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January | 2011

BIOACTIVE SMALL MOLECULES

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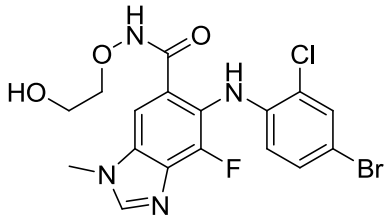
TABLE OF CONTENTS

Mitogen-activated protein kinase 1/2 inhibitor

5-[(4-Bromo-2-chlorophenyl)amino]-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzimidazole-6-carboxamide (ARRY 142886; ARRY-142886; AZD 6244)

- *inhibitor of MEK1/2 kinases, effectively inhibited the proliferation of acute biphenotypic leukemia MV4-11 and acute monocytic leukemia MOLM13 cells. The concentrations that inhibited 50% growth were approximately 0.3 and 1.2 μM, respectively, as measured by thymidine uptake on day 2 of culture. AZD6244 potently down-regulated the levels of phospho-ERK1/2 and its downstream effector, p-p70S6K, in the MV4-11 and MOLM13 cells as measured by Western blot analysis. Four BRAF mutant lines exhibited growth inhibition at low doses of the drug, with GI_{50} concentrations ranging from 14 to 50 nM, predominantly via a G0/G1 arrest, comparable with findings in a sensitive BRAF mutant melanoma cell line. In contrast, two BRAF wild-type lines were significantly less sensitive, with GI_{50} values greater than 200 nM. Nude mouse xenograft tumors derived from the BRAF mutant line ARO exhibited dosedependent growth inhibition by AZD6244, with effective treatment at 10 mg/kg by oral gavage. This effect was primarily cytostatic and associated with marked inhibition of ERK phosphorylation.*



Chemical Formula: $C_{17}H_{15}BrClFN_4O_3$
Molecular Weight: 457.68

OTAVA Catalogue Number: 1183194
CAS Registry Number: 606143-52-6
Purity: 97%+

Ref. 1: Revill et al. **AZD-6244.** *Drugs of the Future* (**2006**), *31*, 854-858
The MEK/ERK-dependent mitogen-activated protein (MAP) kinase pathway mediates cellular responses to growth signals, and aberrant regulation of the pathway has been implicated in many human cancers. Because of its key position as the only known activator of ERK, and its location downstream of the oncogenes ras and raf, MEK offers an attractive target for chemotherapeutic intervention. **AZD-6244 (ARRY-142886)** is an orally active, highly specific inhibitor of MEK that has shown tumor-suppressive activity in a wide range of preclinical models of human cancer. **AZD-6244** is currently in phase II development for the treatment of melanoma, non-small cell lung and pancreatic cancer.

Ref. 2: Yeh et al. **Biological Characterization of ARRY-142886 (AZD6244), a Potent, Highly Selective Mitogen-Activated Protein Kinase Kinase 1/2 Inhibitor.** *Clinical Cancer Research* (**2007**), *13*, 1576-1583
Purpose: The Ras-Raf-mitogen-activated protein kinase kinase (MEK) pathway is overactive in many human cancers and is thus a target for novel therapeutics. We have developed a highly potent and selective inhibitor of MEK1/2. The purpose of these studies has been to show the biological efficacy of ARRY-142886 (AZD6244) in enzymatic, cellular, and animal models.

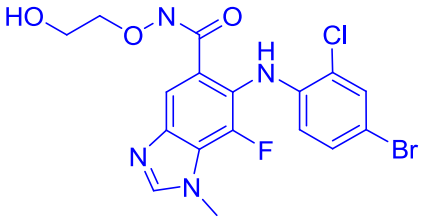
Experimental Design: The ability of ARRY-142886 to inhibit purified MEK1 as well as other kinases was evaluated. Its effects on extracellular signal-regulated kinase (ERK) phosphorylation and proliferation in several cell lines were also determined. Finally, the inhibitor was tested in HT-29 (colorectal) and BxPC3 (pancreatic) xenograft tumor models.

Results: The IC_{50} of ARRY-142886 was determined to be 14 nmol/L against purified MEK1. This activity is not competitive with ATP, which is consistent with the high specificity of compound for MEK1/2. Basal and epidermal growth factor–induced ERK1/2 phosphorylation was inhibited in several cell lines as well as 12-O-tetradecanoylphorbol-13-acetate–induced ERK1/2 phosphorylation in isolated peripheral blood mononuclear cells. Treatment with ARRY-142886 resulted in the growth inhibition of several cell lines containing B-Raf and Ras mutations but had no effect on a normal fibroblast cell line. When dosed orally, ARRY-142886 was capable of inhibiting both ERK1/2 phosphorylation and growth of HT-29 xenograft tumors in nude mice. Tumor regressions were also seen in a BxPC3 xenograft model. In addition, tumors remained responsive to growth inhibition after a 7-day dosing holiday.

Conclusions: ARRY-142886 is a potent and selective MEK1/2 inhibitor that is highly active in both in vitro and in vivo tumor models. This compound is currently being investigated in clinical studies.

iso-AZD6244 (AVAILABLE ECLUSIVELY FROM OTAVA)

6-(4-bromo-2-chlorophenylamino)-7-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzo[*d*]imidazole-5-carboxamide

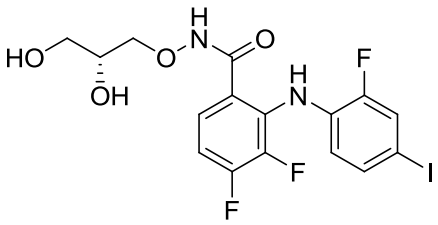


Chemical Formula: $C_{17}H_{15}BrClFN_4O_3$
Molecular Weight: 457.68

OTAVA Catalogue Number: 1901577
CAS Registry Number: N/A
Purity: 97%+

Mitogenic extracellular kinase 1/2 (MEK1/2) inhibitor

N-[(2*R*)-2,3-Dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-benzamide (PD-0325901)



Chemical Formula: $C_{16}H_{14}F_3IN_2O_4$
Molecular Weight: 482.19

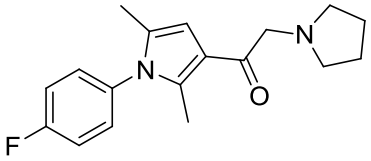
OTAVA Catalogue Number: 7070707062
CAS Registry Number: 391210-10-9
Purity: 97%+

Ref.: Brown et al. **Pharmacodynamic and toxicokinetic evaluation of the novel MEK inhibitor, PD0325901, in the rat following oral and intravenous administration.** *Cancer Chemotherapy and Pharmacology* (**2007**), *59*, 671-679

The MEK-mitogen-activated protein kinase (MAPK) signal transduction pathway is involved with numerous cellular processes including cell growth and differentiation. Phosphorylation of MAPK (pMAPK) by MEK results in activation of this pathway. In various solid tumors, the MEK-MAPK pathway is constitutively active; therefore inhibition of this pathway may provide a therapeutic strategy for treating cancer. The objective of this study was to determine the extent and duration of inhibition of pMAPK in selected normal tissues in rats following single oral or intravenous (IV) doses of the novel MEK inhibitor, **PD0325901**. Male Sprague-Dawley rats (9/group) received either single oral (PO) or IV doses of **PD0325901** at 10, 30, or 100 mg/kg (60, 180, and 600 mg/m2, respectively). Controls received vehicle alone which was aqueous 0.5% hydroxypropylmethyl-cellulose/0.2% Tween 80 for PO dosing and 20% beta-cyclodextran sulfobutyl ether in water (w:v) for IV dosing. Animals (3/group/day) were euthanized on Days 2, 3, and 4, at approximately 24, 48, and 72 h after dosing, respectively. The effects on pMAPK in liver and lung were determined by Western blot analysis and compared with plasma **PD0325901** levels. Satellite animals (6/dose/route) received single PO or IV doses and serial blood samples were collected for determination of toxicokinetic parameters of **PD0325901** and its major metabolite. In general, systemic exposure to **PD0325901** was comparable between routes of administration due to high PO bioavailability (56-109%). Plasma area under the concentration-time curve values of the pharmacologically inactive carboxylic acid metabolite ranged from 18 to 40% of **PD0325901**. Clinical signs of toxicity occurred at 100 mg/ kg PO or IV, indicating the maximum-tolerated dose had been achieved. On Day 2, pMAPK was inhibited 57-95% in liver and 86-99% in lung at all doses, irrespective of route of administration. On Day 3, lung pMAPK remained inhibited 75-91% at all IV doses and by 88% after the 100-mg/kg PO dose. Liver pMAPK remained inhibited 79 and 91 % on Day 3 after 100 mg/ kg by IV and PO doses, respectively. On Day 4, liver pMAPK was still inhibited 66% after the 100-mg/kg PO dose. The EC_{50} and EC_{90} plasma drug levels for inhibition of lung pMAPK were calculated to be 20 and 99 ng/ ml, respectively. Liver pMAPK levels were inhibited at least 50% at plasma **PD0325901** concentrations ≥ 50 ng/ ml. In conclusion, single PO or IV doses of **PD0325901** resulted in dose-dependent inhibition of pMAPK in liver and lung. Inhibition of pMAPK in liver was comparable between routes of administration at ≤ 30mg/kg, whereas inhibition of pMAPK in lung occurred for a longer duration following IV administration. Measurement of pMAPK in normal tissues served as a means for assessing the pharmacologic activity of **PD0325901** and should be included in toxicity studies to evaluate toxicity-pharmacology relationships.

Inhibitor of the deubiquitinating activity of human USP14

1-[1-(4-Fluorophenyl)-2,5-dimethyl-1*H*-pyrrol-3-yl]-2-(1-pyrrolidinyl)-ethanone (IU1)



Chemical Formula: $C_{18}H_{21}FN_2O$
Molecular Weight: 300.37

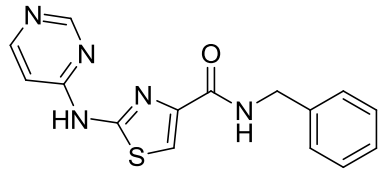
OTAVA Catalogue Number: 0129720262
CAS Registry Number: 314245-33-5
Purity: 97%+

Ref.: King, Finley et al. **Enhancement of proteasome activity by a small-molecule inhibitor of USP14.** *Nature* (**2010**), *467*, 179-184

Proteasomes, the primary mediators of ubiquitin–protein conjugate degradation, are regulated through complex and poorly understood mechanisms. Here we show that USP14, a proteasome-associated deubiquitinating enzyme, can inhibit the degradation of ubiquitin–protein conjugates both in vitro and in cells. A catalytically inactive variant of USP14 has reduced inhibitory activity, indicating that inhibition is mediated by trimming of the ubiquitin chain on the substrate. A high-throughput screen identified a selective small-molecule inhibitor of the deubiquitinating activity of human USP14. Treatment of cultured cells with this compound enhanced degradation of several proteasome substrates that have been implicated in neurodegenerative disease. USP14 inhibition accelerated the degradation of oxidized proteins and enhanced resistance to oxidative stress. Enhancement of proteasome activity through inhibition of USP14 may offer a strategy to reduce the levels of aberrant proteins in cells under proteotoxic stress

Thiazovivin

_N_-Benzyl-2-(pyrimidin-4-ylamino)thiazole-4-carboxamide



Chemical Formula: $C_{15}H_{13}N_5OS$
Molecular Weight: 311.36

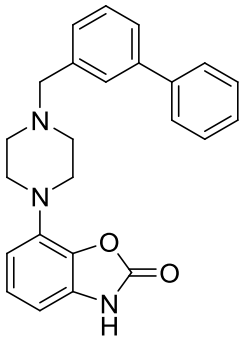
OTAVA Catalogue Number: 7070707131
CAS Registry Number: 1226056-71-8
Purity: 95%+

Ref.: Ding et al. **A chemical platform for improved induction of human iPSCs.** *Nature Methods* (**2009**), *6*, 805-809

The slow kinetics and low efficiency of reprogramming methods to generate human induced pluripotent stem cells (iPSC s) impose major limitations on their utility in biomedical applications. Here we describe a chemical approach that dramatically improves (>200-fold) the efficiency of iPSC generation from human fibroblasts, within seven days of treatment. This will provide a basis for developing safer, more efficient, nonviral methods for reprogramming human somatic cells.

Partial dopamine D_2 agonist; 5-HT_{1A} agonist

7-[4-([1,1'-Biphenyl]-3-ylmethyl)-1-piperazinyl]-2(3*H*)-benzoxazolone (Bifeprunox)



Chemical Formula: $C_{24}H_{23}N_3O_2$
Molecular Weight: 385.46

OTAVA Catalogue Number: 7070707030
CAS Registry Number: 350992-10-8
Purity: 97%+

Ref. 1: Feenstra et al. **New 1-aryl-4-(biarylmethylene)piperazines as potential atypical antipsychotics sharing dopamine D2-receptor and serotonin 5-HT1A-receptor affinities.** *Bioorganic & Medicinal Chemistry Letters* (**2001**), *11*, 2345-2349
1-Aryl-4-(biarylmethylene)piperazines were prepared and their affinity for D2 and 5-HT1A receptors was determined. A selection of these compounds was evaluated in vivo, resulting in the identification of a drug candidate **Bifeprunox** which is being clinically evaluated as a potential atypical antipsychotic with reduced extrapyrimidal side effects.

Ref. 2: Watanabe, Mark D. **Bifeprunox. A partial dopamine-receptor agonist for the treatment of schizophrenia.** *Formulary* (**2007**), *42*, 371-377
A review. Schizophrenia is a chronic psychiatric disorder that affects an estimated 1% of the population. This disorder may be treated with typical (first-generation) or atypical (second-generation) agents; a recognized concern regarding these agents is that long-term use has been associated with increased risks of serious side effects, either neurologic or metabolic in nature. **Bifeprunox** is a partial dopamine-receptor agonist under investigation for the treatment of patients with schizophrenia. As a partial dopamine-receptor agonist, **bifeprunox** acts as a dopamine-system stabilizer. This proposed mechanism of action is similar to that of aripiprazole but different from that of the other currently marketed antipsychotic medications. Available clinical and safety data are limited but describe positive effects in treating acute psychotic symptoms and prolonging time to deterioration, with a generally tolerable side-effect profile. If approved, **bifeprunox** may serve as an additional option for the acute and maintenance treatment of schizophrenia.

