is currently undergoing clinical evaluation as a possible anticancer drug, such as, hormone-resistant prostate cancer, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, pancreatic cancer, osteosarcoma, colorectal cancer and NSCL cancer.[445,446]

Storage / Stability: Stable if stored -20 °C.[447]

Clinical Trials: Stage 3 completed.[448]

Prices: 5 mg - 52 EUR; 25 mg - 208 EUR; 100 mg - 624 EUR.[349]

SB202190



IUPAC Name: 4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)-1*H*-imidazole.

CAS: 152121-30-7.

First Report: Leroy *et al*. in 1993.[449]

Activity: SB202190 is an inhibitor of the p38 mitogen-activated protein (MAP) kinases that regulate signal transduction in response to environmental stress. It inhibits SAPK2a and SAPK2b (p38 beta2) with I_{50} values of 50 nM and 100 nM, respectively. It also targets BRAF and cRAF kinases. In cells, SB202190 induces cell death, with typical apoptotic features such as nucleus condensation, caspase activation and intranucleosomal DNA fragmentation. These

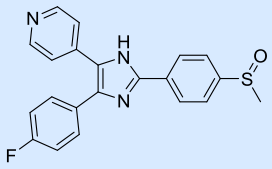
results were obtained using HeLa, Sh-SY5Y, WM1617, WM793 cells.[450,451]

Storage / Stability: Stable if storage -20 °C.[452]

Clinical Trials: No studies in the moment.[453]

Prices: 5 mg - 52 EUR; 25 mg - 208 EUR; 100 mg - 624 EUR.[349]

SB203580



IUPAC Name: 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1*H*-imidazole.

CAS: 152121-47-6.

First Report: Leroy *et al*. in 1993.[449]

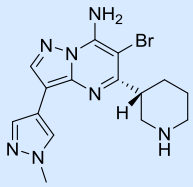
Activity: SB203580 is an inhibitor of the p38 mitogen-activated protein (MAP) kinases, selectively inhibiting SAPK2a and SAPK2b (p38 beta2) with IC_{50} values of 50 nM and 500 nM, respectively.[454] It was originally prepared as inflammatory cytokine synthesis inhibitor, but recently a study showed that with 50 µg/mL of SB203580, the proliferation of esophageal were significantly inhibited.[455]

Storage / Stability: Stable if stored -20 °C.[456]

Clinical Trials: No studies in the moment.[457]

Prices: 5 mg - 60 EUR; 25 mg - 120 EUR; 100 mg - 360 EUR.[349]

SCH900776



IUPAC Name: 6-bromo-3-(1-methyl-1*H*-pyrazol-4-yl)-5-(3*R*)-3-piperidinylpyrazolo(1,5-*a*)pyrimidin-7-amine.

CAS: 891494-63-6.

First Report: Guz *et al*. in 2006.[458]

Activity: SCH900776 is a potent and selective inhibitor of check-point kinase 1 (CHK1) with IC_{50} value of 3 nM. Sensitivity of CHK2 is 500 fold lower (IC_{50} value of 1500 nM). Consistently with its kinase inhibitory activity, SCH900776 abrogates cell-cycle arrest induced by SN38. It interacts synergistically with DNA antimetabolite agents *in vitro* and *in vivo* to selectively induce double strand DNA breaks and cell death in tumour cells.[459]

Storage / Stability: Stable if stored at -20 °C.[460]

Clinical Trials: Stage 2 completed.[461]

Prices: 5 mg - 160 EUR; 25 mg - 640 EUR; 100 mg - 1920 EUR.[349]

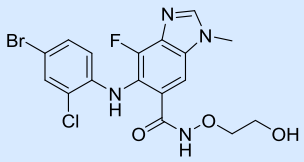
Selumetinib

IUPAC Name: 5-((4-bromo-2-chlorophenyl)amino)-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzimidazole-6-carboxamide.

CAS: 606143-52-6.

First Report: was invented by Array BioPharma Inc. (Nasdaq: ARRY) and licensed to AstraZeneca, in 2016.[462]

Activity: Selumetinib is a potent and selective MEK1/2 ATP-uncompetitive inhibitor with nanomolar IC_{50} values. It is highly active in both *in vitro* and *in vivo* tumour models. This compound is currently being investigated in clinical trials as a cancer drug, such as, differentiated thyroid cancer, locally advanced or metastatic NSCL Cancer Stage IIIb – IV, uveal melanoma, pancreatic cancer and breast cancer [463,464]

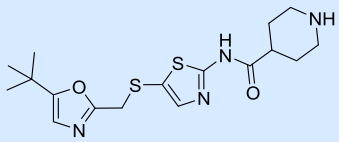


Storage / Stability: Stable is stored at -20 °C.[465]

Clinical Trials: Stage 3.[466]

Prices: 25 mg - 55 EUR; 100 mg - 220 EUR; 250 mg - 440 EUR.[349]

SNS-032



IUPAC Name: *N*-(5-((5-tert-butyl-1,3-oxazol-2-yl)methylsulfanyl)-1,3-thiazol-2-yl)piperidine-4-carboxamide.

CAS: 345627-80-7.

