Review Article

Roscovitine in cancer and other diseases

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Abstract: Roscovitine [CY-202, (R)-Roscovitine, Seliciclib] is a small molecule that inhibits cyclin-dependent kinases (CDKs) through direct competition at the ATP-binding site. It is a broad-range purine inhibitor, which inhibits CDK1, CDK2, CDK5 and CDK7, but is a poor inhibitor for CDK4 and CDK6. Roscovitine is widely used as a biological tool in cell cycle, cancer, apoptosis and neurobiology studies. Moreover, it is currently evaluated as a potential drug to treat cancers, neurodegenerative diseases, inflammation, viral infections, polycystic kidney disease and glomerulonephritis. This review focuses on the use of roscovitine in the disease model as well as clinical model research.

Keywords: Cyclin-dependent kinases (CDK); small molecule inhibitor; roscovitine; cancer; neurodegeneration; kidney diseases

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Introduction

Protein phosphorylation by protein kinases plays a central role in the regulation of various cell processes, such as proliferation, cell cycle, differentiation and apoptosis. Because of that, deregulation of kinase activity can result in remarkable changes of these processes. Deregulated kinases are often found to be oncogenic and can be central for the survival and spread of cancer cells (1). Likewise, the phosphorylation of some proteins, such as AKT (2-4), EGFR (5,6), ERBB2 (5,7-9), SCH1 (10) and RB1 (11) is associated with prognosis in cancers.

Cyclin-dependent kinases (CDK) are protein kinases of CMGC group of kinases, which play an essential role in the control of the cell cycle and/or proliferation and transcription. There are 21 CDK genes in human genome, 11 of which are so called "classical" CDKs. These CDKs are responsible for the activation of the cell cycle of quiescent cells as well as for the from G1/M and G2/S transitions of the cell cycle. Different CDKs are involved in different checkpoints of the cells cycle. CDK4 and 6 initiate the transition from quiescence to proliferation; CDK2 coordinates cell progression from G1 through S-phase, while CDK1 is a universal M-phase promoting factor. These CDKs also associate with different cyclins: CDK4/6 with cyclin D, CDK2 first with cyclin E and then with cyclin A and CDK1 with cyclin B (12). Increased levels of CDK4, CDK6 and CDK2 activities have been observed in many different cancers. Overexpression of CDK activators such as cyclin D1, cyclin E and cyclin A and the activating phosphatases CDC25A and CDC25B or loss of function of the CDK inhibitors CDKN2A, CDKN1A and CDKN1B are major causes for the overactivation of CDKs (13). The fundamental role of CDKs in the cell cycle and proliferation, and their well-recognized role in the pathology of cancer make them attractive drug targets. Therefore, the search for the inhibitors of CDKs has been one of the interests of both academic and

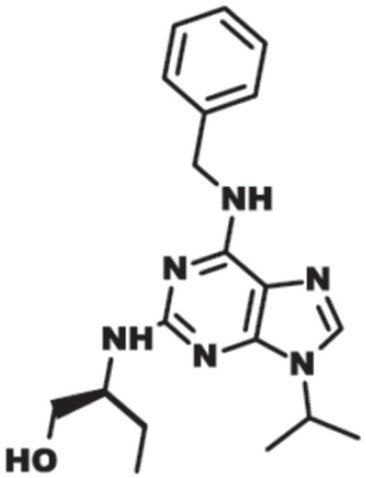

Figure 1 Roscovitine.

Table 1 CDKs inhibited by roscovitine

CDK	IC_{50} (μM)	Reference
CDK1/cyclin B	0.65	(20)
CDK2/cyclin A	0.70	(20)
CDK2/cyclin E	0.70	(20)
CDK4/cyclin D1	>100	(20)
CDK5/p25	0.16	(20)
CDK6/cyclin D3	>100	(20)
CDK7/cyclin H	0.46	(19)
CDK8/cyclin C	>100	(21)
CDK9/cyclin T1	0.60	(21)