Ref. 3: Newman-Tancredi et al. **Neuropharmacological profile of bifeprunox: merits and limitations in comparison with other third-generation antipsychotics.** *Current Opinion in Investigational Drugs (Thomson Scientific)* (**2007**), *8*, 539-554
A review. Schizophrenia is characterized by a range of positive and negative symptoms, and cognitive deficits. While positive symptoms respond to current antipsychotic agents, negative symptoms and cognitive deficits are often resistant to pharmacopea. Thus research is now focused on developing third-generation antipsychotics that combine antagonism or partial agonism at dopamine D(2)-like receptors with agonism at serotonin 5-HT(1A) receptors. Such an association is anticipated to provide therapeutic benefits against a

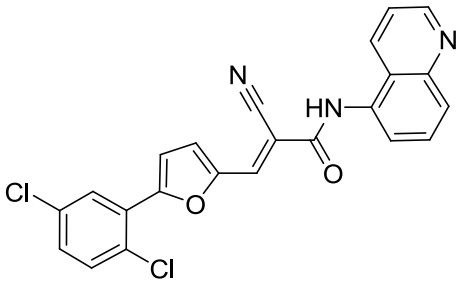
broader range of schizophrenia symptoms. **Bifeprunox** is one such third-generation antipsychotic agent which acts as a partial agonist at D(2)-like receptors and is an efficacious agonist at 5-HT(1A) receptors, with little interaction at 5HT(2A/2C), muscarinic or histaminergic H(1) receptors. This review summarizes the pharmacological profiles of the current antipsychotic agents and describes the rationale behind the development of third-generation antipsychotics. It also evaluates current data concerning **bifeprunox** in comparison with currently available antipsychotics, as well as those that are still under clinical development.

Web: http://www.drugdevelopment-technology.com/projects/bifeprunox/

SIRT2 Inhibitor

2-Cyano-3-[5-(2,5-dichlorophenyl)-2-furanyl]-*N*-5-quinolinyl-2-propenamide (AGK-2)

- *potent inhibitor of sirtuin 2 (SIRT2) with IC_{50} = 3.5 μM. Displays no activity at SIRT1 and SIRT3 at concentrations up to 40 μM*



Chemical Formula: $C_{23}H_{13}Cl_2N_3O_2$
Molecular Weight: 434.27

OTAVA Catalogue Number: 0117392020
CAS Registry Number: 304896-28-4
Purity: 97%+

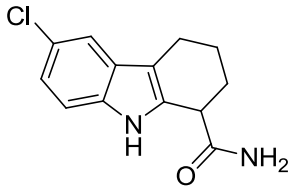
Ref.:

Kazantsev et al. **Sirtuin 2 Inhibitors Rescue α-Synuclein-Mediated Toxicity in Models of Parkinson's Disease.** *Science* (**2007**), *317*, 516-519

The sirtuins are members of the histone deacetylase family of proteins that participate in a variety of cellular functions and play a role in aging. A potent inhibitor of sirtuin 2 (SIRT2) was identified and it was found that inhibition of SIRT2 rescued α-synuclein toxicity and modified inclusion morphology in a cellular model of Parkinson's disease. Genetic inhibition of SIRT2 via small interfering RNA similarly rescued α-synuclein toxicity. Furthermore, the inhibitors protected against dopaminergic cell death both in vitro and in a Drosophila model of Parkinson's disease. The results suggest a link between neurodegeneration and aging.

Inhibitor of the deacetylase SIRT1

6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxamide (EX-527) *(racemic)*



Chemical Formula: $C_{13}H_{13}ClN_2O$
Molecular Weight: 248.71

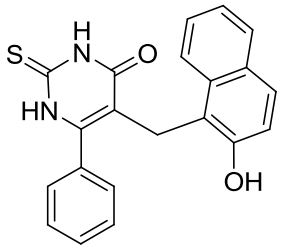
OTAVA Catalogue Number: 7020402314
CAS Registry Number: 49843-98-3
Purity: 97%+

Ref. 1: Napper et al. **Discovery of Indoles as Potent and Selective Inhibitors of the Deacetylase SIRT1.** *Journal of Medicinal Chemistry* (**2005**), *48*, 8045-8054
The most potent compounds described in this paper inhibit SIRT1 with IC_{50} values of 60 -100 nM, representing a 500-fold improvement over previously reported SIRT inhibitors.

Ref. 2: Nayagam et al. **SIRT1 Modulating Compounds From High-Throughput Screening as Anti-Inflammatory and Insulin-Sensitizing Agents.** *Journal of Biomolecular Screening* (**2006**), *11*, 959-967

SIRT1/2 Inhibitor IV, Cambinol

5-(2-Hydroxy-naphthalen-1-ylmethyl)-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (NSC-112546)



Chemical Formula: $C_{21}H_{16}N_2O_2S$
Molecular Weight: 360.43

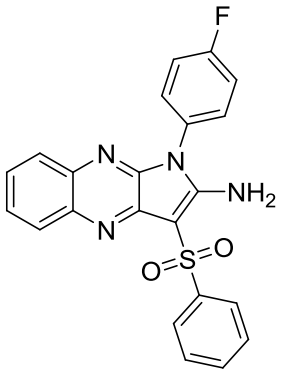
OTAVA Catalogue Number: 7020402315
CAS Registry Number: 14513-15-6
Purity: 97%+

Ref.: Heltweg et al**. Antitumor activity of a small-molecule inhibitor of human silent information regulator 2 enzymes.** *Cancer Research* (**2006**), *66*, 4368-4377

Cambinol inhibits NAD-dependent deacetylase activity of human SIRT1 and SIRT2. Consistent with the role of SIRT1 in promoting cell survival during stress, inhibition of SIRT1 activity with cambinol during genotoxic stress leads to hyperacetylation of key stress response proteins and promotes cell cycle arrest. Treatment of BCL6-expressing Burkitt lymphoma cells with cambinol as a single agent induced apoptosis, which was accompanied by hyperacetylation of BCL6 and p53. Because acetylation inactivates BCL6 and has the opposite effect on the function of p53 and other checkpoint pathways, the antitumor activity of cambinol in Burkitt lymphoma cells may be accomplished through a combined effect of BCL6 inactivation and checkpoint activation. Cambinol was well tolerated in mice and inhibited growth of Burkitt lymphoma xenografts. Inhibitors of NAD-dependent deacetylases may constitute novel anticancer agents.

SIRT1 activator

1-(4-Fluorophenyl)-3-(phenylsulfonyl)-1*H*-pyrrolo[2,3-b]quinoxalin-2-amine



Chemical Formula: $C_{22}H_{15}FN_4O_2S$
Molecular Weight: 418.44

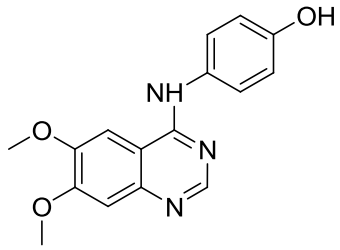
OTAVA Catalogue Number: 1091797
CAS Registry Number: 374922-43-7
Purity: 97%+

Ref.: Nayagam et al. **SIRT1 Modulating Compounds from High-Throughput Screening as Anti-Inflammatory and Insulin-Sensitizing Agents.** *Journal of Biomolecular Screening* (**2006**), *11*, 959-967

The nicotinamide adenine dinucleotide (NAD^+)–dependent protein deacetylase SIRT1 has been linked to fatty acid metabolism via suppression of peroxysome proliferator-activated receptor gamma (PPAR-γ) and to inflammatory processes by deacetylating the transcription factor NF-κB. First, modulation of SIRT1 activity affects lipid accumulation in adipocytes, which has an impact on the etiology of a variety of human metabolic diseases such as obesity and insulin-resistant diabetes. Second, activation of SIRT1 suppresses inflammation via regulation of cytokine expression. Using high-throughput screening, the authors identified compounds with SIRT1 activating and inhibiting potential. The biological activity of these SIRT1-modulating compounds was confirmed in cell-based assays using mouse adipocytes, as well as human THP-1 monocytes. SIRT1 activators were found to be potent lipolytic agents, reducing the overall lipid content of fully differentiated NIH L1 adipocytes. In addition, the same compounds have anti-inflammatory properties, as became evident by the reduction of the proinflammatory cytokine tumor necrosis factor–alpha (TNF-α). In contrast, a SIRT1 inhibitory compound showed a stimulatory activity on the differentiation of adipocytes, a feature often linked to insulin sensitization

Janus kinase 3 inhibitor

4-[(6,7-Dimethoxy-4-quinazolinyl)amino]-phenol (4-(4'-Hydroxyphenyl)amino-6,7-dimethoxyquinazoline; **JANEX-1; WHI-P131**)



Chemical Formula: $C_{16}H_{15}N_3O_3$
Molecular Weight: 297.31

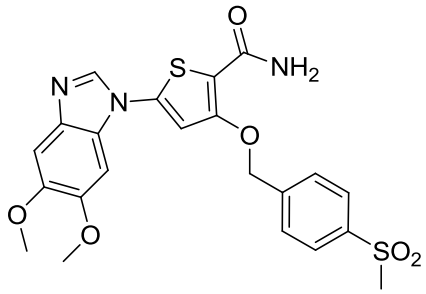
OTAVA Catalogue Number: 7015070103
CAS Registry Number: 202475-60-3
Purity: 97%+

Ref.: D'Cruz et al. **Targeting mast cells in endometriosis with Janus kinase 3 inhibitor, JANEX-1.** *American Journal of Reproductive Immunology* (**2007**), *58*, 75-97
JANEX-1/WHI-P131 is a rationally designed novel JAK3 inhibitor with potent anti-inflammatory activity in several cellular and in vivo animal models of inflammation, including mouse models of peritonitis, colitis, cellulitis, sunburn, and airway inflammation with favorable toxicity and pharmacokinetic profile.

Polo-like kinase 1 (PLK1) inhibitor

5-(5,6-Dimethoxy-1*H*-benzimidazol-1-yl)-3-[[4-(methylsulfonyl)phenyl]methoxy]-2-thiophenecarboxamide

- *PLK1 inhibitor with pIC ~6.9*



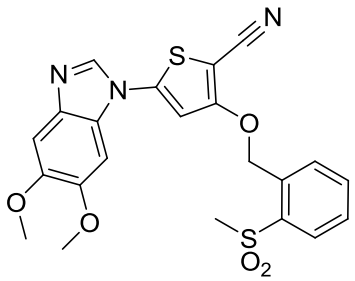
Chemical Formula: $C_{22}H_{21}N_3O_6S_2$
Molecular Weight: 487.55

OTAVA Catalogue Number: 7020402323
CAS Registry Number: 916985-21-2
Purity: 97%+

Inhibitor of IKK-ε kinase

5-(5,6-Dimethoxy-1*H*-benzimidazol-1-yl)-3-[[2-(methylsulfonyl)phenyl]methoxy]-2-thiophenecarbonitrile

- *potent and selective inhibitor of IKK-ε kinase that selectively inhibits IKK-ε with an IC_{50} value of 40 nM and is essentially inactive at IKK-α and IKK-β*



Chemical Formula: $C_{22}H_{19}N_3O_5S_2$
Molecular Weight: 469.53

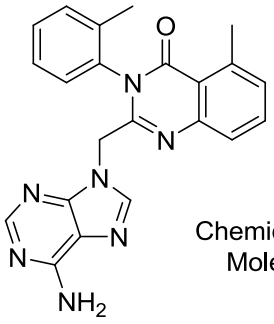
OTAVA Catalogue Number: 7020402324
CAS Registry Number: 862812-98-4
Purity: 97%+

Ref.: Bamborough et al. **5-(1*H*-Benzimidazol-1-yl)-3-alkoxy-2-thiophenecarbonitriles as potent, selective, inhibitors of IKK-ε kinase.** *Bioorganic & Medicinal Chemistry Letters* (**2006**), *16*, 6236-6240
The identification and hit-to-lead exploration of a novel, potent and selective series of substituted benzimidazole-thiophene carbonitrile inhibitors of IKK-ε kinase is described. A 2-thiophenecarbonitrile (CAS RN 862812-98-4) was identified with an IKK-ε enzyme potency of pIC_{50} 7.4, and has a highly encouraging wider selectivity profile, including selectivity within the IKK kinase family.

Inhibitor of the p110δ isoform of PI3 kinase

2-[(6-Amino-9*H*-purin-9-yl)methyl]-5-methyl-3-(2-methylphenyl)-4(3*H*)-quinazolinone (IC87114)

- *selective inhibitor of the p110δ isoform of PI3 kinase*



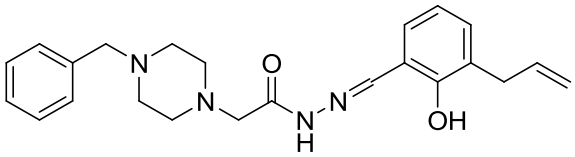
Chemical Formula: $C_{22}H_{19}N_7O$
Molecular Weight: 397.43

OTAVA Catalogue Number: 7070707046
CAS Registry Number: 371242-69-2
Purity: 97%+

Ref.: Billottet et al. **A selective inhibitor of the p110δ isoform of PI 3-kinase inhibits AML cell proliferation and survival and increases the cytotoxic effects of VP16.** *Oncogene* (**2006**), *25*, 6648-6659
Current therapy for acute myeloid leukemia (AML) is suboptimal with a high incidence of relapse. There is strong evidence that constitutive phosphoinositide 3-kinase (PI3K) activity plays a significant role in the pathophysiol. of AML. PI3K products are derived from the activity of a no. of PI3K catalytic isoforms (class I, II and III) but the relative contribution of these enzymes in AML remains unknown. As nonisoform-selective inhibitors of PI3K such as LY294002 may produce unwanted toxicity to normal tissues, the authors have investigated the role of the leukocyte-restricted p110δ PI3K isoform in 14 cases of AML. The isoform p110δ was detected in all cases whereas the expression levels of the other class I PI3Ks varied more widely, and were often undetectable. The p110δ-selective compd. **IC87114** inhibited constitutive phosphorylation of the PI3K target Akt/PKB and reduced cell no. to a mean of 66±5% (range 14-88%). In eight cases, the combination of **IC87114** and VP16 (a topoisomerase II inhibitor) was synergistic in reducing viable cell no., and was associated with a reduction in constitutive NF-κB activity. **IC87114** did not have direct adverse effects or enhance the activity of VP16 on the proliferation and survival of normal hemopoietic progenitors. Overall, our results identify the p110δ isoform as a potential therapeutic target in AML and support a clinical approach to use isoform-selective over broad-spectrum PI3K inhibitors.