First Report: was licsensed from Bristol-Myers Squibb (BMS) in 2005.[467]

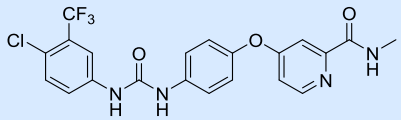
Activity: SNS-032 is a potent and selective inhibitor of cyclin-dependent kinases (CDKs) with IC_{50} values of 4, 62 and 38 nM for CDK9, CDK2/cyclin A and CDK7/Cyclin H, respectively. Its antiproliferative activity was established in an A2780 cellular cytotoxicity assay, in which it showed an IC_{50} value of 95 nM.[468] This compound is currently being investigated in clinical trials for the treatment for B-lymphoid malignancies, chronic lymphocytic leukaemia, mantle cell lymphoma and multiple myeloma.[469]

Storage / Stability: Stable if stored at -20 °C.[470]

Clinical Trials: Stage 2 completed.[471]

Prices: 5 mg - 140 EUR; 25 mg - 560 EUR; 100 mg - 1680 EUR.[349]

Sorafenib



IUPAC Name: 4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino]phenoxy]-*N*-methyl-pyridine-2-carboxamide.

CAS: 475207-59-1.

First Report: Riedl *et al*. in 2000.[472]

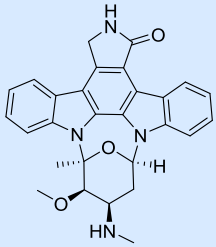
Activity: Sorafenib is a biarylurea derivative that selectively targets several receptor tyrosine kinases and Raf kinases. It has IC_{50} values of 6, 22, 38 nM for Raf-1, wt BRAF and V599E mutant BRAF. It has been approved for use in the treatment of advanced renal cancer and hepatocellular carcinoma.[473]

Storage / Stability: Stable if stored at -20 °C.[474]

Clinical Trials: Stage 4 completed.[475]

Prices: 5 mg - 85 EUR; 25 mg - 340 EUR; 100 mg - 1020 EUR.[349]

Staurosporine



IUPAC Name: (*9S,10R,11R,13R*)-2,3,10,11,12,13-Hexahydro-10-methoxy-9-methyl-11-(methylamino)-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-j][1,7]benzodiazonin-1-one.

CAS: 62996-74-1

First Report: Omura *et al.* in 1977.[476]

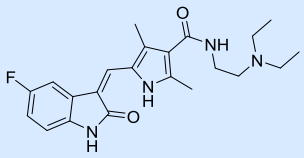
Activity: Staurosporine is a microbial alkaloid that was originally found to inhibit phospholipid/Ca^{2+} dependent protein kinase (protein kinase C) in low nanomolar concentrations. Later it was proved that staurosporin is potent non-selective inhibitor of many protein kinases. It displays strong cytotoxic and proapoptotic activity in many cultured cells.[477]

Storage / Stability: Stable if stored at -20 °C.[478]

Clinical Trials: Stage 3.[479]

Prices: 5 mg - 142 EUR; 25 mg - 568 EUR; 100 mg - 1704 EUR.[349]

Sunitinib



IUPAC Name: *N*-(2-diethylaminoethyl)-5-[(*Z*)-(5-fluoro-2-oxo-1*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide.

CAS: 341031-54-7.

First Report: was discovered at SUGEN/Pharmacia (which was acquired by Pfizer in 2003) in 2000.[480]

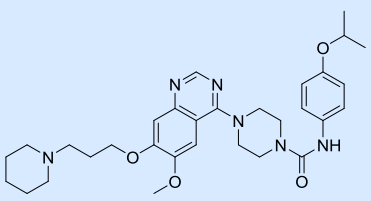
Activity: Sunitinib is a small molecule receptor tyrosine kinase inhibitor with direct antitumour as well as antiangiogenic activity. It targets the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), KIT, and FLT3 receptor tyrosine kinases, and has Ki values of 9 and 8 nM for FLK-1 and PDGFR, respectively. Sunitinib has been approved for use in the treatment of kidney cancer, gastrointestinal stromal tumours and pancreatic neuroendocrine tumours.[481]

Storage / Stability: Stable if the container was kept tightly closed in a dry and well-ventilated place.[482]

Clinical Trials: Stage 4 completed[483]

Prices: 25 mg - 43 EUR; 100 mg - 129 EUR; 250 mg - 258 EUR.[349]

Tandutinib



IUPAC Name: 4-[6-methoxy-7-[3-(1-piperidinyl)propoxy]-4-quinazolinyl]-*N*-[4-(1-methylethoxy)phenyl]-1-piperazinecarboxamide.

CAS: 387867-13-2.