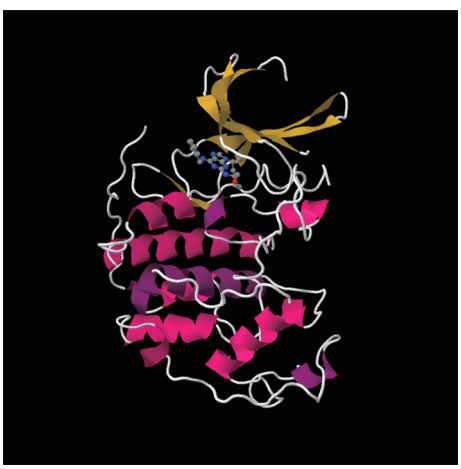

Figure 2 Crystal structure of CDK2 in complex with roscovitine. Image from the RCSB PDB (www.rcsb.org). DOI: 10.2210/pdb2a4l/pdb (19).

industrial scientific communities. To date, more than 30 different CDK small molecule inhibitors are developed: broad-range inhibitors (such as flavopiridol, olomoucine, roscovitine, kenpaullone, SNS-032, AT7519, AG-024322, R547), specific inhibitors (such as fascaplysin, ryuvidine, purvalanol A, NU2058, BML-259, SU 9516, PD 0332991, P-276–00) and third generation inhibitors (such as CR8#13, dinaciclib). Many of these inhibitors had entered different stages of clinical trials (14-18).

Roscovitine (named after Roscoff—a French town, where the lab which discovered the compound was located) (*Figure 1*) is also known as (R)-Roscovitine, CY-202, and Seliciclib. The systematic name of roscovitine is (2R)-2-{[6-(Benzylamino)-9-isopropyl-9H-purin-2-yl] amino}-1-butanol, chemical formula $C_{19}H_{26}N_6O$, molecular weight—354.45. It is a white powder that is soluble in DMSO (up to 50 mM) and in 50 mM HCl with the pH adjusted to 2.5. Roscovitine belongs to the family of purines, which all share the basic ring structure and include biologically important molecules such as ATP, cyclic AMP, NAD, FAD, adenine and guanine, etc. It acts by competing with ATP for binding at the ATP-binding site of CDKs by interacting with the amino acids that line up the ATP-binding pocket of the CDK catalytic domain. In case of CDK2, the interaction mostly consists of two hydrogen bonds (involving N7 and N6 of the purine) with backbone atoms of Leu83. A weak hydrogen bond is also formed between O1 and a water molecule and the benzyl ring of roscovitine is facing the outside of the ATP-binding pocket. This interaction prevents ATP from binding the kinase, and thus catalytic reaction cannot be performed (19). Roscovitine is a broad-range purine analog inhibitor, which inhibits CDK1, CDK2, CDK5, CDK7and CDK9 (IC_{50} ~0.2-0.7 μM) but is a poor inhibitor for CDK4, CDK6 and CDK8 (IC_{50} >100 μM) (*Table 1*). Only several kinases are sensitive to roscovitine in the 1-40 μM range (CaMK2, CK1α, CK1δ, DYRK1A, EPHB2, ERK1, ERK2, FAK, and IRAK4), but other kinases are insensitive to roscovitine (20,22,23). It has been shown that roscovitine acts by competing with ATP for binding at the ATP-binding site of CDKs. This binding at the catalytic site was confirmed by direct cocrystallization of roscovitine with CDK2 (19) (*Figure 2*) and CDK5/p25 (24) (*Figure 3*). Affinity chromatography with sepharose-immobilized roscovitine shown that roscovitine interacts with PDXK from all species that have been investigated (22). Roscovitine has been cocrystallized with sheep pyridoxal kinase (PDXK) (25) (*Figure 4*) and the interaction investigated in depth.

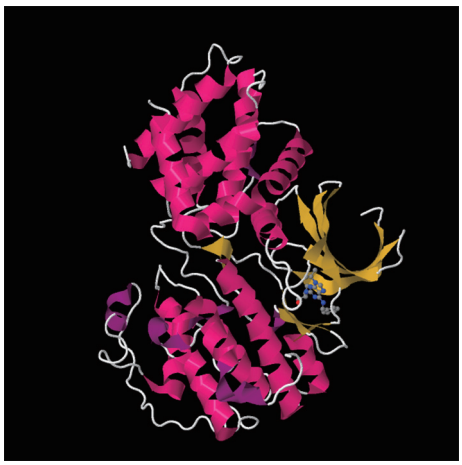

Figure 3 Crystal structure of CDK5-p25 in complex with roscovitine. Image from the RCSB PDB (www.rcsb.org). DOI: 10.2210/pdb1unl/pdb (23).