Antitumor agent activating procaspase-3 to caspase-3

2-[[2-Hydroxy-3-(2-propen-1-yl)phenyl]methylene]hydrazide 4-(phenylmethyl)-1-piperazineacetic acid (PAC-1)



Chemical Formula: $C_{23}H_{28}N_4O_2$
Molecular Weight: 392.49

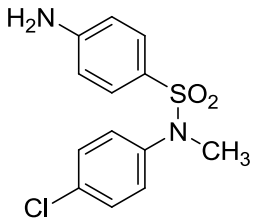
OTAVA Catalogue Number: 7210801533
CAS Registry Number: 315183-21-2
Purity: 97%+

Ref.: Putt et al. **Small-molecule activation of procaspase-3 to caspase-3 as a personalized anticancer strategy.** *Nature Chemical Biology* (**2006**), *2*, 543-550
PAC-1 is the first small molecule known to directly activate procaspase-3 to caspase-3, a transformation that allows induction of apoptosis even in cells that have defective apoptotic machinery.

Wikipedia: http://en.wikipedia.org/wiki/PAC-1

Benzenesulfonanilide-type cyclooxygenase-1-selective inhibitor

4-Amino-*N*-(4-chlorophenyl)-*N*-methyl-benzenesulfonamide (ZXX2-77)



Chemical Formula: $C_{13}H_{13}ClN_2O_2S$
Molecular Weight: 296.77

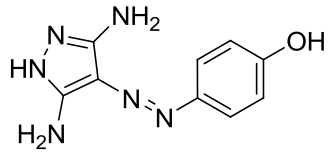
OTAVA Catalogue Number: 7070707001
CAS Registry Number: 304913-22-2
Purity: 97%+

Ref.: Zheng et al. **Analgesic agents without gastric damage: Design and synthesis of structurally simple benzenesulfonanilide-type cyclooxygenase-1-selective inhibitors.** *Bioorganic & Medicinal Chemistry* (**2007**), *15*, 1014-1021

N-methyl-*N*-(4-chlorophenyl) 4-aminobenzenesulfonamide and *N*-methyl-*N*-(4-aminophenyl) 4-chlorobenzenesulfonamide, which possess a *p*-amino group on the benzenesulfonyl moiety and *p*-chloro group on the anilino moiety, showed COX-1-selective inhibition. Moreover, ***N*-methyl-*N*-(4-chlorophenyl) 4-aminobenzenesulfonamide**, which is the most potent compound in this study showed more potent analgesic activity than that of aspirin at 30 mg/kg by po. The anti-inflammatory activity and gastric damage, however, were very weak or not detectably different from aspirin. Since the structure of our COX-1 inhibitors are very simple, they may be useful as lead compounds for superior COX-1 inhibitors as analgesic agents without gastric disturbance.

CDK9 Inhibitor II

4-(3,5-Diamino-1*H*-pyrazol-4-ylazo)-phenol (CAN508)



Chemical Formula: $C_9H_{10}N_6O$
Molecular Weight: 218.22

OTAVA Catalogue Number: 7020402317
CAS Registry Number: 140651-18-9
Purity: 97%+

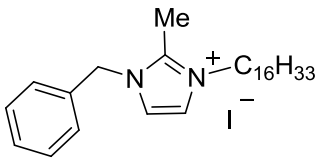
Ref.: Krystof et al. **4-Arylazo-3,5-diamino-1H-pyrazole CDK Inhibitors: SAR Study, Crystal Structure in Complex with CDK2, Selectivity, and Cellular Effects.** *Journal of Medicinal Chemistry* (**2006**), *49*, 6500-6509

The most potent inhibitor, **4-[(3,5-diamino-1*H*-pyrazol-4-yl)diazenyl]phenol**, reduced the frequency of S-phase cells of the cancer cell line HT-29 in antiproliferation assays. Further observed cellular effects included decreased phosphorylation of the retinoblastoma protein and the C-terminal domain of RNA polymerase II, inhibition of mRNA synthesis, and induction of the tumor suppressor protein p53, all of which are consistent with inhibition of CDK9.

eEF-2 Kinase Inhibitor

1-Hexadecyl-2-methyl-3-(phenylmethyl)-1*H*-imidazolium iodide (NH125)

- *eEF-2 Kinase Inhibitor (inhibitor of eukaryotic elongation factor 2 kinase against human cancer cell lines & potent antibacterial agent against drug-resistant bacteria)*
- *histidine protein kinase and eukaryotic elongation factor 2 (eEF-2) kinase (CaMK III) inhibitor (IC_{50} = 60 nM) that displays 125-fold, >1300-fold and >1500-fold selectivity over PKC, PKA and CaMK II respectively. Exhibits anticancer activity in a variety of malignant cell lines (IC_{50} values are 0.7 - 4.8 μM) and blocks G_1/S cell cycle progression. Also is an effective antibacterial agent in vitro (IC_{50} = 6.6 μM) and in vivo*



Chemical Formula: $C_{27}H_{45}IN_2$
Molecular Weight: 524.56

***Tautomeric double bonds in the structure ***

OTAVA Catalogue Number: 7070707012
CAS Registry Number: 278603-08-0
Purity: 97%+ (CHN analysis, ^{13}C NMR & ^{1}H NMR)

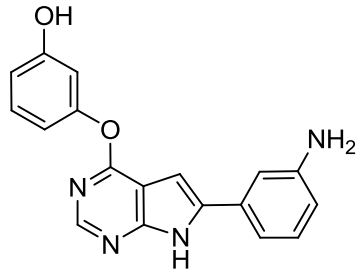
Ref. 1: Arora et al. **Identification and Characterization of an Inhibitor of Eukaryotic Elongation Factor 2 Kinase against Human Cancer Cell Lines.** *Cancer Research* (**2003**), *63*, 6894-6899
NH125 inhibited eEF-2 kinase activity (IC_{50} = 60 nM) in vitro, blocked the phosphorylation of eEF-2 in intact cells, and showed relative selectivity over other protein kinases: protein kinase C (IC_{50} = 7.5 mM), protein kinase A (IC_{50} = 80 mM), and calmodulin-dependent kinase II (IC_{50} > 100 mM). **NH125** decreased the viability of 10 cancer cell lines with IC_{50}s ranging from 0.7 to 4.7 mM. Forced overexpression of eEF-2 kinase in a glioma cell line produced 10-fold resistance to **NH125**. These results suggest that identification of potent inhibitors of eEF-2 kinase may lead to the development of new types of anticancer drugs.

Ref. 2: Yamamoto et al. **Identification and characterization of a potent antibacterial agent, NH125, against drug-resistant bacteria.** *Bioscience, Biotechnology, and Biochemistry* (**2000**), *64*, 919-923
New imidazole compounds were synthesized to develop a novel and effective antibacterial agent: 1-benzyl-3-cetyl-2-methylimidazolium iodide (**NH125**). *In vitro* experiments demonstrated that **NH125** effectively inhibited a number of different histidine protein kinases. Furthermore, oxacillin-resistant Staphylococcus aureus (ORSA), vancomycin-resistant Enterococcus faecalis (VRE), penicillin-resistant Streptococcus pneumoniae (PRS), and other Gram-positive and Gram-negative bacteria were found to be very sensitive to **NH125**.

Glycogen synthase kinase-3 (GSK-3) inhibitor

3-[[6-(3-aminophenyl)-1*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy]-phenol (TWS119)

- *TWS119 is a 4,6 disubstituted pyrrolopyrimidine that potently inhibits GSK3β with an IC_{50} value of 30 nM. At 400 nM, TWS119 induces neurogenesis in murine embryonic stem cells making it a useful tool to regulate stem cell self-renewal and differentiation*



Chemical Formula: $C_{18}H_{14}N_4O_2$
Molecular Weight: 318.33

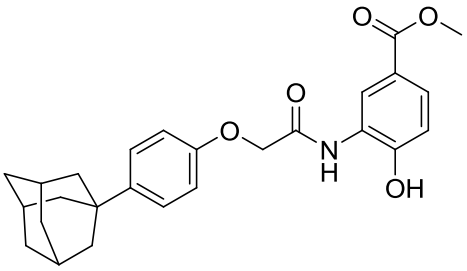
OTAVA Catalogue Number: 7070707013
CAS Registry Number: 601514-19-6
Purity: 97%+

Ref. 1: Dessalew et al. **Investigation of potential glycogen synthase kinase 3 inhibitors using pharmacophore mapping and virtual screening.** *Chemical Biology & Drug Design* (**2006**), *68*, 154-165
To investigate the identification of new potential glycogen synthase kinase-3 inhibitors, a pharmacophore mapping study was carried out using a set of 21 structurally diverse glycogen synthase kinase-3 inhibitors. The best hypothesis was used to screen electronically the NCI2000 database. The hits obtained were docked into glycogen synthase kinase-3β active site. A total of five novel potential leads were proposed after: (i) visual examination of how well they dock into the glycogen synthase kinase-3β-binding site, (ii) comparative analysis of their FlexX, G-Score, PMF-Score, ChemScore and D-Scores values, (iii) comparison of their best fit value with the known inhibitors and (iv) examination of the how the hits retain interactions with the important amino acid residues of glycogen synthase kinase-3β-binding site.

Ref. 2: Ding et al. **Synthetic small molecules that control stem cell fate.** Proceedings *of the National Academy of Sciences of the United States of America* (**2003**), *100*, 7632-7637
A high-throughput phenotypic cell-based screen of kinase-directed combinatorial libraries led to the discovery of **TWS119**, a 4,6-disubstituted pyrrolopyrimidine that can induce neurogenesis in murine ESCs. The target of **TWS119** was shown to be glycogen synthase kinase-3β (GSK-3β) by both affinity-based and biochemical methods. This study provides evidence that GSK-3β is involved in the induction of mammalian neurogenesis in ESCs. This and such other molecules are likely to provide insights into the molecular mechanisms that control stem cell fate and may ultimately be useful to *in vivo* stem cell biology and therapy.

Hypoxia Inducible Factor-1α Inhibitor

4-Hydroxy-3-[[2-(4-tricyclo[3.3.1.13,7]dec-1-ylphenoxy)acetyl]amino]-benzoic acid methyl ester (LW6)



Chemical Formula: $C_{26}H_{29}NO_5$
Molecular Weight: 435.51

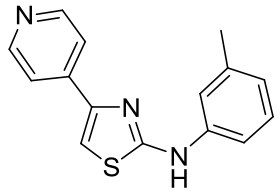
OTAVA Catalogue Number: 7070707015
CAS Registry Number: 934593-90-5
Purity: 97%+

Ref.: Lee et al. **(Aryloxyacetylamino)benzoic Acid Analogues: A New Class of Hypoxia-Inducible Factor-1 Inhibitors.** *Journal of Medicinal Chemistry* (**2007**), *50*, 1675-1684
Structural modification of a compound discovered during screening using an HRE-dependent reporter assay has revealed a novel class of HIF-1 inhibitors, which potently inhibit the HIF-1α protein accumulation and its target gene expression under hypoxic conditions in human hepatocellular carcinoma Hep3B cells.

Autophagy Inducer

N-(3-Methylphenyl)-4-(4-pyridinyl)-2-thiazolamine (STF-62247)

- *selectively induces cell death in VHL-deficient cells*



Chemical Formula: $C_{15}H_{13}N_3S$
Molecular Weight: 267.35

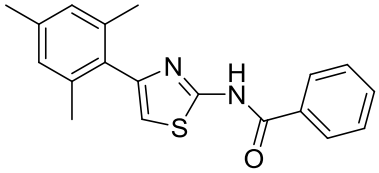
OTAVA Catalogue Number: 7211760086
CAS Registry Number: 315702-99-9
Purity: 97%+

Ref.: Turcotte et al. **A molecule targeting VHL-deficient renal cell carcinoma that induces autophagy.** *Cancer Cell* (**2008**), *14*, 90-102

Renal cell carcinomas (RCCs) are refractory to standard therapies. The von Hippel-Lindau (VHL) tumor suppressor gene is inactivated in 75% of RCCs. By screening for small molecules selectively targeting VHL-deficient RCC cells, we identified **STF-62247**. **STF-62247** induces cytotoxicity and reduces tumor growth of VHL-deficient RCC cells compared to genetically matched cells with wild-type VHL. **STF-62247**-stimulated toxicity occurs in a HIF-independent manner through autophagy. Reduction of protein levels of essential autophagy pathway components reduces sensitivity of VHL-deficient cells to **STF-62247**. Using a yeast deletion pool, we show that loss of proteins involved in Golgi trafficking increases killing by **STF-62247**. Thus, we have found a small molecule that selectively induces cell death in VHL-deficient cells, representing a paradigm shift for targeted therapy.