First Report: Yu *et al.* in 2001.[484]

Activity: It is an orally active small-molecule tyrosine kinase inhibitor that targets the kinase insert domain receptor (KDR; VEGFR-2) and the FMS-related tyrosine kinase 4 (FLT4; VEGFR-3). Treatment with telatinib inhibits angiogenesis and cellular proliferation in tumours in which

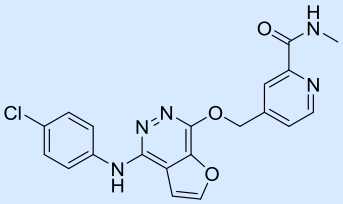
these receptors are upregulated. At this time, it is under clinical evaluation to the treatment for prostate cancer, renal cell carcinoma, glioblastoma, gliosarcoma, anaplastic astrocytoma, anaplastic oligodendroglioma, adult brain tumour and myelogenous leukaemia.[485-487]

Clinical Trials: Stage 2 completed.[488]

Storage / Stability: Stable if stored in a tightly closed container, in a dry and well-ventilated place, at -20 °C.[489]

Prices: 25 mg - 85 EUR, 100 mg - 255 EUR, 250 mg - 510 EUR.[490]

Telatinib



IUPAC Name: 4-((4-((4-chlorophenyl)amino)furo[2,3-d]pyridazin-7-yl)oxy)methyl)-*N*-methylpicolinamide.

CAS: 332012-40-5.

First Report: Dumas *et al*. from Bayer Corporation, in 2001.[491]

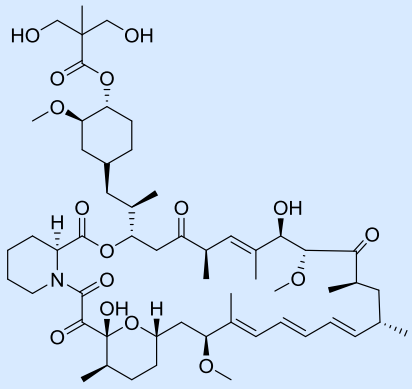
Activity: It is an orally active small-molecule tyrosine kinase inhibitor that targets the kinase insert domain receptor (KDR; VEGFR-2) and the FMS-related tyrosine kinase 4 (FLT4; VEGFR-3). Telatinib inhibits angiogenesis and cellular proliferation in tumours in which these receptors are upregulated, such as, colorectal cancer, ovarian cancer, adreanal cancer, esophageal cancer and soft tissue sarcoma.[492]

Clinical Trials: Stage 1 completed.[493]

Storage / Stability: Stable if stored in a tightly closed container, in a dry and well-ventilated place, at -20 °C.[494]

Prices: 5 mg - 194 EUR, 25 mg - 776 EUR, 100 mg - 2328 EUR.[490]

Temsirolimus



IUPAC Name: 1*R*,2*R*,4*S*)-4-{(2*R*)-2-[(3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosahydro-3*H*-23,27-epoxypyrido[2,1-*c*][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxycyclohexyl3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate.

CAS: 162635-04-3.

First Report: Wyeth Pharmaceuticals, Inc. in 2000.[495]

Activity: It is a water-soluble synthetic rapamycin ester that has been developed for both oral and intravenous applications. Like rapamycin, temsirolimus is an inhibitor of the protein kinase mTOR, which is important for the synthesis of proteins that regulate proliferation and thus for cellular growth and survival. Inhibition of mTOR abrogates pathway-mediated cellular transcription and translation, leading to cell cycle arrest, antiangiogenesis and apoptosis. Temsirolimus has significant *in vitro* antitumour effects against a number of cancer cell lines and has demonstrated *in vivo* cytostatic activity in xenograft models. Patients receiving

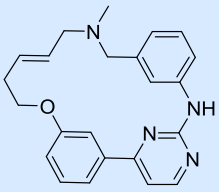
temsirolimus alone achieved longer survival than those receiving interferon alone or temsirolimus plus interferon in a randomized phase III trial. It has been approved as a drug for the treatment of renal cell carcinoma.[496,497]

Clinical Trials: Stage 4 completed.[498]

Storage / Stability: Stable if stored in a tightly closed container, in a dry and well-ventilated place, at -20 °C.[499]

Prices: 5 mg - 56 EUR, 25 mg - 224 EUR, 100 mg - 672 EUR.[490]

TG2



IUPAC Name: (16*E*)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene.

CAS: 937270-47-8.

First Report: discovered by S*BIO and licensed to Tragara Pharmaceuticals in 2008.[500]

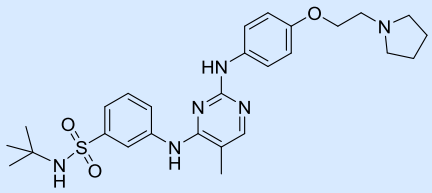
Activity: It is a novel pyrimidine-based multi-kinase inhibitor that inhibits CDKs 1, 2, 7 and 9 together with JAK2 and FLT3; IC_{50} values are 13, 73, and 56 nM for CDK2, JAK2 and FLT3, respectively. TG02 is cytotoxic in a broad range of tumour cell lines, inducing G1 cell cycle arrest, both the intrinsic and extrinsic pathways of apoptosis, depletion of XIAP and the key multiple myeloma survival protein MCL-1. It is currently undergoing clinical trials in advanced leukaemias and multiple myeloma.[501]

Clinical Trials: Stage 1.[502]

Storage / Stability: Stable if stored in a tightly closed container, in a dry and well-ventilated place, away from direct sunlight at -20 °C.[503]

Prices: 5 mg - 280 EUR, 25 mg - 1120 EUR, 100 mg - 3360 EUR.[490]

TG101348



IUPAC Name: *N*-tert-butyl-3-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-benzenesulfonamide.