Figure 4 Crystal structure of pyridoxal kinase in complex with roscovitine. Image from the RCSB PDB (www.rcsb.org). DOI: 10.2210/pdb1ygk/pdb (24).

Unexpectedly, roscovitine was located in the pyridoxal-binding site, instead of the ATP-binding site and the atoms of roscovitine involved in the binding to PDXK were different from those involved in the binding to CDKs. The roscovitine/CDK cocrystal structures bred a lot of interest and significantly stimulated the search for new CDK inhibitors or the rational optimization of the existing ones. To date, more than 20 inhibitors have been cocrystallized with CDKs. Roscovitine is a widely used inhibitor in both basic research and disease research. It has been tested in several phase I and II clinical trials both as monotherapy and combination therapy in several human cancers.

Cellular effects and preclinical tests

The effects of roscovitine had been evaluated on a wide variety of cancer cell lines.

Roughly, two main processes have been observed: cell cycle arrest and an initiation of apoptosis. Roscovitine arrests the cell cycle in all tested cancer cell lines with the average IC_{50} value of about 15 μM (19,26). Roscovitine blocks cell cycle in G0, G1, S or G2/M, depending on the dose, time or cell line, by directly inhibiting CDKs. Moreover, there are many molecular processes that depend on the activity of CDKs activity, and thus, are inhibited by roscovitine. Those include pathways such as Ras-MAPK (27), NF-κB (28), p53 (28,29), estrogen receptor (30), JAK-STAT (31), etc.

Roscovitine induces apoptosis in many cancer cell lines at all phases of the cell cycle (32). It has been shown to downregulate Bcl-2 (33), Mcl-1 (34), survivin (35) and XIAP (35) and upregulate p53 (36), p53AIP1 (37) and Bcl-x (38) and others (39).

In addition, roscovitine has been shown to have a synergistic effect with other anti-cancer agents, such as doxorubicin (40,41), taxol (41), 5-fluorouracil (41), vinblastine (41), alemtuzumab (42), paclitaxel (43), trastuzumab (44), cisplatin (45), radiation (46), irinotecan (47), etoposide (48) and tamoxifen (49).

The anti-cancer action of roscovitine has also been investigated in various cancer xenografts. Xenograft experiment using LoVo human colorectal cancer cells grafted into CD1 nude mice showed a significant antitumor effect of roscovitine (100 mg/kg administered intraperitonealy, 3 times daily for 5 days) with a 45% reduction in tumor growth compared to control animals (32). Same publication shows xenograft experiment using MESSA-DX5 human uterine carcinoma cells grafted into CD1 nude mice. Roscovitine (orally administered, 500 mg/kg 3 times daily for 4 days) displayed a significant reduction in tumor growth (62%). MDA-MB 231 tumor xenografts in nude mice increased growth inhibition of 73% combined treatment group (100 mg/kg roscovitine + 7.5 Gy irradiation) as compared with 54% for the irradiation only group (P=0.02) (46). Roscovitine (administered orally 500 mg/kg) caused a 79% reduction in the tumor growth compared to controls at day 5 (P<0.05) in the HCT116 human colon cancer xenograft model in nude mice (50).

Mice xenografts of A4573 Ewing's sarcoma cells treated with roscovitine (administered intraperitonealy 50 mg/kg, for 5 days) had grown only ~1.25-fold relative to their size at the time of treatment start, while tumors in untreated mice had already reached ~14.5-fold their original size (51). Roscovitine also showed 35% tumor growth inhibition in a PC-3 prostate cancer xenograft model (52). Osteosarcoma tumor xenograft in B6D2F1 mice weight was reduced by 55% in the animals receiving roscovitine (administered orally 300 mg/kg a day) during resting time and by 35% in those treated at active time compared with untreated controls (P<0.001) (53). HT29 human colon cancer xenografts in nude mice had a 68% and 80% tumor reduction using 10 and 40 mg/kg roscovitine respectively, administered intraperitoneally (P<0.001) (47). MCF7 breast cancer xenografts in nude mice showed statistically significant inhibition of tumor growth of 48% and 70%, when treated single agent (orally administered 1.5 mg/kg doxorubicin or 400 mg/kg roscovitine, twice a day) compared with seliciclib + doxorubicin, respectively relative to the vehicle control group (P<0.05) (54). Immunodeficient mice, subcutaneously injected with RAMOS or HBL-2 cell lines, treated with roscovitine (12.5 mg/mouse) and TRAIL (250 µg/mouse), as single agents or in combination, showed that significantly suppressed the growth of both RAMOS (P=0.0221) and HBL-2 (P=0.0014) tumors compared to single-agent approaches (55). Xenograft study, using hormone therapy-resistant breast cancer cell lines (MCF-7-TamR, MCF-7-LTLTca and MCF-7-HER2), treated with roscovitine (administered orally at a dose of 100 mg/kg), showed significantly smaller tumor volumes and smaller tumor sizes (P<0.05) (56). DNA synthesis was inhibited 75% by 50 µM roscovitine treatment in tissue mini-units were prepared from tumor specimens obtained from the rat G2 glioma model (57). The preclinical studies, described in this section, are summarized in *Table 2*.