Inhibitors of Nek2/Hec1

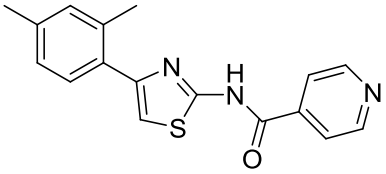
N-[4-(2,4,6-Trimethylphenyl)-2-thiazolyl]-benzamide



Chemical Formula: $C_{19}H_{18}N_2OS$
Molecular Weight: 322.42

OTAVA Catalogue Number: 7070707071
CAS Registry Number: 1001753-24-7
Purity: 97%+

N-[4-(2,4-Dimethylphenyl)-2-thiazolyl]-4-pyridinecarboxamide



Chemical Formula: $C_{17}H_{15}N_3OS$
Molecular Weight: 309.39

OTAVA Catalogue Number: 7070707072
CAS Registry Number: 560103-80-2
Purity: 97%+

Ref.: Qiu et al. **Synthesis and Biological Evaluation of a Series of Novel Inhibitor of Nek2/Hec1 Analogues.** *Journal of Medicinal Chemistry* (**2009**), *52*, 1757-1767

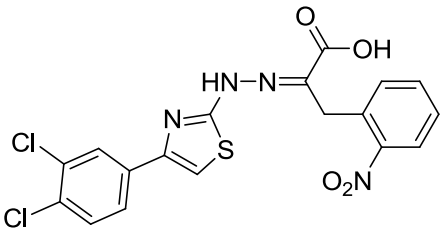
High expression in cancer 1 (Hec1) is an oncogene overly expressed in many human cancers. Small molecule inhibitor of Nek2/Hec1 (INH) targeting the Hec1 and its regulator, Nek2, in the mitotic pathway,

was identified to inactivate Hec1/Nek2 function mediated by protein degradation that subsequently leads to chromosome mis-segregation and cell death. To further improve the efficacy of INH, a series of INH analogues were designed, synthesized, and evaluated. Among these 33 newly synthesized analogues, three of them, 6, 13, and 21, have 6−8 fold more potent cell killing activity than the previous lead compound INH1. Compounds 6 and 21 were chosen for analyzing the underlying action mechanism. They target directly the Hec1/Nek2 pathway and cause chromosome mis-alignment as well as cell death, a mechanism similar to that of INH1. This initial exploration of structural/functional relationship of INH may advance the progress for developing clinically applicable INH analogue

eIF4E/eIF4G Interaction Inhibitor

2-((4-(3,4-Dichlorophenyl)-thiazol-2-ylhydrazono)-3-(2-nitrophenyl))propionic acid (4EGI-1)

- *A cell-permeable hydrazone compound that reversibly binds eukaryotic translation initiation factor 4E (eIF4E; K_d = 25 μM) and disrupts eIF4E/eIF4G, but not eIF4E/4E-BP1, complex formation.*



Chemical Formula: $C_{18}H_{12}Cl_2N_4O_4S$
Molecular Weight: 451.28

OTAVA Catalogue Number: 7070707011
CAS Registry Number: 315706-13-9
Purity: 97%+

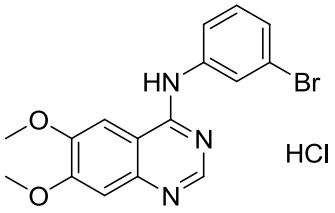
Ref.: Moerke et al. **Small-molecule inhibition of the interaction between the translation initiation factors eIF4E and eIF4G.** *Cell* (**2007**), *128*, 257-267

Assembly of the eIF4E/eIF4G complex has a central role in the regulation of gene expression at the level of translation initiation. This complex is regulated by the 4E-BPs, which competes with eIF4G for binding to eIF4E and which have tumor-suppressor activity. To pharmacological mimic 4E-BP function the authors developed a high-throughput screening assay for identifying small-mol. inhibitors of the eIF4E/eIF4G interaction. The most potent compound identified **4EGI-1**, binds eIF4E, disrupts eIF4E/eIF4G association, and inhibits cap-dependent translation but not initiation factor-independent translation. While **4EGI-1** displaces eIF4G from eIF4E, it effectively enhances 4E-BP1 association both in vitro and in cells. **4EGI-1** inhibits cellular expression of oncogenic proteins encoded by weak mRNAs, exhibits activity against multiple cancer cell lines, and appears to have a preferential effect on transformed vs. nontransformed cells. The identification of this compound. provides a new tool for studying translational control and establishes a possible new strategy for cancer therapy.

EGFR-kinase inhibitor

N-(3-Bromophenyl)-6,7-dimethoxy-4-quinazolinamine hydrochloride (AG 1517; NSC 669364; PD 153035; SU 5271; WHI-P79)

- *extremely potent inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase, with an IC_{50} of 25 pM. Inhibits other purified tyrosine kinases only at micromolar or higher concentrations*



Chemical Formula: $C_{16}H_{15}BrClN_3O_2$
Molecular Weight: 396.67

OTAVA Catalogue Number: 7020540711
CAS Registry Number: 153436-54-5
Purity: 97%+

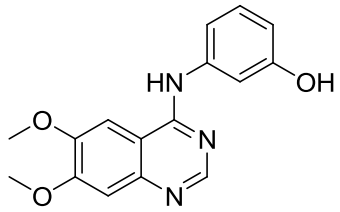
Ref.:

Grunt et al. **An EGF receptor inhibitor induces RAR-β expression in breast and ovarian cancer cells.** *Biochemical and Biophysical Research Communications* (**2005**), *329*, 1253-1259
Inhibition of the epidermal growth factor (EGF)-receptor (EGFR) has become a promising anticancer treatment strategy. Application of retinoids yields encouraging results for cancer prevention and therapy. Many tumors express no or low amounts of retinoic acid receptor-β2 (RAR-β2) due to epigenetic silencing via DNA hypermethylation. RAR-β2 is the main mediator of the antiproliferative effect of retinoids. RAR-β2 re-expression causes reversal of transformation, cell cycle arrest, and restoration of retinoid sensitivity. RAR-β2 is thus a tumor suppressor. Western blotting, colorimetric in vitro cell proliferation assays, and reverse transcription-polymerase chain reaction demonstrated that the EGFR inhibitor **PD153035** not only blocked activation of EGFR and inhibited cell growth, but also stimulated RAR-β expression in MDA-MB-468 breast and OVCAR-3 ovarian carcinoma cells. Upregulation of RAR-β by PD153035 was confirmed by real-time reverse transcription-polymerase chain reaction. In contrast, expression of other retinoid receptors and of estrogen receptor-α was not affected. **PD153035**-mediated re-induction of RAR-β was associated with demethylation of the RAR-β2 gene promoter P2 as demonstrated by methylation-specific polymerase chain reaction. These novel results on the ErbB/retinoid receptor cross-talk may be useful for designing future anticancer combination regimens.

Cyclin-dependent Kinase (CDK) Inhibitor

3-[(6,7-Dimethoxy-4-quinazolinyl)amino]-phenol (Janex 3; WHI-P180)

- *potent inhibitor of IgE-mediated mast cell responses to allergens in vitro and in vivo. Also inhibits cyclin-dependent kinase 2 (CDK2; IC_{50} = 1μM) by blocking the ATP site*



Chemical Formula: $C_{16}H_{15}N_3O_3$
Molecular Weight: 297.31

OTAVA Catalogue Number: 7015070102
CAS Registry Number: 211555-08-7
Purity: 97%+

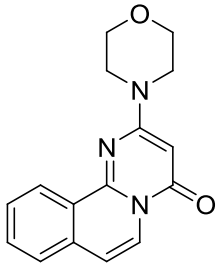
Ref. 1: Shewchuk et al. **Binding mode of the 4-anilinoquinazoline class of protein kinase inhibitor: X-ray crystallographic studies of 4-anilinoquinazolines bound to cyclin-dependent kinase 2 and p38 kinase.** *Journal of Medicinal Chemistry* (**2000**), *43*, 133-138
4-Anilinoquinazolines represent an important class of protein kinase inhibitor. Modes of binding for two members of this inhibitor class were determined by x-ray of one inhibitor (4-[3-hydroxyanilino]-6,7-dimethoxyquinazoline) in complex with cyclin-dependent kinase 2 (CDK2) and the other (4-[3-methylsulfanylanilino]-6,7-dimethoxyquinazoline) in complex with p38 kinase.

Ref. 2: Chen et al. **Pharmacokinetics and biologic activity of the novel mast cell inhibitor, 4-(3'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline in mice.** *Pharmaceutical Research* (**1999**), *16*, 117-122
The purpose of the present study was to examine the pharmacodynamic and pharmacokinetic features of the novel mast cell inhibitor 4-(3'-Hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (**WHI-P180**) in mice. Notably, **WHI-P180**, when administered in two consecutive nontoxic i.p. bolus doses of 25 mg/kg, inhibited IgE/antigen-induced vascular hyperpermeability in a well-characterized murine model of passive cutaneous anaphylaxis. **WHI-P180** is an active inhibitor of IgE-mediated mast cell responses in vitro and in vivo. Further preclinical characterization of **WHI-P180** may improve the efficacy of **WHI-P180** in vivo and provide the basis for design of effective treatment and prevention programs for mast cell- mediated allergic reactions.

Selective DNA-PK and mTOR inhibitor

2-(4-Morpholinyl)-4*H*-Pyrimido[2,1-*a*]isoquinolin-4-one (Compound 401)

- *Reversible and selective inhibitor of DNA-dependent protein kinase (DNA-PK) and mammalian target of rapamycin (mTOR) (IC_{50} values are 0.28 and 5.3 μM respectively). Displays little affinity for other commonly studied kinases including PI 3-K, ATM and ATR (IC_{50} values are all > 100 μM). Induces apoptosis in vitro.*



Chemical Formula: $C_{16}H_{15}N_3O_2$
Molecular Weight: 281.31

OTAVA Catalogue Number: 7070707024
CAS Registry Number: 168425-64-7
Purity: 97%+

Ref. 1: Ballou et al. **Inhibition of Mammalian Target of Rapamycin Signaling by 2-(Morpholin-1-yl)pyrimido[2,1-a]isoquinolin-4-one.** *Journal of Biological Chemistry* (**2007**), *282*, 24463-24470
Signalling through the mammalian target of rapamycin (mTOR) is hyperactivated in many human tumors, including hamartomas associated with tuberous sclerosis complex (TSC). Several small molecules such as LY294002 inhibit mTOR kinase activity, but they also inhibit phosphatidylinositol 3-kinase (PI3K) at similar concns. **Compound 401** is a synthetic inhibitor of DNA-dependent protein kinase (DNA-PK) that also targets mTOR but not PI3K in vitro (Griffin, R. J., Fontana, G., Golding, B. T., Guiard, S., Hardcastle, I. R., Leahy, J. J., Martin, N., Richardson, C., Rigoreau, L., Stockley, M., and Smith, G. C. (2005) J. Med. Chem. 48, 569-585). **Compound 401** was used to test the cellular effect of mTOR inhibition without the complicating side effects on PI3K. Treatment of cells with 401 blocked the phosphorylation of sites modified by mTOR-Raptor and mTOR-Rictor complexes (ribosomal protein S6 kinase 1 Thr389 and Akt Ser473, resp.). By contrast, there was no direct inhibition of Akt Thr308 phosphorylation, which is dependent on PI3K. Similar effects were also observed in cells that lack DNA-PK. The proliferation of TSC1-/- fibroblasts was inhibited in the presence of 401, but TSC1+/+ cells were resistant. In contrast to rapamycin, long-term treatment of TSC1-/- cells with 401 did not up-regulate phospho-Akt Ser473. Because increased Akt activity promotes survival, this may explain why the level of apoptosis was increased in the presence of 401 but not rapamycin. These results suggest that mTOR kinase inhibitors might be more effective than rapamycins in controlling the growth of TSC hamartomas and other tumors that depend on elevated mTOR activity.

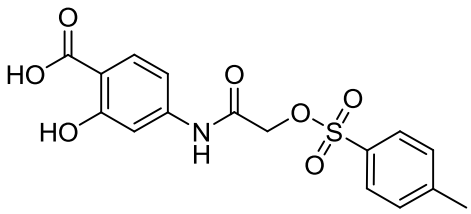
Ref. 2: Griffin et al. **Selective benzopyranone and pyrimido[2,1-a]isoquinolin-4-one inhibitors of DNA-dependent protein kinase: Synthesis, structure-activity studies, and radiosensitization of a human tumor cell line in vitro.** *Journal of Medicinal Chemistry* (**2005**), *48*, 569-585
A diverse range of chromen-2-ones, chromen-4-ones, and pyrimidoisoquinolin-4-ones was synthesized and evaluated for inhibitory activity against the DNA repair enzyme DNA-dependent protein kinase (DNA-PK),

with a view to elucidating structure-activity relationships for potency and kinase selectivity. DNA-PK inhibitory activity varied widely over the series of compounds evaluated (IC_{50} values ranged from 0.19 to >10 mM), with excellent activity being observed for the 7,8-benzochromen-4-one and pyrimido[2,1-*a*]isoquinolin-4-one templates. By contrast, inhibitors based on the benzochromen-2-one (coumarin) or 2-aryl-7,8-benzochromen-4-one (flavone) scaffolds were less potent. Crucially, these studies revealed a very constrained structure-activity relationship at the 2-position of the benzopyranone and pyrimido[2,1-a]isoquinolin-4-one pharmacophore, with only a 2-morpholino or 2-(2'-methylmorpholino) group being tolerated at this position. More detailed biological studies conducted with the most potent inhibitor NU7163 (IC_{50} = 0.19 mM) demonstrated ATP-competitive DNA-PK inhibition, with a K_i value of 24 nM, and NU7163 exhibited selectivity for DNA-PK compared with the related enzymes ATM, ATR, mTOR, and PI 3-K (p110alpha). NU7163 sensitized the HeLa human tumor cell line to the cytotoxic effects of ionizing radiation in vitro, a dose modification factor of 2.3 at 10% survival being observed with an inhibitor concentration of 5 mM. This study identified these structural classes as novel DNA-PK inhibitors and delineated initial structure-activity relationships against DNA-PK.