CAS: 936091-26-8.

First Report: TargeGen in 2008.[504]

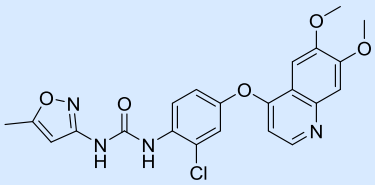
Activity: It is a potent and selective ATP-competitive JAK2 inhibitor with an IC_{50} of 3 nM; it is active also towards the JAK2 V617F mutant. TG101348 also inhibits the FLT3 and Ret kinases with IC_{50} values of 15 and 48 nM, respectively. It exhibits significantly less activity against other tyrosine kinases, including JAK3 (IC_{50}=169 nM). In treated cells, it blocks downstream cellular signalling (JAK-STAT), suppressing proliferation and inducing apoptosis. It is currently being developed for the treatment of patients with myeloproliferative diseases including myelofibrosis.[504,505]

Clinical Trials: Stage 2 completed.[506]

Storage / Stability: Stable if stored in a tightly closed container, in a dry and well-ventilated place, away from direct sunlight, at -20 °C.[507]

Prices: 5 mg - 140 EUR, 25 mg - 560 EUR, 100 mg - 1680 EUR.[490]

Tivozanib



IUPAC Name: *N*-{2-chloro-4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl}-*N'*-(5-methyl-3-isoxazole-yl)urea.

CAS: 475108-18-0.

First Report: AVEO Pharmaceuticals, in 2008.[508]

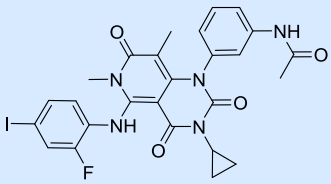
Activity: It is an orally active, ATP-competitive inhibitor of VEGFR tyrosine kinase developed for the potential treatment of cancer. Tivozanib inhibits activation of VEGFR-1, VEGFR-2 and VEGFR-3 at picomolar concentrations. In preclinical studies, tivozanib produced a significant inhibition of tumour growth and angiogenesis in several different animal models, such as, colorectal cancer, renal cancer, pancreatic cancer, NSCL cancer, esophageal cancer and melanoma.[509]

Clinical Trials: Stage 3 completed.[510]

Storage / Stability: Stable if stored in a tightly closed container, in a dry and well-ventilated place, away from direct sunlight at -20 °C.[511]

Prices: 5 mg - 80 EUR, 25 mg - 320 EUR, 100 mg - 960 EUR.[490]

Trametinib



IUPAC Name: *N*-(3-(3-cyclopropyl-5-(2-fluoro-4-iodophenylamino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2*H*)-yl)phenyl)acetamide.

CAS: 871700-17-3.

First Report: Abe *et al.* in 2011.[512]

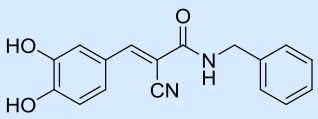
Activity: It is a potent and selective allosteric inhibitor of the MEK1 and MEK2 kinases with strong antitumour activity. Trametinib inhibits prevents Raf-dependent MEK phosphorylation (S217 for MEK1), producing prolonged p-ERK1/2 inhibition. Cell growth inhibition is significant in most tumour lines with mutant BRAF or Ras. It undergoes trials in patients with metastatic BRAF-mutant melanoma.[513,514]

Clinical Trials: Stage 4.[515]

Storage / Stability: Stable if stored in a tightly closed container, in a dry and well-ventilated place, away from direct sunlight and sources of ignition at -20 °C.[516]

Prices: 5 mg - 85 EUR, 25 mg - 340 EUR, 100 mg - 1020 EUR.[490]

Tyrphostin AG 490



IUPAC Name: 2-cyano-3-(3,4-dihydroxyphenyl)-*N*-(benzyl)-2-propenamide-2-cyano-3-(3,4-dihydroxyphenyl)-*N*-(phenylmethyl)-2-propenamide.

CAS: 134036-52-5.

First Report: Gazit *et al.* in 1991.[517]

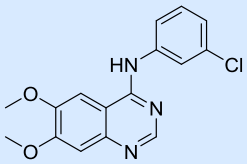
Activity: AG-490 potently inhibits the kinase activities of JAK2 and JAK3. Inhibition of JAK-2 activity by AG-490 selectively blocks leukaemic cell growth *in vitro* and *in vivo* by inducing programmed cell death (acute lymphoblastic leukaemia), with no deleterious effect on normal haematopoiesis. AG490 also suppresses cell proliferation and induces apoptosis in IL-6-dependent multiple myeloma cell lines. AG-490 inhibits JAK3-dependent activation of STAT5a/b and downstream signal transduction and cellular proliferation of antigen-activated human T cells.[518]

Clinical Trials: No studies in the moment.[519]

Storage / Stability: Stable if stored in a tightly closed container, in a dry and well-ventilated place at -20 °C.[520]

Prices: 5 mg - 52 EUR, 25 mg - 208 EUR, 100 mg - 624 EUR.[490]

Tyrphostin AG 1478



IUPAC Name: *N*-(3-chlorophenyl)-6,7-dimethoxy-4-quinazolinamine.