Preclinical studies of roscovitine in other pathologies

Cancers, however, are not the only diseases, that have been investigated in animal models. Apparently, CDKs are involved in quite a few disorders, and thus CDK inhibition by roscovitine can help to overcome them. One of the most investigated groups of diseases in animal models is kidney diseases. Polycystic kidney disease is one of those, and roscovitine produces effective arrest of it in jck and cpk mouse models of polycystic kidney disease (75). In a Pkd1 conditional knockout mouse model, which results in a rapid onset polycystic kidney disease at day 5, roscovitine-treated group (administered 100 mg/kg, once a day) showed a significant inhibition of polycystic kidney disease, revealed by a decrease in kidney to body weight ratio, cystic volume and blood urea nitrogen (P<0.05) (76). Glomerulonephritis is another highly investigated disease, or rather an outcome of a number of diseases. In mice with systemic lupus, roscovitine treatment (100 or 200 mg/kg), combined with methylprednisolone extended the survival (71% and 77% of those treated with 100 and 200 mg/kg, respectively, as compared with 31% of control), limited proteinuria (43% in the group receiving 100 mg/kg of roscovitine and 23% in the group receiving 200 mg/kg of roscovitine, compared with 85% in control) and renal damage and reduced immunologic signs of disease more than treatment with any of the compound separately (79). There was a 30% decrease in the urine protein/creatinine ratio at day 10 in rats with Thy1 glomerulonephritis given roscovitine compared to control (P<0.05) (62). Mesangial cell proliferation was reduced by >50% at days 5 and 10 in the Roscovitine prevention group, and at day 5 in the treatment group (P<0.0001). Similar study showed, that roscovitine treatment in rats with Thy1 glomerulonephritis preserved renal function, such as increased creatinine clearance (P<0.007), reduced proteinuria (P<0.02), increased urinary excretion (P<0.02), reduced haematuria (P<0.02) (63). In the study of rats with passive Heymann nephritis, compared to control group, treatment with low-dose roscovitine (25 mg/kg/day) decreased the number of glomerular mitotic figures at day 30 by 22% and by 61% in the high-dose group (50 mg/kg/day) (66). Cell proliferation was significantly lower in the high-dose roscovitine-treated group as compared to the vehicle-only–treated group (P<0.05). Rat model of ischemia–reperfusion injury showed protective effect of roscovitine: there was noticeable acute tubular necrosis in control animals, but roscovitine-treated group showed negligible histologic signs of ischemic injury (68). The roscovitine-treated group showed lower values of both blood urea nitrogen and creatinine than control group (P<0.05).

Roscovitine was also investigated in pain treatment in animal models. Bone cancer mice models were used to investigate whether roscovitine could attenuate bone cancer pain. At day 14 after inoculation, osteosarcoma significantly enhanced mechanical allodynia and thermal hyperalgesia, which was reduced by roscovitine (intrathecal administration 5, 10 or 20 µg) by downregulation of the