STAT3 Inhibitor VI

2-Hydroxy-4-[[[[(4-methylphenyl)sulfonyl]oxy]acetyl]amino]-benzoic acid (NSC 74859; S3I-201)

- *inhibitor of STAT3 with anti-tumor activity;* ***NSC 74859*** *in inhibition of STAT3 dimerization assays demonstrated an* IC_{50} *of < 500* μM



Chemical Formula: $C_{16}H_{15}NO_7S$
Molecular Weight: 365.36

OTAVA Catalogue Number: 7070707021
CAS Registry Number: 501919-59-1
Purity: 97%+

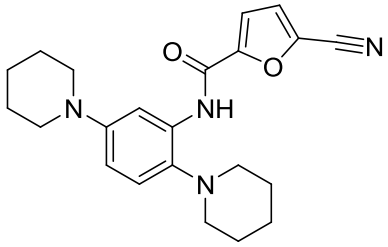
Ref. :

Siddiquee et al. **Selective chemical probe inhibitor of Stat3, identified through structure-based virtual screening, induces antitumor activity.** *Proceedings of the National Academy of Sciences of the United States of America* (**2007**), *104*, 7391-7396

S3I-201 (**NSC 74859**) is a chemical probe inhibitor of Stat3 activity, which was identified from the National Cancer Institute chemical libraries by using structure-based virtual screening with a computer model of the Stat3 SH2 domain bound to its Stat3 phosphotyrosine peptide derived from the x-ray crystal structure of the Stat3β homodimer. S3I-201 inhibits Stat3·Stat3 complex formation and Stat3 DNA-binding and transcriptional activities. Furthermore, S3I-201 inhibits growth and induces apoptosis preferentially in tumor cells that contain persistently activated Stat3. Constitutively dimerized and active Stat3C and Stat3 SH2 domain rescue tumor cells from S3I-201-induced apoptosis. Finally, S3I-201 inhibits the expression of the Stat3-regulated genes encoding cyclin D1, Bcl-xL, and survivin and inhibits the growth of human breast tumors in vivo. These findings strongly suggest that the antitumor activity of S3I-201 is mediated in part through inhibition of aberrant Stat3 activation and provide the proof-of-concept for the potential clinical use of Stat3 inhibitors such as S3I-201 in tumors harboring aberrant Stat3.

cFMS Receptor Tyrosine Kinase Inhibitor

5-Cyano-*N*-(2,5-di-1-piperidinylphenyl)-2-furancarboxamide



Chemical Formula: $C_{22}H_{26}N_4O_2$
Molecular Weight: 378.47

OTAVA Catalogue Number: 7070707032
CAS Registry Number: 959626-45-0
Purity: 97%+

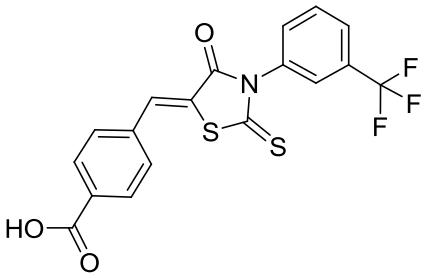
Ref.: Player et al. **Potent 2'-aminoanilide inhibitors of cFMS as potential anti-inflammatory agents.** *Bioorganic & Medicinal Chemistry Letters* (**2007**), *17*, 6070-6074

A series of 2'-aminoanilides have been identified which exhibit potent and selective inhibitory activity against the cFMS tyrosine kinase. Initial SAR studies within this series are described which examine aroyl and amino group substitutions, as well as the introduction of hydrophilic substituents on the benzene core.

Voltage-independent, selective CFTR chloride channel blocker

4-[[4-Oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]-benzoic acid ($CFTR_{inh}$-172)

- *It blocks CFTR-dependent Cl^- currents in airway cells with K_I ~ 300 nM, nearly 500-fold more potent than that of the reference CFTR blocker glibenclamide*



Chemical Formula: $C_{18}H_{10}F_3NO_3S_2$
Molecular Weight: 409.40

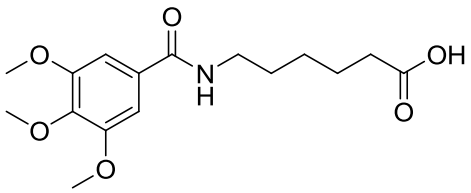
OTAVA Catalogue Number: 0129690030
CAS Registry Number: 307510-92-5
Purity: 97%+

Ref.: Verkman et al. **Thiazolidinone CFTR inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion.** *Journal of Clinical Investigation* (**2002**), *110*, 1651-1658
Secretory diarrhea is the leading cause of infant death in developing countries and a major cause of morbidity in adults. The cystic fibrosis transmembrane conductance regulator (CFTR) protein is required for fluid secretion in the intestine and airways and, when defective, causes the lethal genetic disease cystic fibrosis. The most potent compound discovered by screening of structural analogs, **$CFTR_{inh}$-172**, reversibly inhibited CFTR short-circuit current in less than 2 min in a voltage-independent manner with KI approx. 300 nM. **$CFTR_{inh}$-172** was nontoxic at high concentrations in cell culture and mouse models. Fully inhibiting CFTR, **$CFTR_{inh}$-172** did not prevent elevation of cellular cAMP or inhibit non-CFTR Cl- channels, multidrug resistance protein-1 (MDR-1), ATP-sensitive K+ channels, or a series of other transporters. A single i.p. injection of **$CFTR_{inh}$-172** (250 μg/kg) in mice reduced by more than 90% cholera toxin-induced fluid secretion in the small intestine over 6 h. Thiazolidinone CFTR inhibitors may be useful in developing large-animal models of cystic fibrosis and in reducing intestinal fluid loss in cholera and other secretory diarrheas.

Cardial depressant (antiarrhythmic)

6-[(3,4,5-Trimethoxybenzoyl)amino]-hexanoic acid

- *ATBAC; C-3; C-Tre;* ***Capobenic acid****; N-(3,4,5-Trimethoxybenzoyl)-ε-aminocaproic acid; NSC230936; TB-ACA – a vasodilator which has been used in the prevention and treatment of myoeardial infarction and other cardiac disorders*



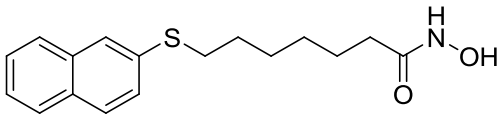
Chemical Formula: $C_{16}H_{23}NO_6$
Molecular Weight: 325.36

OTAVA Catalogue Number: **7110950124**
CAS Registry Number: 21434-91-3
Purity: 97%+

Histone Deacetylase Inhibitor VI

N-Hydroxy-7-(2-naphthalenylthio)-heptanamide (HNHA)

- *HNHA is a cell-permeable inhibitor of histone deacetylase (HDAC) activity (IC_{50} = 100 nM)*



Chemical Formula: $C_{17}H_{21}NO_2S$
Molecular Weight: 303.42

OTAVA Catalogue Number: 7070707016
CAS Registry Number: 926908-04-5
Purity: 97%+

Ref.:

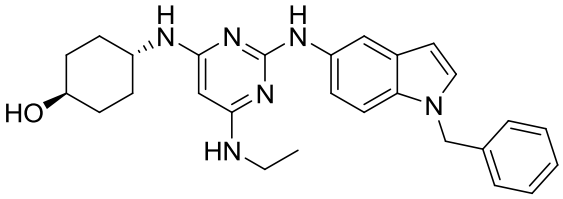
Kim et al. **Anti-tumor activity of N-hydroxy-7-(2-naphthylthio)heptanomide, a novel histone deacetylase inhibitor.** *Biochemical and Biophysical Research Communications* (**2007**), *356*, 233-238
N-Hydroxy-7-(2-naphthylthio)heptanamide (**HNHA**) is a histone deacetylase (HDAC) inhibitor with antitumor activity both in vitro and in vivo. The compound inhibited HDAC enzyme activity as well as proliferation of human fibrosarcoma cells (HT1080) in vitro. Treatment of cells with HNHA elicited histone hyperacetylation leading to an up-regulation of p21 transcription, cell cycle arrest, and an inhibition of HT1080 cell invasion. Moreover, HNHA effectively inhibited the growth of tumor tissue in a mouse xenograph assay in vivo. Together, these data demonstrate that this novel HDAC inhibitor could be developed as a potential antitumor agent targeting HDAC.

Cdk4/6 Inhibitor IV

trans-4-[[6-(Ethylamino)-2-[[1-(phenylmethyl)-1_H_-indol-5-yl]amino]-4-pyrimidinyl]amino]-cyclohexanol (CINK4)

- *Cell-permeable triaminopyrimidine compound acting as a reversible and ATP-competitive inhibitor of Cdk4/6 (IC_{50} = 1.5 μM and 5.6 μM for Cdk4/D1 and Cdk6/D1, respectively)*

Relative stereochemistry



Chemical Formula: $C_{27}H_{32}N_6O$
Molecular Weight: 456.58

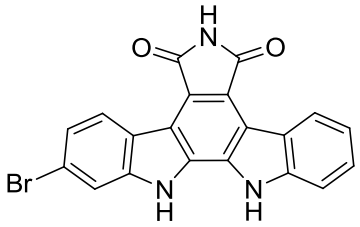
OTAVA Catalogue Number: 1112092
CAS Registry Number: 359886-84-3
Purity: 97%+

Ref.: Soni et al. **Selective in vivo and in vitro effects of a small molecule inhibitor of cyclin-dependent kinase 4.** *Journal of the National Cancer Institute* (**2001**), *93*, 436-446
Like p16, the natural inhibitor of Cdk4, **CINK4** inhibits Cdk4 activity in vitro and slows tumor growth in vivo.

Cdk4 Inhibitor

2-Bromo-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-c]carbazole-5,7(6*H*)-dione

- *A cell-permeable, unsymmetrical indolocarbazole compound that displays antiproliferative properties. Acts as a potent, selective, and ATP-competitive inhibitor of Cdk4/D1 (IC_{50} = 76 nM)*



Chemical Formula: $C_{20}H_{10}BrN_3O_2$
Molecular Weight: 404.22

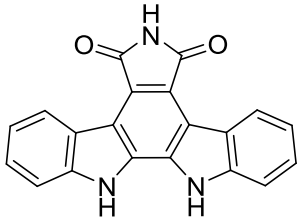
OTAVA Catalogue Number: 7070707035
CAS Registry Number: 546102-60-7
Purity: 97%+

Ref.: Zhu et al. **Synthesis, Structure-Activity Relationship, and Biological Studies of Indolocarbazoles as Potent Cyclin D1-CDK4 Inhibitors.** *Journal of Medicinal Chemistry* (**2003**), *46*, 2027-2030
6-Substituted indolocarbazoles were found to be potent and selective D1/CDK4 inhibitors and exhibited potent and ATP-competitive D1/CDK4 activities (IC_{50} values of 76 and 42 nM). Two compoundts had high selectivity against the other kinases. These D1/CDK4 inhibitors inhibited tumor cell growth, arrested tumor cells at the G1 phase, and inhibited pRb phosphorylation.

Cdk4 Inhibitor

12,13-Dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (Arcyriaflavin A)

- *Inhibitor of cdk4/cyclin D1 (IC_{50} = 59 nM). Active against CaM kinase II (IC_{50} = 25 nM) but displays selectivity over several other kinases in vitro (IC_{50} values for inhibition of PKA and PKC are > 2 and > 100 μM respectively). Inhibits human cytomegalovirus (HCMV) replication in vitro (IC_{50} = 200 nM).*



Chemical Formula: $C_{20}H_{11}N_3O_2$
Molecular Weight: 325.32

OTAVA Catalogue Number: 7070707137
CAS Registry Number: 118458-54-1
Purity: 97%+

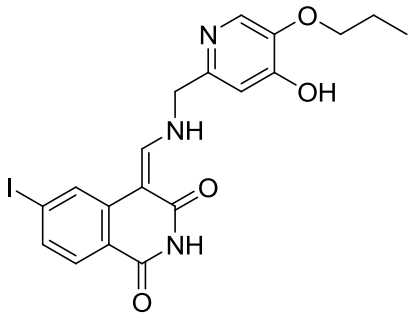
Ref.:

Zhu et al. **Synthesis of quinolinyl/isoquinolinyl[a]pyrrolo [3,4-c] carbazoles as cyclin D1/CDK4 inhibitors.** *Bioorganic & Medicinal Chemistry Letters* (**2003**), *13*, 1231-1235
A novel series of pyrrolo[3,4-*c]* carbazoles fused with a quinolinyl/isoquinolinyl moiety were synthesized and their D1/CDK4 inhibitory and antiproliferative activity were evaluated. Compound 8H,14H-isoquinolinyl[6,5-a]-pyrrolo[3,4-c]carbazole-7,9-dione (1d) was found to be a highly potent D1/CDK4 inhibitor with an IC_{50} of 69 nM. Compound 1d also inhibited tumor cell growth, arrested tumor cells in G1 phase and inhibited pRb phosphorylation.