CAS: 175178-82-2.

First Report: Barker from Zeneca Ltd. in 1993.[521]

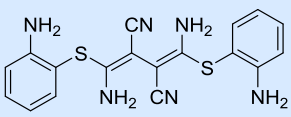
Activity: It is a specific inhibitor of the EGF-receptor tyrosine kinase (ERBB1) activity with an IC_{50} of about 3 nM *in vitro*. It is also very active against L858R and L861Q EGFR mutants. According to *in vitro* gene profiling, it displays moderate activity also against ERBB2 (HER2) and ERBB4 (HER4) receptors, LYNA and LYNB. AG1478 has very weak activity on PDGF and HER2-NEU kinases (IC_{50} values over 100 microM), in human myeloma cells.[522,523]

Clinical Trials: No studies in the moment.[524]

Storage / Stability: Stable if stored, as supplied at –20 °C. Upon solubilization, apportion into working aliquots and store at –20 °C. Avoid repeated freeze/thaw cycles. Solutions are stable at –20 °C for up to three months.[525]

Prices: 5 mg - 52 EUR, 25 mg - 208 EUR, 100 mg - 624 EUR.[490]

U0126



IUPAC Name: 1,4-diamino-2,3-dicyano-1,4-bis(2-aminophenylthio)butadiene.

CAS: 109511-58-2.

First Report: W. J. Middleton *et al.* in 1958.[526]

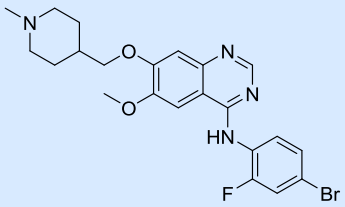
Activity: U0126 was originally found to functionally antagonize AP-1 transcriptional activity via non-competitive inhibition of the dual specificity kinases MEK with an IC_{50} of 70 nM for MEK1 and 60 nM for MEK2. Later, U0126 was reported to inhibit MKK1, and five-fold less potently also SAPK2a/p38, PRAK and PKB alpha.[527,528] It is currently being clinical evaluated as a anticancer drug for lung cancer, multiple myeloma, fallopian tube carcinoma, primary peritoneal carcinoma and recurrent ovarian carcinoma.[529]

Clinical Trials: Stage 3.[530]

Storage / Stability: Stable if stored, as supplied, at room temperature for up to one year and in solution at –20 °C for up to three months.[531]

Prices: 5 mg - 52 EUR, 25 mg - 208 EUR, 100 mg - 624 EUR.[532]

Vandetanib



IUPAC Name: *N*-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine.

CAS: 443913-73-3.

First Report: Hennequin *et al.* from AstraZeneca Canada Inc., in 2002.[533]

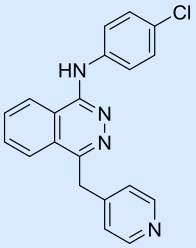
Activity: It is a tyrosine kinase inhibitor that targets the VEGFR (IC_{50} = 40 nM) and EGFR (IC_{50} = 500 nM) receptors. It is a potent *in vitro* inhibitor of VEGFA-stimulated endothelial cell proliferation (IC_{50} = 60 nM) and has been demonstrated to selectively inhibit VEGF signalling *in vivo* in a growth factor-induced hypotension rat model.[533,534] It is currently being clinical evaluated as a cancer drug for invasive breast cancer, differentiated thyroid cancer, prostate cancer, gastric cancer, lung cancer, colorectal cancer, thyroid cancer, HNC and breast cancer.[535]

Clinical Trials: Stage 4.[536]

Storage / Stability: Stable if stored in a tightly closed container, in a dry and well-ventilated place, away from direct sunlight and sources of ignition at -20 °C.[537]

Prices: 25 mg - 103 EUR, 100 mg - 309 EUR, 250 mg - 618 EUR.[538]

Vatalanib (dihydrochloride)



IUPAC Name: *N*-(4-chlorophenyl)-4-(pyridin-4-ylmethyl)phthalazin-1-amine dihydrochloride.

CAS: 212141-51-0.

First Report: Department of Oncology Research of Novartis Pharmaceuticals, in collaboration with the Institute of Molecular Medicine (Tumour Biology Center) in 2000.[539]

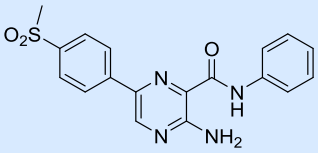
Activity: It is a potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases, active in the submicromolar range. It also inhibits other class III kinases, such as the platelet-derived growth factor (PDGF) receptor beta tyrosine kinase, c-KIT, and c-FMS, but at higher concentrations. It is not active against kinases from other receptor families, such as epidermal growth factor receptor, fibroblast growth factor receptor-1, c-MET, and TIE-2, or intracellular kinases such as c-SRC, c-ABL and protein kinase C-alpha.[539,540] It is currently being clinical evaluation for breast cancer, prostate cancer, pancreatic cancer, kidney cancer, NSCl cancer and pleural mesothelioma, ovarian cancer, endometrial cancer, cervical cancer, fallopian tube cancer, peritoneal cancer, brain and central nervous system tumours and leukaemia treament.[541]

Clinical Trials: Stage 3 completed.[542]

Storage / Stability: Stable if stored in a tightly closed container, in a dry and well-ventilated place at -20 °C.[543]

Prices: 25 mg - 88 EUR, 100 mg - 264 EUR, 250 mg - 528 EUR.[538]

VE-821



IUPAC Name: 3-amino-6-(4-(methylsulfonyl)phenyl)-*N*-phenylpyrazine-2-carboxamide-3-amino-6-[4-(methylsulfonyl)phenyl]-*N*-phenyl-2-pyrazinecarboxamide.