Table 2 Preclinical and clinical studies of roscovitine in different diseases

Disease	Preclinical/Clinical tests	Effects	Reference
Adenocarcinoma of unknown primary	Phase I clinical trial	Tumor stabilization	(58)
Advanced malignancies	Phase I clinical trial	Disease stabilization observed in 38% patients (8/21)	(59)
B-cell malignancies	Phase II clinical trial	NA	(60)
B-cell lymphoma	HBL-2 xenograft model in nude mice (combination TRAIL)	Significant suppression of tumor growth compared to single-agent approaches (P=0.0014)	(55)
Breast cancer	MDA-MB 231 xenograft model in nude mice (combination with irradiation)	Increased growth inhibition of 73% combined treatment group as compared with 54% for the irradiation only group	(46)
	MCF7 xenograft model in nude mice	70% reduction in the tumor growth	(54)
	MCF-7-TamR, MCF-7-LTLTca and MCF-7-HER2 xenograft models in nude mice	Significantly smaller tumor volumes and smaller tumor sizes (P<0.05)	(56)
Breast cancer (metastatic)	Phase II clinical trial (combination with capecitabine)	NA	(60)
Burkitt's lymphoma	RAMOS xenograft model in nude mice (combination TRAIL)	Significant suppression of tumor growth compared to single-agent approaches (P=0.0221)	(55)
Colorectal cancer	LoVo xenograft model in CD1 nude mouse	45% reduction in tumor growth	(32)
	HT29 xenograft model in nude	68% and 80% tumor reduction using 10 and 40 mg/kg roscovitine respectively	(47)
	HCT116 xenograft model in nude mouse	79% reduction in the tumor growth	(50)
Corticosurrenaloma	Phase I clinical trial	Partial response	(58)
Ewing's sarcoma	A4573 xenograft model in nude mouse	91% reduction in the tumor growth	(51)
Glaucoma	Rabbit glaucoma model	Lowering of the intraocular pressure and increase of oxygen-glucose deprivation-induced cell death	(61)
Glioma	Rat G2 glioma model	75% reduction in DNA synthesis	(57)
Glomerulonephritis	Rat Thy1 glomerulonephritis model	30% decrease in the urine protein/creatinine ratio; mesangial cell proliferation reduced by >50%	(62)
	Rat Thy1 glomerulonephritis model	Increased creatinine clearance and urinary excretion, reduced proteinuria and haematuria	(63)
Graft versus host disease	Graft versus host disease B6D2F1 mouse model	Protection against acute graft versus host disease	(64)
Hepatocellular carcinoma	Phase I clinical trial	Partial response	(58)
Herpes simplex virus infection	Vero cells, infected with wild-type HSV-, model	Inhibition of virus replication by targeting cellular, not viral, proteins	(21)
Herpetic keratitis	New Zealand white rabbits, infected with HSV-1, keratitis model	Partial decrease of herpetic keratitis	(65)
Heymann nephritis	Rat passive Heymann nephritis model	22% and 61% decrease in glomerular mitosis in high- and low-dose groups, respectively	(66)

Table 2 (*continued*)

Table 2 (*continued*)

Disease	Preclinical/clinical tests	Effects	Reference
HIV1 virus infection	CEMx174 cells, infected with wild-type HSV-, model	Inhibition of virus replication by targeting cellular, not viral, proteins	(21)
Inflammation	Lung inflammation mouse model	Lung inflammation reduction	(67)
Ischemia-reperfusion injury	Rat ischemia–reperfusion injury model	Roscovitine-treated group showed negligible histologic signs of ischemic injury	(68)
Nasopharyngeal carcinoma	Phase I/II clinical trial	NA	(69)
Neurotoxicity	HIV protein gp120 transgenic mouse model	Protection against HIV protein gp120 neurotoxicity	(70)
Non-small cell lung cancer	Phase I clinical trial	Partial response	(58)
	Phase II clinical trial	NA	(71)
	Phase II clinical trial (combination with gemcitabine/cisplatin)	NA	(60)
	Phase II clinical trial (combination with docetaxel)	NA	(60)
Osteosarcoma	Osteosarcoma tumor xenograft model in B6D2F1 mouse	Tumor weight reduced by 55% in the animals treated during resting time and by 35% in those treated at active time	(53)
Pain	Mouse bone cancer model	Reduction of mechanical allodynia and thermal hyperalgesia, caused by osteosarcoma; by downregulation of the expression of NR2A	(72)
	Rat model of chronic compression of dorsal root ganglion	Pain alleviation by downregulation of the expression of NR2A	(73)
	Remifentanil-induced postoperative hyperalgesia of spinal cord model	Reduction thermal hyperalgesia and mechanical allodynia by downregulation of the phosphorylation of NR2A and glutamate receptor 5	(74)
Parotid cylindroma	Phase I clinical trial	Partial response	(58)
Polycystic kidney disease	Jck and cpk mouse models	Effective arrest of disease	(75)
	Pkd1 conditional knockout mouse model	Decrease in kidney to body weight ratio, cystic volume and blood urea nitrogen	(76)
Prostate cancer	PC-3 xenograft model in nude mouse	35% reduction in tumor growth	(52)
Retinal degeneration	Rd1 retinal degeneration mouse model	Decreased apoptosis of retinal photoreceptor cells	(77)
Salivary gland dysfunction	Radiation-induced salivary gland dysfunction mouse model	Radiation-induced salivary gland dysfunction prevention	(78)
Systemic lupus	Mouse systemic lupus model (combination with methylprednisolone)	Survival extension (71% and 77% in high- and low-dose groups, respectively, compared with 31% of control), limited proteinuria (43% and 23% compared with 85% in control) and renal damage and reduction of immunologic signs of disease	(79)
Thymic carcinoma	Phase I clinical trial	Partial response	(58)
Uterine carcinoma	MESSA-DX5 xenograft model in CD1 nude mice	62% reduction in tumor growth	(32)