Cdk4 Inhibitor

4-[[[(4-Hydroxy-5-propoxy-2-pyridinyl)methyl]amino]methylene]-6-iodo-1,3(2*H*,4H)-isoquinolinedione (WAY-265497)

- *Potent and selective inhibitors of the Cyclin-Dependent Kinase 4*



Chemical Formula: $C_{19}H_{18}IN_3O_4$
Molecular Weight: 479.27

OTAVA Catalogue Number: 7070707068
CAS Registry Number: 943746-57-4
Purity: 95%+

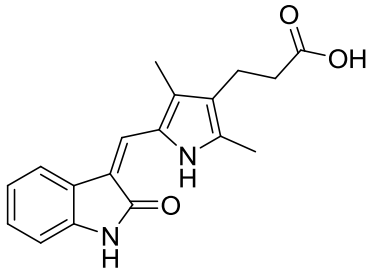
Ref.: Tsou et al. **Discovery of 4-(Benzylaminomethylene)isoquinoline-1,3-(2H,4H)-diones and 4-[(Pyridylmethyl)aminomethylene]isoquinoline-1,3-(2H,4H)-diones as Potent and Selective Inhibitors of the Cyclin-Dependent Kinase 4.** *Journal of Medicinal Chemistry* (**2009**), *52*, 2289-2310

The series of 4-(benzylaminomethylene)isoquinoline-1,3-(2H,4H)-dione and 4-[(pyridylmethyl)aminomethylene]isoquinoline-1,3-(2H,4H)-dione derivatives reported here represents a novel class of potential antitumor agents, which potently and selectively inhibit CDK4 over CDK2 and CDK1. In the benzylamino headpiece, a 3-OH substituent is required on the phenyl ring for CDK4 inhibitory activity, which is further enhanced when an iodo, aryl, heteroaryl, t-butyl, or cyclopentyl substituent is introduced at the C-6 position of the isoquinoline-1,3-dione core. To circumvent the metabolic liability associated with the phenolic OH group on the 4-substituted 3-OH phenyl headpiece, we take two approaches: first, introduce a nitrogen o- or p- to the 3-OH group in the phenyl ring; second, replace the phenyl headpiece with N-substituted 2-pyridones. We present here the synthesis, SAR data, metabolic stability data, and a CDK4 mimic model that explains the binding, potency, and selectivity of our CDK4 selective inhibitors

PDGFR, VEGFR and FGFR inhibitor

5-[(1,2-Dihydro-2-oxo-3*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-propanoic acid (NSC 702827; SU 6668; TSU 68)

- *ATP-competitive PDGFR, VEGF and FGFR inhibitor (IC_{50} values are 0.06, 2.43, 3.04 and > 100 μM at PDGFRβ, VEGFR2, FGFR1 and EGFR respectively). Inhibits proliferation of HUVEC and NIH3T3 cells in vitro (IC_{50} values are 0.41, 9.3 and 16.5 μM for VEGF, FGF and PDGF-stimulated growth respectively) and induces > 75% growth inhibition against a broad range of tumor types in vivo.*



Chemical Formula: $C_{18}H_{18}N_2O_3$
Exact Mass: 310.13

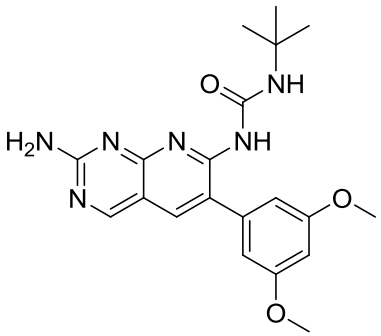
OTAVA Catalogue Number: 1156360
CAS Registry Number: 252916-29-3
Purity: 97%+

Ref. 1: Fabbro & Manley. **SU-6668, SUGEN.** *Current Opinion in Investigational Drugs* (**2001**), *2,* 1142-1148
SUGEN is developing **SU-6668**, a tyrosine kinase inhibitor that inhibits three distinct growth factor receptor targets, for the potential treatment of cancer.

Ref. 2: Sun et al. **Design, Synthesis, and Evaluations of Substituted 3-[(3- or 4-Carboxyethylpyrrol-2-yl)methylidenyl]indolin-2-ones as Inhibitors of VEGF, FGF, and PDGF Receptor Tyrosine Kinases.** *Journal of Medicinal Chemistry* (**1999**), *42*, 5120-5130
Receptor tyrosine kinases (RTKs) have been implicated as therapeutic targets for the treatment of human diseases including cancers, inflammatory diseases, cardiovascular diseases including arterial restenosis, and fibrotic diseases of the lung, liver, and kidney. Three classes of 3-substituted indolin-2-ones containing propionic acid functionality attached to the pyrrole ring at the C-3 position of the core have been identified as catalytic inhibitors of the vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) RTKs. Some of the compounds were found to inhibit the tyrosine kinase activity associated with isolated vascular endothelial growth factor receptor 2 (VEGF-R2) [fetal liver tyrosine kinase 1 (Flk-1)/kinase insert domain-containing receptor (KDR)], fibroblast growth factor receptor (FGF-R), and platelet-derived growth factor receptor (PDGF-R) tyrosine kinase with IC_{50} values at nanomolar level.

Inhibitor of basic Fibroblast Growth Factor (bFGF)

N-[2-Amino-6-(3,5-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidin-7-yl]-*N'*-(1,1-dimethylethyl)-urea (PD166866)



Chemical Formula: $C_{20}H_{24}N_6O_3$
Molecular Weight: 396.44

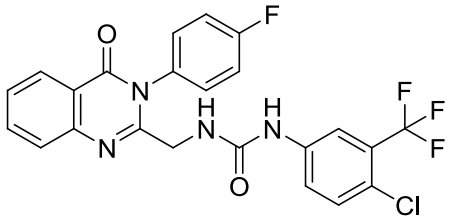
OTAVA Catalogue Number: 7070707041
CAS Registry Number: 192705-79-6
Purity: 97%+

Ref.: Calandrella et al. **Reduction of cell proliferation induced by PD166866: an inhibitor of the basic Fibroblast Growth Factor.** *Journal of Experimental & Clinical Cancer Research* (**2007**), *26,* 405-409
Cell proliferation control plays a key role in tumor development. The basic Fibroblast Growth Factor (bFGF), as well as other growth factors, is involved in several pathologies characterized by dysregulation of cell proliferation. In the present work the effects of **PD166866**, a very potent and selective tyrosine kinase inhibitor were evaluated. Cultured murine fibroblasts (the cell line 3T6) were used to assess the FGFR-1 inhibition mediated by **PD166866**. Evaluation of cell viability and molecular biology techniques were adopted. **PD166866** controls negatively the bFGF/FGFR-1 system thus promoting a significant reduction of cell proliferation and loss of viability in 3T6 cells. The drug possibly controls proliferation via induction of apoptosis as evidenced by a relevant chromatin degradation. Conclusion: This study demonstrated that **PD166866** might be used in the control of fibrotic proliferative diseases, as well as in other tumor pathologies

Inhibitor of the Hedgehog Signalling Pathway

_N_-[4-chloro-3-(trifluoromethyl)phenyl]-_N'_-[[3-(4-fluorophenyl)-3,4-dihydro-4-oxo-2-quinazolinyl]methyl]-urea

- *inhibitor of the Hedgehog Signalling Pathway with IC_{50} = 70 nM*



Chemical Formula: $C_{23}H_{15}ClF_4N_4O_2$
Molecular Weight: 490.84

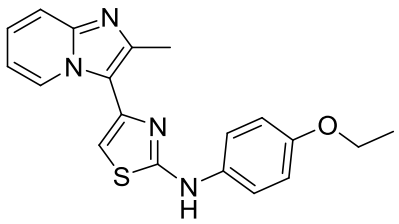
OTAVA Catalogue Number: 1156359
CAS Registry Number: 330796-24-2
Purity: 97%+

Ref.: Brunton et al. **Potent Inhibitors of the Hedgehog Signaling Pathway.** *Journal of Medicinal Chemistry* (**2008**), *51*, 1108-1110
A small family of phenyl quinazolinone ureas is reported as potent modulators of Hedgehog protein function. Preliminary SAR studies of the urea substituent led to a nanomolar Hedgehog antagonist.

Inhibitor of the Hedgehog Signalling Pathway

N-(4-Ethoxyphenyl)-4-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-2-thiazolamine (JK 184)

- *Hedgehog signaling inhibitor that prevents Gli-dependent transcriptional activity (IC_{50} = 30 nM). Exhibits antiproliferative activity in a range of cancer cell lines (GI_{50} = 3 - 21 nM) and in human xenografts in vivo. Inhibits alcohol dehydrogenase 7 (Adh7) (IC_{50} = 210 nM) and acts as a microtubule depolymerizing agent in vitro*



Chemical Formula: $C_{19}H_{18}N_4OS$
Molecular Weight: 350.44

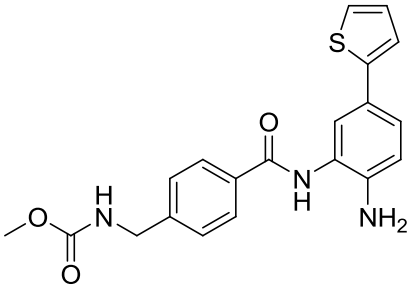
OTAVA Catalogue Number: 7211760148
CAS Registry Number: 315703-52-7
Purity: 98%+

Ref. 1: Schultz et al. **A small-molecule antagonist of the Hedgehog signaling pathway.** *ChemBioChem* (**2007**), *8*, 1916-1919
JK184 was identified as an antagonist of Hedgehog signaling through a cell-based screen of chemical libraries. Results from biochemical and cellular experiments suggest that **JK184** functions by inhibiting class IV alcohol dehydrogenase. This molecule should serve as a useful tool for studying Hedgehog signaling.

Ref. 2: Chen et al. **The imidazopyridine derivative JK184 reveals dual roles for microtubules in hedgehog signaling.** *Angewandte Chemie, International Edition* (**2009**), *48*, 2321-2324
Eradicating hedgehogs: The title molecule has been previously identified as a potent inhibitor of the Hedgehog signaling pathway, which gives embryonic cells information needed to develop properly. This molecule is shown to modulate Hedgehog target gene expression by depolymerizing microtubules, thus revealing dual roles of the cytoskeleton in pathway regulation.

HDAC1 & 2 Inhibitors

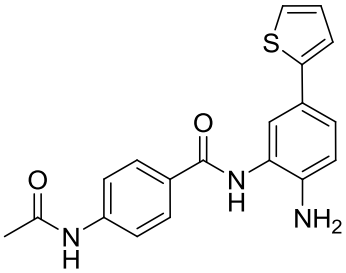
Methyl ester of *N*-[[4-[[[2-amino-5-(2-thienyl)phenyl]amino]carbonyl]phenyl]methyl]-carbamic acid



Chemical Formula: $C_{20}H_{19}N_3O_3S$
Molecular Weight: 381.45

OTAVA Catalogue Number: 7070707089
CAS Registry Number: 1013330-84-1
Purity: 97%+

4-(Acetylamino)-*N*-[2-amino-5-(2-thienyl)phenyl]-benzamide



Chemical Formula: $C_{19}H_{17}N_3O_2S$
Molecular Weight: 351.42

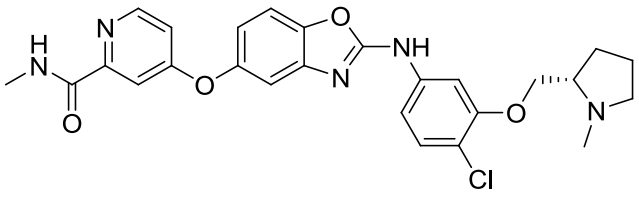
OTAVA Catalogue Number: 7070707091
CAS Registry Number: 849234-64-6
Purity: 97%+

Ref.: Witter et al. **Optimization of biaryl Selective HDAC1&2 Inhibitors (SHI-1:2).** *Bioorganic & Medicinal Chemistry Letters* (**2008**), *18*, 726-731

A class of biaryl benzamides was identified and optimized as selective HDAC1 & 2 inhibitors (SHI-1:2). These agents exhibit selectivity over class II HDACs 4-7, as well as class I HDACs 3 and 8; providing examples of selective HDAC inhibitors for the HDAC isoforms most closely assocd. with cancer. The hypothesis for the increased selectivity is the binding of a pendant arom. group in the internal cavity of the HDAC1&2 enzymes. SAR development based on an initial lead led to a series of potent and selective inhibitors with reduced off-target activity and tumor growth inhibition activity in a HCT-116 xenograft model.

VEGFR-2 inhibitor

4-((2-((4-Chloro-3-((((2*S*)-1-methyl-2-pyrrolidinyl)methyl)oxy)-phenyl)amino)-1,3-benzoxazol-5-yl)oxy)-*N*-methyl-2-pyridinecarboxamide



Chemical Formula: $C_{26}H_{26}ClN_5O_4$
Molecular Weight: 507.97

OTAVA Catalogue Number: 1156358
CAS Registry Number: 769960-39-6
Purity: 97%+

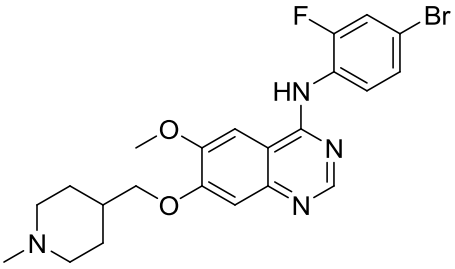
Ref.: Potashman et al. **Design, Synthesis, and Evaluation of Orally Active Benzimidazoles and Benzoxazoles as Vascular Endothelial Growth Factor-2 Receptor Tyrosine Kinase Inhibitors.** *Journal of Medicinal Chemistry* (**2007**), *50*, 4351-4373

Inhibition of the VEGF signaling pathway has become a valuable approach in the treatment of cancers. Guided by X-ray crystallography and molecular modeling, a series of 2- aminobenzimidazoles and 2-aminobenzoxazoles were identified as potent inhibitors of VEGFR-2 (KDR) in both enzymatic and HUVEC cellular proliferation assays. The synthesis and structure-activity relationship of a series of 2-aminobenzimidazoles and benzoxazoles, culminating in the identification of a benzoxazole (structure above) as a potent and selective VEGFR-2 inhibitor displaying a good pharmacokinetic profile, is described. This compound demonstrated efficacy in both the murine matrigel model for vascular permeability (79% inhibition observed at 100 mg/kg) and the rat corneal angiogenesis model (ED_{50} = 16.3 mg/kg).