CAS: 1232410-49-9.

First Report: Reaper *et al*. in 2011.[544]

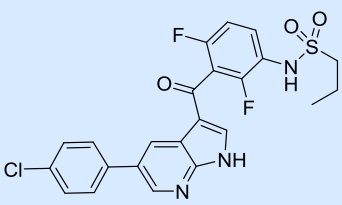
Activity: VE-821 was described as a potent and selective inhibitor of protein kinase ATR. The compound acts as an ATP competitor with IC_{50} value of 50 nM for ATR at 50 microM ATP. It exhibited no significant activity against a panel of 50 kinases. A VE-821 significantly enhanced the sensitivity of pancreatic cancer cells to radiation. ATR inhibition by VE-821 led to suppression of radiation-induced G2/M arrest in cancer cells and reduced cancer cell survival, accompanied by increased DNA damage and inhibition of homologous recombination repair. Growth arrest induced by ATR inhibition in normal cells is reversible and VE-821 does not induce cytotoxicity in normal cells.[545-547]

Clinical Trials: Stage 4.[548]

Storage / Stability: Stable if stored in a tightly closed container, in a dry and well-ventilated place, away from direct sunlight and sources of ignition at -20 °C.[549]

Prices: 5 mg - 85 EUR, 25 mg - 199 EUR, 100 mg - 599 EUR.[538]

Vemurafenib



IUPAC Name: *N*-(3-{[5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-b]pyridin-3-yl]carbonyl}-2,4-difluorophenyl)propane-1-sulfonamide.

CAS: 918504-65-1.

First Report: Plexxikon (now part of Daiichi-Sankyo) and Genentech in 2005.[550]

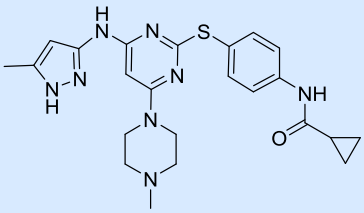
Activity: Vemurafenib is a BRAF inhibitor approved for the treatment of late-stage melanoma and for the treatment of adult patients with BRAF V600E unresectable or metastatic melanoma. In preclinical models, vemurafenib inhibited the growth of BRAF V600E-positive melanoma cell lines both *in vitro* and *in vivo*. Purified kinase assays have demonstrated that PLX-4032 and its related analogs are highly potent inhibitors of B-RAF activity, with 3-fold selectivity for the V600E mutation over the wild-type kinase.[551,552]

Clinical Trials: Stage 4.[553]

Storage / Stability: Stable if stored in a tightly closed container, in a dry and well-ventilated place, protected from the light at -20 °C.[554]

Prices: 5 mg - 55 EUR, 25 mg - 220 EUR, 100 mg - 660 EUR.[538]

VX-680



IUPAC Name: *N*-(4-(4-(5-methyl-1*H*-pyrazol-3-ylamino)-6-(4-methylpiperazin-1-yl)pyrimidin-2-ylthio)phenyl)cyclopropanecarboxamide.

CAS: 639089-54-6.

First Report: Vertex's Oxford in 2002.[555]

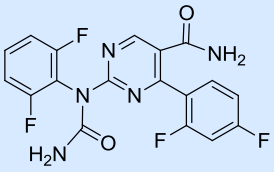
Activity: It is a highly potent and selective small-molecule inhibitor of Aurora kinases. In addition, it has activity against BCR-ABL, including the T315I BCR-ABL mutant. It also, blocks cell-cycle progression and induces apoptosis in a diverse range of human tumour types both *in vitro* and *in vivo*.[556,557,558] This compound is currently being evaluated for the treatment of colorectal cancer, NSCL carcinoma and leukaemia.[559]

Clinical Trials: Stage 2 completed.[560]

Storage / Stability: Keep container tightly sealed in cool, in well-ventilated area. Keep away from direct sunlight and sources of ignition. Recommended storage temperature: Store at -20 °C.[561]

Prices: 5 mg - 62 EUR, 25 mg - 248 EUR, 100 mg - 744 EUR.[538]

VX-702



IUPAC Name: 1-(5-carbamoyl-6-(2,4-difluorophenyl)pyridin-2-yl)-1-(2,6-difluorophenyl)urea.