expression of NR2A (72). Downregulation of the expression of NR2A is also involved in pain alleviation by roscovitine in a rat model of chronic compression of dorsal root ganglion (73). Roscovitine (intrathecal administration 25, 50 or 100 μg) reduced thermal hyperalgesia ($P<0.05$) and mechanical allodynia ($P<0.05$) induced by intraoperative remifentanil administration (74).

Neurodegeneration and retinal degeneration is another well studied field with regard to roscovitine. In rabbit glaucoma model, instillation roscovitine significantly lowered the increased intraocular pressure, amplified the effects of tunicamycin and increased oxygen-glucose deprivation-induced cell death (61). Roscovitine decreased apoptosis of retinal photoreceptor cells in Rd1 retinal degeneration mouse model ($P<0.01$) (77). Pretreatment with roscovitine at 20 μmol/L for 24 h was protective against HIV protein gp120 toxicity in an animal model of HIV-protein mediated neurotoxicity ($P<0.05$) (70).

Roscovitine was also shown to reduce lung inflammation (67), protect against acute graft versus host disease (64), prevent radiation-induced salivary gland dysfunction (78) and had somewhat decreased Herpetic keratitis (65). Roscovitine was also shown to inhibit the replication of herpes simplex virus and HIV1 by targeting cellular proteins (21). The preclinical studies, described in this section, are summarized in *Table 2*.

Clinical trials

A phase I clinical trial with roscovitine showed no objective tumor responses, but disease stabilization was observed in 38% patients (8/21) (59). Patients were treated with doses of 100, 200 and 800 mg twice daily. Dose-limiting toxicities were seen at 800 mg and included fatigue, skin rash, hyponatremia and hypokalemia. Emesis and reversible abnormal liver function were also observed. Another phase I clinical trial enrolled 56 patients, which were treated according to three schedules: schedule A consisted of 5 consecutive days every 3 weeks, schedule B of 10 consecutive days followed by 2 weeks off and schedule C of 3 consecutive days every 2 weeks. In schedule A, the dose of 1,600 mg two times daily was considered intolerable, causing asthenia, nausea, vomiting and hypokalaemia. In schedule B, 800 mg two times daily was considered intolerable, causing hypokalaemia. In schedule C, 1,800 mg two times daily are considered intolerable, causing hypokalaemia. One patient with hepatocellular carcinoma showed partial response (800 mg bid, schedule B) and six patients achieved tumor stabilization: two patients with non-small cell lung cancer (1,600 mg, schedule A, and 1,800 mg, schedule C), one with parotid cylindroma (100 mg, schedule A), one with corticosurrenaloma (1,000 mg, schedule A), one with thymic carcinoma (1,000 mg, schedule A) and one with adenocarcinoma of unknown primary (400 mg, schedule A) (58).