Antagonist of the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR)

N-(4-Bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-4-quinazolinamine (Vandetanib; ZD6474; Zactima)

- *selectively inhibits the tyrosine kinase activity of vascular endothelial growth factor receptor 2 (VEGF2), thereby blocking VEGF-stimulated endothelial cell proliferation and migration and reducing tumor vessel permeability. This agent also blocks the tyrosine kinase activity of epidermal growth factor receptor (EGFR), a receptor tyrosine kinase that mediates tumor cell proliferation and migration and angiogenesis. It also inhibits RET-tyrosine kinase activity, an important growth driver in certain types of thyroid cancer*



Chemical Formula: $C_{22}H_{24}BrFN_4O_2$
Molecular Weight: 475.35

OTAVA Catalogue Number: 1156355
CAS Registry Number: 443913-73-3
Purity: 97%+

Ref. 1: Hanrahan & Heymach. **Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors Vandetanib (ZD6474) and AZD2171 in Lung Cancer.** *Clinical Cancer Research* (**2007**), *13(15, Pt. 2),* 4617s-4622s
A review. Vascular endothelial growth factor (VEGF) is a rational target for advanced non–small cell lung cancer (NSCLC), a hypothesis validated by the recent Eastern Cooperative Oncology Group E4599 trial showing that the addition of the VEGF monoclonal antibody bevacizumab to chemotherapy prolongs overall survival. Several new tyrosine kinase inhibitors targeting the VEGF pathway are currently in advanced clinical development for NSCLC and offer several possible advantages compared with monoclonal antibodies, including oral administration, more flexible dosing, a broader spectrum of target inhibition, and different toxicity profiles. Among these agents, vandetanib (ZD6474), an inhibitor of the VEGF receptor (VEGFR)-2 and epidermal growth factor receptor tyrosine kinase, has been the most extensively studied. In a randomized phase II study of patients with platinum-refractory NSCLC, including squamous histology, vandetanib prolonged progression-free survival compared with gefitinib. In another phase II trial, an improvement in progression-free survival was observed for vandetanib in combination with docetaxel

compared with docetaxel alone. AZD2171 is an inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 and other tyrosine kinases that has shown clinical activity in NSCLC in combination with carboplatin and paclitaxel. Several phase III trials are under way testing these agents either as monotherapy or in combination with chemotherapy in patients with lung cancer. Early results with these agents, and others being tested, raise the possibility that there will eventually be multiple VEGF-targeted therapies available in the clinic that can potentially benefit a broader range of patients with advanced-stage NSCLC.

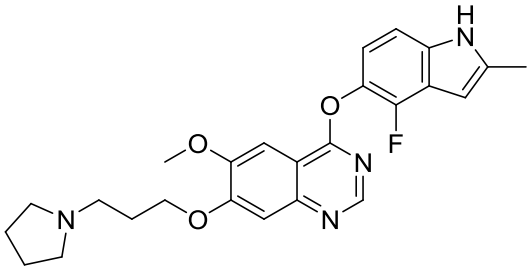
Ref. 2: Sahtornsumetee & Rich. **Vandetanib (ZD6474), a novel multitargeted kinase inhibitor, in cancer therapy.** *Drugs of Today* (**2006**), *42,* 657-670

A review. In clinical trials thus far, single-targeted kinase inhibitors have shown only limited success in demonstrating survival benefits in cancer. This has led to the development of multitargeted kinase inhibitors capable of disrupting various mitogenic pathways in both cancer cells and associated vasculature. Vandetanib is a novel multitargeted kinase inhibitor exhibiting potent activity against vascular endothelial growth factor receptor-2 (VEGFR-2; kinase insert domain-containing receptor [KDR]) and, to a lesser extent, epidermal growth factor receptor (EGFR) and RET kinase. Vascular endothelial growth factor (VEGF) and VEGFR-2 play a pivotal role in regulating angiogenesis and vascular permeability in cancers. In addition to its antiangiogenic effects, vandetanib acts against EGFR, which is overexpressed or mutated in several solid tumors. Furthermore, vandetanib exerts activity against oncogenic RET kinase, the overexpression of which is common in medullary and papillary thyroid carcinomas. Therefore, the multitargeted kinase inhibitor vandetanib represents a new approach, targeting both tumor cells and tumor-associated endothelial cells. Preclinical studies of vandetanib have demonstrated antitumor efficacy against multiple human cancer xenografts in subcutaneous, orthotopic and metastatic models. Phase I clinical trials have demonstrated that vandetanib is well tolerated. Common adverse events included rash, diarrhea and asymptomatic QTc prolongation. Phase II clinical studies in patients with non-small-cell lung cancer have shown promising results, employing vandetanib as both monotherapy and in combination with docetaxel. Phase II studies in other cancers have likewise been initiated. This review summarizes preclinical and clinical studies of vandetanib for the treatment of cancers.

Inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases

4-[(4-Fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline (AZD2171; Cediranib)

- *an oral tyrosine kinase inhibitor of all of the VEGF receptors (VEGFR1, VEGFR2, VEGFR3), as well as KIT and (less potently) PDGFRA and PDGFRB*



Chemical Formula: $C_{25}H_{27}FN_4O_3$
Molecular Weight: 450.51

OTAVA Catalogue Number: 1156354
CAS Registry Number: 288383-20-0
Purity: 97%+

Ref. 1: Wedge et al. **AZD2171: A Highly Potent, Orally Bioavailable, Vascular Endothelial Growth Factor Receptor-2 Tyrosine Kinase Inhibitor for the Treatment of Cancer.** *Cancer Research* (**2005**), *65*, 4389-4400

Inhibition of vascular endothelial growth factor-A (VEGF) signaling is a promising therapeutic approach that aims to stabilize the progression of solid malignancies by abrogating tumor-induced angiogenesis. This may be accomplished by inhibiting the kinase activity of VEGF receptor-2 (KDR), which has a key role in mediating VEGF-induced responses. The novel indole-ether quinazoline **AZD2171** is a highly potent (IC_{50} <1 nmol/L) ATP-competitive inhibitor of recombinant KDR tyrosine kinase in vitro. Concordant with this activity, in human umbilical vein endothelial cells, **AZD2171** inhibited VEGF-stimulated proliferation and KDR phosphorylation with IC_{50} values of 0.4 and 0.5 nmol/L, respectively. In a fibroblast/endothelial cell coculture model of vessel sprouting, **AZD2171** also reduced vessel area, length, and branching at subnanomolar concentrations. Once-daily oral administration of **AZD2171** ablated experimental (VEGF-induced) angiogenesis in vivo and inhibited endochondral ossification in bone or corpora luteal development in ovary; physiologic processes that are highly dependent upon neovascularization. The growth of established human tumor xenografts (colon, lung, prostate, breast, and ovary) in athymic mice was inhibited dose-dependently by **AZD2171**, with chronic administration of 1.5 mg per kg per day producing statistically significant inhibition in all models. A histologic analysis of Calu-6 lung tumors treated with **AZD2171** revealed a reduction in microvessel density within 52 hours that became progressively greater with the duration of treatment. These changes are indicative of vascular regression within tumors. Collectively, the data obtained with **AZD2171** are consistent with potent inhibition of VEGF signaling, angiogenesis, neovascular survival, and tumor growth. **AZD2171** is being developed clinically as a once-daily oral therapy for the treatment of cancer.

http://cancerres.aacrjournals.org/cgi/reprint/65/10/4389.pdf

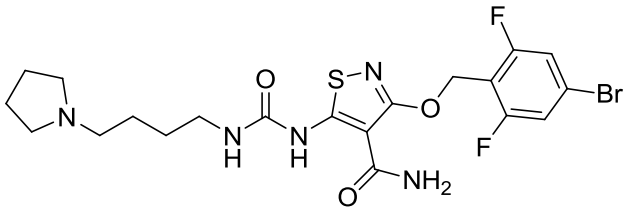
Ref. 2: Sorbera et al. **Cediranib.** *Drugs of the Future* (**2007**), *32*, 577

Angiogenesis is a complex biological event in which vascular endothelial growth factor (VEGF) is considered the rate-limiting step. VEGF mediates both physiological and pathological angiogenesis via binding to specific transmembrane receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR or Flk-1), expressed mainly on vascular endothelial cells. Because angiogenesis in healthy adults is generally absent, interruption of VEGF signaling is an attractive strategy to selectively inhibit angiogenesis in solid tumors. Antagonism of VEGFR-2 has attracted particular attention due to the generally limited expression of this receptor in endothelium and the crucial role it plays in VEGF-mediated angiogenic signaling. Cediranib (AZD-2171, Recentin) is a novel, orally available quinazoline VEGFR inhibitor that was shown to potently inhibit VEGFR-1, VEGFR-2 and VEGFR-3 tyrosine kinase activity and VEGF-mediated signaling in vitro and in vivo. Cediranib exerted marked anticancer effects in vivo in a variety of xenograft models and in patients with advanced solid tumors. It continues to undergo clinical testing alone and in combination with selected chemotherapies for the oral treatment of various cancers.

Inhibitor of the VEGFR-2 and basic fibroblast growth factor (FGF) kinases

3-[(4-Bromo-2,6-difluorophenyl)methoxy]-5-[[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-4-isothiazolecarboxamide (CP-547632)

- *potent inhibitor of the VEGFR-2 and basic fibroblast growth factor (FGF) kinases (IC_{50} = 11 and 9 nM, respectively). It is selective relative to epidermal growth factor receptor, platelet-derived growth factor ß, and other related TKs. It also inhibits VEGF-stimulated autophosphorylation of VEGFR-2 in a whole cell assay with an IC_{50} value of 6 nM*



Chemical Formula: $C_{20}H_{24}BrF_2N_5O_3S$
Molecular Weight: 532.40

OTAVA Catalogue Number: 1156353
CAS Registry Number: 252003-65-9
Purity: 97%+

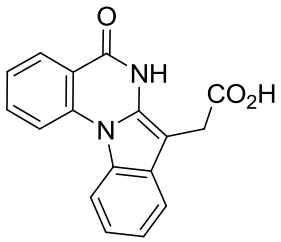
Ref.: Beebe et al. **Pharmacological Characterization of CP-547,632, a Novel Vascular Endothelial Growth Factor Receptor-2 Tyrosine Kinase Inhibitor for Cancer Therapy.** *Cancer Research* (**2003**), *63*, 7301-7309
CP-547,632 is a well-tolerated, orally-bioavailable inhibitor presently under clinical investigation for the treatment of human malignancies.

http://cancerres.aacrjournals.org/cgi/reprint/63/21/7301.pdf

CK2 inhibitor

5,6-Dihydro-5-oxo-indolo[1,2-*a*]quinazoline-7-acetic acid (IQA; CGP029482)

- *potent and selective CK2 inhibitor; K_i = 0.17 μM*



Chemical Formula: $C_{17}H_{12}N_2O_3$
Molecular Weight: 292.29

OTAVA Catalogue Number: 7020402316
CAS Registry Number: 391670-48-7
Purity: 97%+

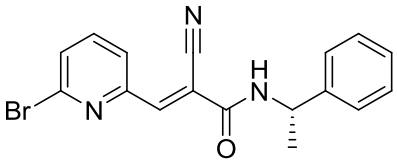
Ref. 1: Vangrevelinghe et al. **Discovery of a Potent and Selective Protein Kinase CK2 Inhibitor by High-Throughput Docking.** *Journal of Medicinal Chemistry* (**2003**), *46*, 2656-2662
To assess the potential of protein kinase CK2 as a target for developing new antitumor agents, we have undertaken a search for inhibitors of this enzyme. As part of this effort, we report here the discovery of the potent and selective CK2 inhibitor **(5-oxo-5,6-dihydroindolo[1,2-*a*]-quinazolin-7-yl)acetic acid**. We identified this inhibitor of a novel structural type by highthroughput docking of our corporate compound collection in the ATP binding site of a homology model of human CK2, using an appropriate protocol. The synthesis of the inhibitor as well as that of related analogues whose CK2 inhibitory activities give support to the binding mode proposed by the docking program is described. The results obtained suggest that virtual screening of a 3D database by molecular docking is a useful approach for lead finding provided that adapted post-docking filtering and reranking procedures are applied to the primary hit list.

Ref. 2: Sarno et al. **Development and exploitation of CK2 inhibitors.** *Molecular and Cellular Biochemistry* (**2005**), *274*, 69-76
A no. of quite specific and fairly potent inhibitors of protein kinase CK2, belonging to the classes of condensed polyphenolic compds., tetrabromobenzimidazole/triazole derivatives and indoloquinazolines are available to date. The structural basis for their selectivity is provided by a hydrophobic pocket adjacent to the ATP/GTP binding site, which in CK2 is smaller than in the majority of other protein kinases due to the presence of a no. of residues whose bulky side chains are generally replaced by smaller ones. Consequently a doubly substituted CK2 mutant V66A,I174A is much less sensitive than CK2 wild type to these classes of inhibitors. The most efficient inhibitors both in terms of potency and selectivity are 4,5,6,7-tetrabromo-1H-benzotriazole, TBB (Ki = 0.4 μM), the TBB derivative 2-dimethylamino-4,5,6,7-tetrabromo-1H-benzimidazole, DMAT (Ki = 0.040 μM), the emodin related coumarinic compound 8-hydroxy-4-methyl-9-nitrobenzo[g]chromen-2-one, NBC (Ki = 0.22 μM) and the indoloquinazoline derivative (**[5-oxo-5,6-dihydroindolo-(1,2a)quinazolin-7-yl]acetic acid), IQA** (Ki = 0.17 μM). These inhibitors are cell permeable as judged from ability to block CK2 in living cells and they have been successfully employed, either alone or

in combination with CK2 mutants refractory to inhibition, to dissect signaling pathways affected by CK2 and to identify the endogenous substrates of this pleiotropic kinase. By blocking CK2 these inhibitors display a remarkable pro-apoptotic efficacy on a no. of tumor derived cell lines, a property which can be exploited in perspective to develop antineoplastic drugs.