CAS: 745833-*23-2.*

First Report: Vertex Pharmaceuticals Inc, in collaboration with Kissei Pharmaceutical Co Ltd, in 2003.[562]

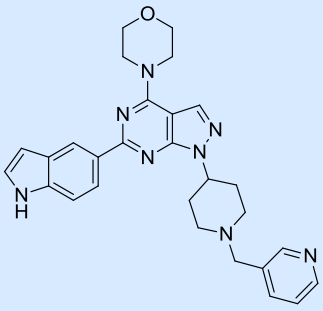
Activity: VX-702 is a p38 MAPK inhibitor, which shows activity against prostate cancer cells PC3 and Du145 and breast cancer cells MDA-MB-231.[563]

Clinical Trials: Stage 2 completed.[564]

Storage / Stability: Stable in the unopened package. The powder is stable for 1 year (at 4 °C desiccated) and in DMSO solution (at -20 °C) is stable for 6 months.[565]

Prices: 5 mg - 62 EUR, 25 mg - 248 EUR, 100 mg - 744 EUR.[538]

WAY-600



IUPAC Name: 4-[6-(1*H*-indol-5-yl)-1-[1-(pyridin-3-ylmethyl)piperidin-4-yl]pyrazolo[3,4-d]pyrimidin-4-yl]morpholine.

CAS: 1062159-35-6.

First Report: Zask *et al.* in 2008.[566]

Activity: It is a single digit nanomolar inhibitor of the mTOR kinases, with significant selectivity for these enzymes over phosphatidylinositol 3-kinase (PI3K) isofoms (>100-fold). WAY-600 inhibited the activity of proteins downstream of AKT and the proliferation of diverse

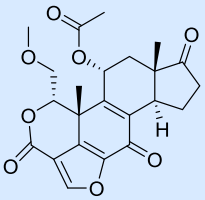
cancer cell lines. These effects correlated with a strong G(1) cell cycle arrest in both rapamycin-sensitive and rapamycin-resistant cells, selective induction of apoptosis, repression of global protein synthesis and down-regulation of angiogenic factors.[567] It is currently being evaluated for the treatment of metastatic colorectal cancer, breast cancer, lung cancer, prostate cancer, esophageal cancer, pancreatic cancer, peritoneal cavity cancer, squamous neck carcinoma of the head and neck cancer (SCCHN), lymphoma, leumkemia, melanoma, osteosarcoma and retinoblastoma.[568]

Clinical Trials: Stage 4 completed.[569]

Storage / Stability: Keep container tightly sealed in cool, well-ventilated area. Keep away from direct sunlight and sources of ignition. Recommended storage temperature: Store at -20 °C.[570]

Prices: 5 mg - 284 EUR, 25 mg - 1136 EUR, 100 mg - 3408 EUR.[571]

Wortmannin



IUPAC Name: (1S,6b*R*,9a*S*,11R,11b*R*)11-(acetyloxy)-1,6b,7,8,9a,10,11,11b-octahydro-1-(methoxymethyl)-9a,11bdimethyl-3*H*-furo[4,3,2-de]indeno[4,5,-*H*]-2-*H*]-2-benzopyran-3,6,9-trione.

CAS: 19545-26-7.

First Report: Isolated from *Penicillium wortmanmii Klöcker* by Norris's Group, in 1957[572] and characterized by Yeboah's group, in 1972.[573]

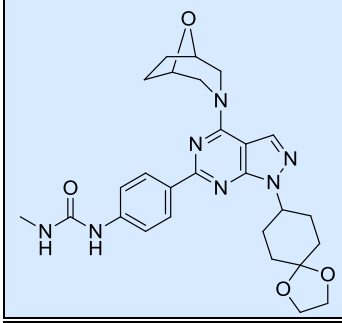
Activity: It is a fungal metabolite that has been shown to act as a selective inhibitor of phosphoinositide 3-kinases with IC_{50} values in low nanomolar range. It has been shown that wortmannin binds irreversibly in proximity to the substrate-binding site of PI3K. Wortmannin inhibits also the ataxia telangiectasia gene (ATM)-related DNA-dependent protein kinase (DNA-PKcs).[574,575] The exposing of KNS-62 and Colo-699 lung cancer cells to wortmannin the proliferation was inhibited in correlation to concentration *in vitro*. *In vivo* the blocking of PI3K by wortmannin prior to xenotransplantation caused a significant delay in the growth of subcutaneously induced tumours. Systemic wortmannin administration increased mean survival after intrapulmonary xenotransplantation of human NSCL cancer significantly by 38% and 47%.[576]

Clinical Trials: Stage 4 completed.[577]

Storage / Stability: Store in cool, well-ventilated area. Keep away from direct sunlight. Keep container tightly sealed until ready for use. Recommended storage temperature: Desiccate at -20 °C.[578]

Prices: 5 mg - 84 EUR, 25 mg - 336 EUR, 100 mg - 1008 EUR.[571]

WYE-125132



IUPAC Name: 1-[4-[1-(1,4-dioxaspiro[4.5]decan-8-yl)-4-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrazolo[3,4-d]pyrimidin-6-yl]phenyl]-3-methylurea.

CAS: 1144068-46-1.