Twenty-three nasopharyngeal carcinoma patients were enrolled in phase II roscovitine clinical trial. Dose limiting toxicities were observed in 4 patients, common adverse events included fatigue, nausea, vomiting, constipation, cough, fever, hypokalemia, hyponatremia, and elevation in aspartate transaminase/ alanine transaminase, most of which were mild or moderate (69). Another phase II study of roscovitine as a single agent in patients with previously-treated non-small cell lung cancer has been closed with no data reported (71). Four phase II studies were announced, however no data is published up to date. One of them was a monotherapy trial in haematological B-cell malignancies, while the other three are combination trials with gemcitabine/cisplatin in first-line non-small cell lung cancer, with docetaxel in second line non-small cell lung cancer and with capecitabine in metastatic breast cancer (60). The clinical studies, described in this section, are summarized in *Table 2*.

The future of roscovitine and its derivatives in cancer and other diseases

Despite many successful preclinical studies with roscovitine, clinical trials are not very encouraging. It would seem that combination therapies with roscovitine could be more promising than monotherapy, thus more chemotherapeutic agents as well as other targeted drugs should be evaluated in combination.

Another hope lies with next generation derivatives of roscovitine. Roscovitine derivative CR8 (*Figure 5*) was also shown to inhibit renal cystogenesis in Pkd1-conditional knockout in above mentioned study (76). It was shown to provide neuroprotection in experimental traumatic brain injury (80). CDK/CK1 dual-specificity inhibitors (*Figure 5*), derived from roscovitine, were shown to inhibit cell proliferation and prevent the production of amyloid-beta and may have applications in Alzheimer's disease and cancers (81). N-&-N (*Figure 5*), another class of roscovitine derivatives, showed improved anticancer properties and caused apoptosis in a panel of different cell lines (82). In addition, these compounds have reduced affinity for Erk2

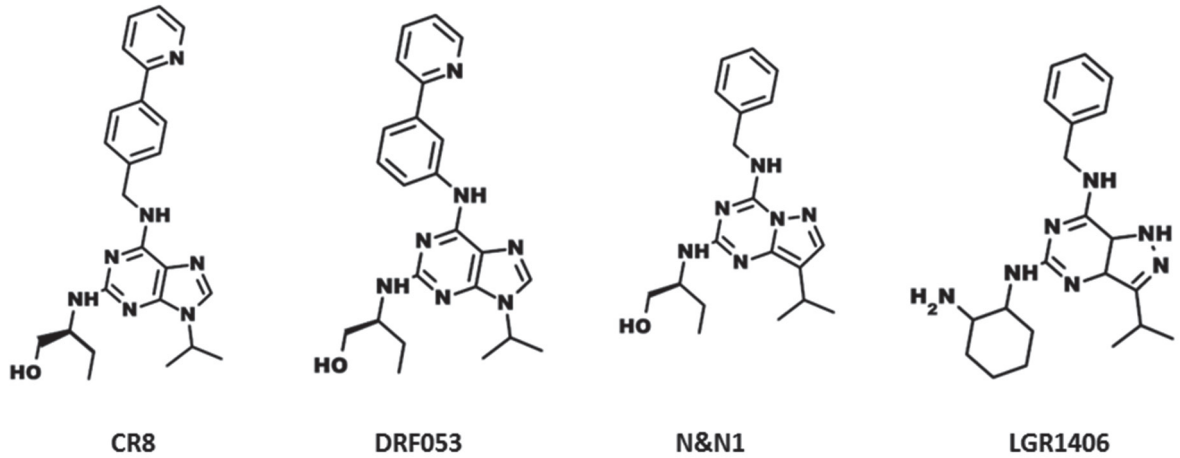

Figure 5 Compounds CR8, DRF053, N-&-N1 and LGR1406.