First Report: Ker Yu *et al.* in 2010.[579]

Activity It is a highly potent (subnanomolar), ATP-competitive, and specific mTOR kinase inhibitor. WYE-132 inhibited mTORC1

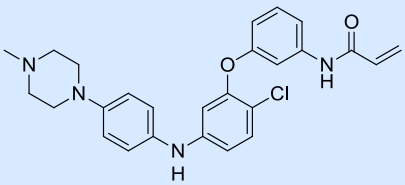
and mTORC2 in diverse cancer models *in vitro* and *in vivo*. Compared to the rapalog temsirolimus/CCI-779, WYE-132 is a significantly more potent inhibitor of cancer cell growth and survival, protein synthesis, cell growth, bioenergetic metabolism and adaptation to hypoxia.[579,580]

Clinical Trials: Stage 4 completed.[581]

Storage / Stability: Store at room temperature. The product can be stored for up to 12 months.[582]

Prices: 5 mg - 284 EUR; 25 mg - 1136 EUR; 100 mg - 3408 EUR.[571]

WZ3146



IUPAC Name: *N*-(3-(5-chloro-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide.

CAS: 1214265-56-1.

First Report: Wenjun Zhou *et al.* in 2009.[583]

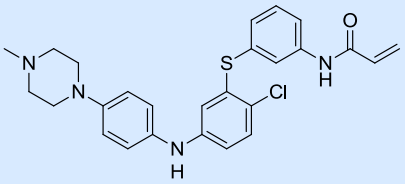
Activity: Similar to WZ8040.[583]

Clinical Trials: No studies in the moment.[584]

Storage / Stability: Storage in dry ambient and in absent of light. If stored to 0 - 4 °C is stable for several days to weeks; if stored at -20 °C remained stable for a period of several months to years.[585]

Prices: 5 mg - 194 EUR; 25 mg - 776 EUR; 100 mg - 2328 EUR.[571]

WZ8040



IUPAC Name: *N*-(3-(5-chloro-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylthio)phenyl)acrylamide.

CAS: 1214265-57-2.

First Report: Wenjun Zhou *et al.* in 2009.[583]

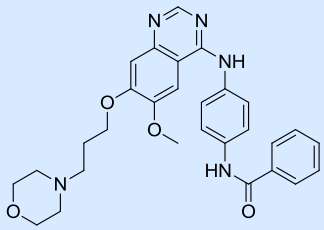
Activity: It is an irreversible inhibitor of EGFR receptor kinase mutants carrying a mutation in an active site gatekeeper residue (T790M), which is detected in 50% of patients exhibiting resistance to gefitinib or erlotinib. WZ8040 is much less potent against wild-type EGFR kinase.[583]

Clinical Trials: Pre-clinical Stage.[583]

Storage / Stability: Stable if stored in cold place (up to one week at 4 °C or six months at -20 °C) and kept the container tightly closed in a dry and well-ventilated place. Containers which are opened must be carefully resealed and kept upright to prevent leakage.[586]

Prices: 5 mg - 194 EUR; 25 mg - 776 EUR; 100 mg - 2328 EUR.[571]

ZM447439



IUPAC Name: *N*-[4-[[6-methoxy-7-[3-(4-morpholinyl)propoxy]-4-uinazolinyl]amino]phenyl]benzamide.

CAS: 331771-20-1.

First Report: Claire Ditchfield *et al.* in 2003.[587]

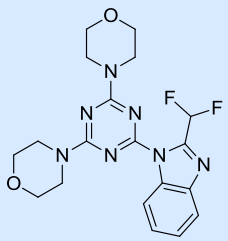
Activity: It is a selective ATP-competitive inhibitor of Aurora B kinase *in vitro*. ZM447439 has a higher over a range of other kinases including CDK1 and PLK1, when analysed in HCT-116 colorectal cancer cells. Inhibits cell division and displays selective toxicity towards proliferating tumour cells versus non-dividing cells.[588]

Storage / Stability: Stable if, stored in cool, well-ventilated area. Keeping away from direct sunlight, in a container tightly sealed until ready for use. After opening, keep the flash at the dissector conditions.[589]

Clinical Trials: Stage 1.

Prices: 5 mg - 103 EUR; 25 mg - 412 EUR; 100 mg - 1236 EUR.[590]

ZSTK474



IUPAC Name: 2-(2-difluoromethylbenzimidazol-1-yl)-4,6-dimorpholino-1,3,5-triazine.

CAS: 475110-96-4.

First Report: Shin-ichi Yaguchi *et al.* from Zenyaku Kogyo Co., Ltd.'s research laboratory in 1997.[591]

Activity: is a potent inhibitor of all four isoforms of class I PI 3-kinase. It has shown strong antitumour activity against human cancer xenografts (in mice by arresting cell growth);[592,593] In addition, it was able to inhibit osteoclast formation and collagen-induced arthritis in a mouse model.[594] It has higher selectivity over the other classes of PI3K and protein kinases. Until now, it not shown any type of toxicity to vital organs.

Storage / Stability: Stable if in powder form storage at -20 °C (years) and DMSO solution at 4 °C (months).[595]

Clinical Trials: Stage 1 completed.[596]

Prices: Manufactured and distributed only in small amounts: 60 EUR; 100 mg - 180 EUR; 250 mg - 360 EUR.[590]

3. Conclusions

This article presented a huge compilation of tyrosine kinase inhibitors, recently approved or under clinical trials, containing important informations that can be used for as a starting point for many medicinal chemists who wish to enter this area.

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