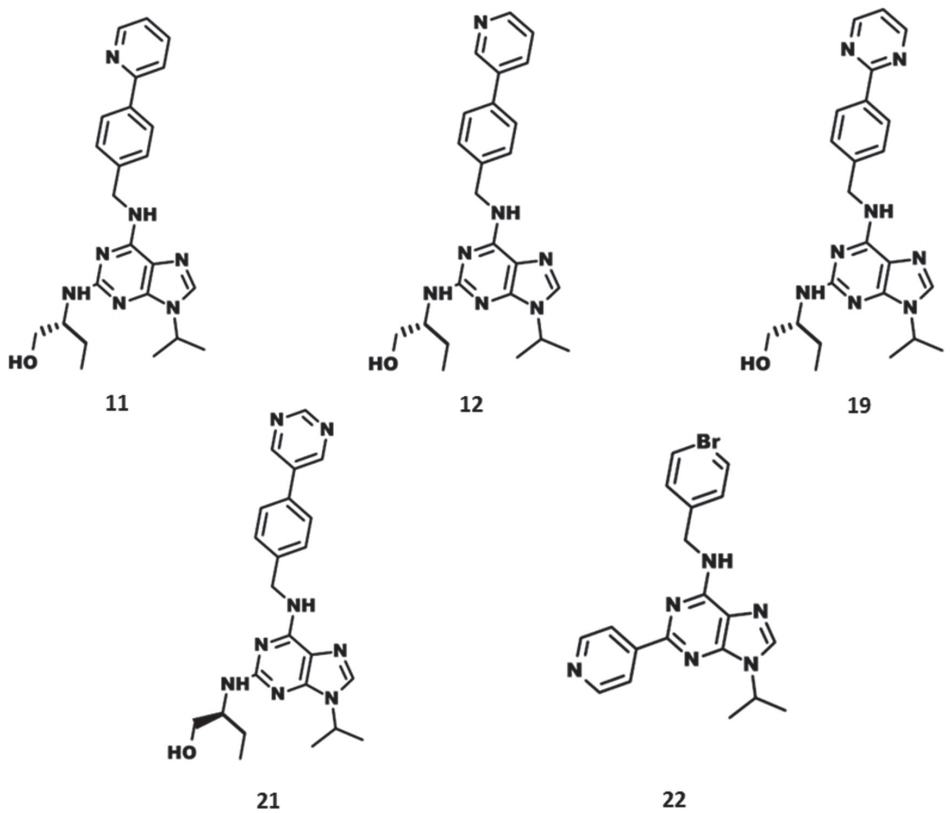

Figure 6 Compounds 11, 12, 19, 21 and 21.

and pyridoxal kinase. The roscovitine derivative LGR1406 (*Figure 5*) showed much more potent (IC_{50} =3.0 μM) antiproliferative activity than roscovitine (IC_{50} =16.9 μM), halting vascular smooth muscle cells (83). Recently, several CDK inhibitors, related to roscovitine (*Figure 6*), were reported as anti-malarial agents (84). The roscovitine derivatives, described in this section, are summarized in *Table 3*.

Table 3 Most promising roscovitine derivatives

Compound	Kinases inhibited (IC50, μM)	Tested	Disease(s)	Reference
CR8	CDK1 (0.090), CDK2 (0.041-0.072), CDK5 (0.110), CDK7 (1.100), CDK9 (0.180)	MDCK cells; Pkd1-conditional knockout mouse model; experimental traumatic brain injury mouse model	Autosomal dominant polycystic kidney disease, traumatic brain injury	(76,80)
DRF053 (13a)	CDK1 (0.220), CDK5 (0.080), CK1 (0.014)	*In vitro*; N2A-APP695 cells	Alzheimer's disease	(81)
N-&-N1	CDK1 (0.073), CDK2 (0.026-0.040), CDK5 (0.070), CDK7 (0.5), CDK9 (0.043)	*In vitro*; HCT116, MDA-MB-231, Huh7, F1, SH-SY5Y and HEK293 cells	Colon cancer, breast cancer, hepatoma, Neuroblastoma	(82)
LGR1406	CDK1 (3.20), CDK2 (0.600-1.000), CDK5 (0.400), CDK9 (1.100); AURKA (0.600)	Vascular smooth muscle cells	NA	(83)
11	CDK1 (0.800), CDK5 (0.400)	*In vitro*; *Plasmodium falciparum* (3D7 and 7G8 strains)	Malaria	(84)
12	CDK1 (0.200), CDK5 (0.100)	*In vitro*; *Plasmodium falciparum* (3D7 and 7G8 strains)	Malaria	(84)
19	CDK1 (0.500), CDK5 (0.270)	*In vitro*; *Plasmodium falciparum* (3D7 and 7G8 strains)	Malaria	(84)
21	CDK1 (0.040), CDK5 (0.060)	*In vitro*; *Plasmodium falciparum* (3D7 and 7G8 strains)	Malaria	(84)
22	CDK1 (0.600), CDK5 (0.600)	*In vitro*; *Plasmodium falciparum* (3D7 and 7G8 strains)	Malaria	(84)

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