JAK2 Inhibitor

(2*E*)-3-(6-Bromo-2-pyridinyl)-2-cyano-*N*-[(1*S*)-1-phenylethyl]-2-propenamide (WP1066)



Chemical Formula: $C_{17}H_{14}BrN_3O$
Molecular Weight: 356.22

OTAVA Catalogue Number: 7070707057
CAS Registry Number: 857064-38-1
Purity: 97%+

Ref.: Verstovsek et al. **WP1066, a Novel JAK2 Inhibitor, Suppresses Proliferation and Induces Apoptosis in Erythroid Human Cells Carrying the JAK2 V617F Mutation.** *Clinical Cancer Research* (**2008**), *14*, 788-796

The discovery of an activating somatic mutation in codon 617 of the gene encoding the Janus kinase (JAK)-2 (JAK2 V617F) in patients with myeloproliferative disorders has opened new avenues for the development of targeted therapies for these malignancies. However, no effective JAK2 inhibitors are currently available for clinical use.

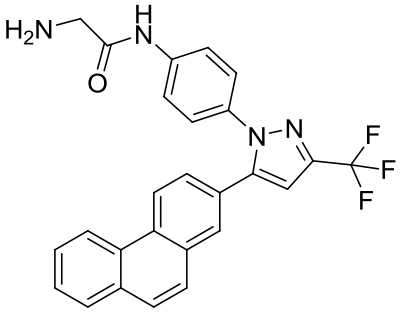
(*E*)-3(6-bromopyridin-2-yl)-2-cyano-*N*-(S-1phenylethyl)acrylamide (WP1066), a novel analogue of the JAK2 inhibitor AG490, significantly inhibited JAK2 and its downstream signal transducer and activator of transcription-3, signal transducer and activator of transcription-5, and extracellular signal-regulated kinase-1/2 pathways in a dose- and time-dependent manner. As a result, **WP1066** concentrations in the low micromolar range induced time- and dose-dependent antiproliferative and proapoptotic effects in HEL cells. As expected, **WP1066** inhibited the proliferation of peripheral blood hematopoietic progenitors of patients with polycythemia vera carrying the JAK2 V617F mutation in a dose-dependent manner.

WP1066 is active both in vitro and ex vivo and should be further developed for the treatment of neoplasms expressing the JAK2 V617F mutation.

PDK1 Inhibitor

2-Amino-*N*-[4-[5-(2-phenanthrenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl]-acetamide (OSU03012)

- ***OSU03012*** *has an IC_{50} of 5 μM for inhibition of 3-phosphoinositide-dependent kinase-1 (PDK-1), and therefore Akt activation, with no measurable COX-2 inhibition up to 50 μM.* ***OSU03012*** *is a potent inhibitor of tumor cell growth with an average inhibitory concentration of 1.1 μM across a panel of 60 cancer cell lines. It does not inhibit signal transduction through the mitogen-activated protein kinase (MAPK) pathway.* ***OSU03012*** *induces apoptosis of chronic lymphocytic leukemia (CLL) cells independent of bcl-2 overexpression using both caspase-dependent and independent pathways*



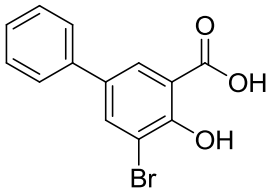
Chemical Formula: $C_{26}H_{19}F_3N_4O$
Molecular Weight: 460.45

OTAVA Catalogue Number: 7070707053
CAS Registry Number: 742112-33-0
Purity: 97%+

Human 20α-hydroxysteroid dehydrogenase (AKR1C1) inhibitor

3-Bromo-5-phenylsalicylic acid (NSC109116)

- *metabolism of progesterone in AKR1C1-overexpressed cells was potently inhibited by 3-bromo-5-phenylsalicylic acid, which was effective from 10 nM with an IC_{50} value equal to 460 nM*



Chemical Formula: $C_{13}H_9BrO_3$
Molecular Weight: 293.11

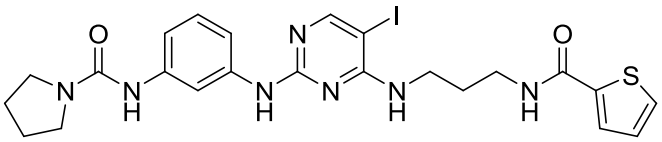
OTAVA Catalogue Number: 7070707133
CAS Registry Number: 4906-68-7
Purity: 97%+

Ref.: El-Kabbani et al. **Structure-Guided Design, Synthesis, and Evaluation of Salicylic Acid-Based Inhibitors Targeting a Selectivity Pocket in the Active Site of Human 20α-Hydroxysteroid Dehydrogenase (AKR1C1).** *Journal of Medicinal Chemistry* (**2009**), *52*, 3259-3264

The first design, synthesis, and evaluation of human 20α-hydroxysteroid dehydrogenase (AKR1C1) inhibitors based on the recently published crystal structure of its ternary complex with inhibitor are reported. While the enzyme-inhibitor interactions observed in the crystal structure remain conserved with the newly designed inhibitors, the additional phenyl group of the most potent compound, 3-bromo-5-phenylsalicylic acid, targets a nonconserved hydrophobic pocket in the active site of AKR1C1 resulting in 21-fold improved potency (K_i = 4 nM) over the structurally similar 3α-hydroxysteroid dehydrogenase isoform (AKR1C2). The compound is hydrogen bonded to Tyr55, His117, and His222, and the phenyl ring forms additional van der Waals interactions with residues Leu308, Phe311, and the nonconserved Leu54 (Val in AKR1C2). Additionally, the metabolism of progesterone in AKR1C1-overexpressed cells was potently inhibited by 3-bromo-5-phenylsalicylic acid, which was effective from 10 nM with an IC_{50} value equal to 460 nM.

BX-795, BX-912, and BX-320: potent PDK1 inhibitors (IC_{50} = 11-30 nM)

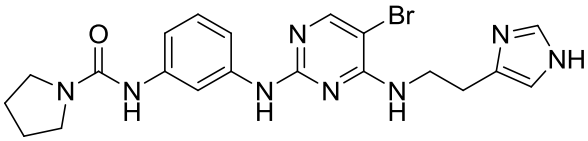
N-[3-[[5-Iodo-4-[[3-[(2-thienylcarbonyl)amino]propyl]amino]-2-pyrimidinyl]amino]phenyl]-1-pyrrolidinecarboxamide (BX-795)



Chemical Formula: $C_{23}H_{26}IN_7O_2S$
Molecular Weight: 591.47

OTAVA Catalogue Number: 7070707044
CAS Registry Number: 702675-74-9
Purity: 97%+

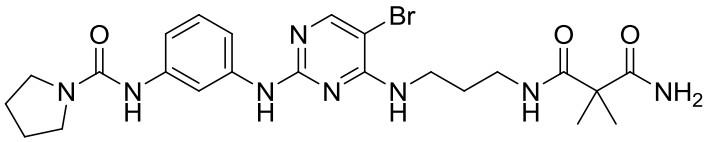
N-[3-[[5-Bromo-4-[[2-(1H-imidazol-4-yl)ethyl]amino]-2-pyrimidinyl]amino]phenyl]-1-pyrrolidinecarboxamide (BX-912)



Chemical Formula: $C_{20}H_{23}BrN_8O$
Molecular Weight: 471.35

OTAVA Catalogue Number: 7070707060
CAS Registry Number: 702674-56-4
Purity: 97%+

N^1-[3-[[5-Bromo-2-[[3-[(1-pyrrolidinylcarbonyl)amino]phenyl]amino]-4-pyrimidinyl]amino]propyl]-2,2-dimethylpropanediamide (BX-320)



Chemical Formula: $C_{23}H_{31}BrN_8O_3$
Molecular Weight: 547.45

OTAVA Catalogue Number: 7070707045
CAS Registry Number: 702676-93-5
Purity: 97%+

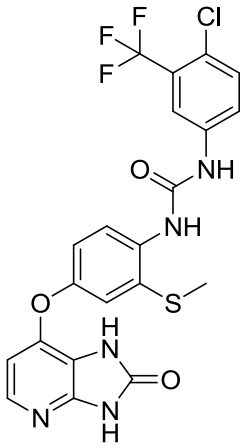
Ref.: Feldman et al. **Novel Small Molecule Inhibitors of 3-Phosphoinositide-dependent Kinase-1.** *Journal of Biological Chemistry* (**2005**), *280*, 19867-19874

The phosphoinositide 3-kinase/3-phosphoinositide-dependent kinase 1 (PDK1)/Akt signaling pathway plays a key role in cancer cell growth, survival, and tumor angiogenesis and represents a promising target for anticancer drugs. Here, we describe three potent PDK1 inhibitors, **BX-795**, **BX-912**, and **BX-320** (IC_{50} = 11–30 nM) and their initial biological characterization. The inhibitors blocked PDK1/Akt signaling in tumor cells and inhibited the anchorage-dependent growth of a variety of tumor cell lines in culture or induced apoptosis. A number of cancer cell lines with elevated Akt activity were >30-fold more sensitive to growth inhibition by PDK1 inhibitors in soft agar than on tissue culture plastic, consistent with the cell survival function of the PDK1/Akt signaling pathway, which is particularly important for unattached cells. **BX-320** inhibited the growth of LOX melanoma tumors in the lungs of nude mice after injection of tumor cells into the tail vein. The effect of **BX-320** on cancer cell growth in vitro and in vivo indicates that PDK1 inhibitors may have clinical utility as anticancer agents.

BRAF Inhibitor

N-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[4-[(2,3-dihydro-2-oxo-1*H*-imidazo[4,5-*b*]pyridin-7-yl)oxy]-2-(methylthio)phenyl]-urea

- *BRAF IC_{50} = 1 nm; pERK = 610 nM; SRB GI_{50} = 470 nM*



Chemical Formula: $C_{21}H_{15}ClF_3N_5O_3S$
Molecular Weight: 509.89

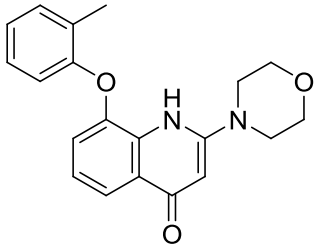
OTAVA Catalogue Number: 7070707132
CAS Registry Number: 884339-61-1
Purity: 97%+

Ref.: Springer et al. **Novel Potent BRAF Inhibitors: Toward 1 nM Compounds through Optimization of the Central Phenyl Ring.** *Journal of Medicinal Chemistry* (**2009**), *52*, 3881-3891.

BRAF, a serine/threonine specific protein kinase that is part of the MAPK pathway and acts as a downstream effector of RAS, is a potential therapeutic target in melanoma. We have developed a series of small-molecule BRAF inhibitors based on a 1H-imidazo[4,5-b]pyridine-2(3H)-one scaffold (ring A) as the hinge binding moiety and a number of substituted phenyl rings C that interact with the allosteric binding site. The introduction of various groups on the central phenyl ring B combined with appropriate A- and C-ring modifications afford very potent compounds that inhibit ^{V600E}BRAF kinase activity in vitro and oncogenic BRAF signaling in melanoma cells. Substitution on the central phenyl ring of a 3-fluoro, a naphthyl, or a 3-thiomethyl group improves activity to yield compounds with an IC_{50} of 1 nM for purified ^{V600E}BRAF and nanomolar activity in cells.

Inhibitor of PI3 kinase

8-(2-Methylphenoxy)-2-(4-morpholinyl)-4(1*H*)-quinolinone (TGX115)



Chemical Formula: $C_{20}H_{20}N_2O_3$
Molecular Weight: 336.38

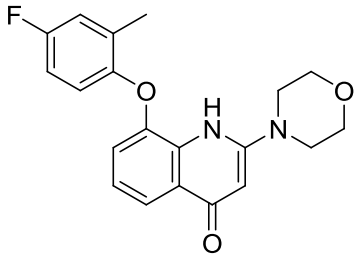
OTAVA Catalogue Number: 7070707058
CAS Registry Number: 351071-62-0
Purity: 97%+

Ref.: Knight et al. **Isoform-specific phosphoinositide 3-kinase inhibitors from an arylmorpholine scaffold.** *Bioorganic & Medicinal Chemistry* (**2004**), *12*, 4749-4759

Phosphoinositide 3-kinases (PI3-Ks) are an ubiquitous class of signaling enzymes that regulate diverse cellular processes including growth, differentiation, and motility. Physiological roles of PI3-Ks have traditionally been assigned using two pharmacological inhibitors, LY294002 and wortmannin. Although these compounds are broadly specific for the PI3-K family, they show little selectivity among family members, and the development of isoform-specific inhibitors of these enzymes has been long anticipated. Herein, we prepare compounds from two classes of arylmorpholine PI3-K inhibitors and characterize their specificity against a comprehensive panel of targets within the PI3-K family. We identify multiplex inhibitors that potently inhibit distinct subsets of PI3-K isoforms, including the first selective inhibitor of p110β/p110δ (IC_{50} p110β = 0.13 μM, p110δ = 0.63 μM). We also identify trends that suggest certain PI3-K isoforms may be more sensitive to potent inhibition by arylmorpholines, thereby guiding future drug design based on this pharmacophore.

PI3K Inhibitor

8-(4-Fluoro-2-methylphenoxy)-2-(4-morpholinyl)-4(1*H*)-quinolinone (TGX155)



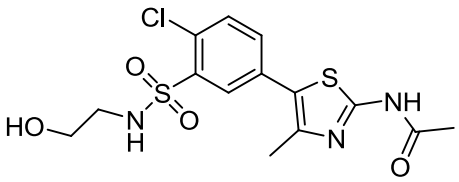
Chemical Formula: $C_{20}H_{19}FN_2O_3$
Molecular Weight: 354.37

OTAVA Catalogue Number: 7070707047
CAS Registry Number: 351071-90-4
Purity: 97%+

PI4-kinase inhibitor

***N*-[5-[4-chloro-3-[[(2-hydroxyethyl)amino]sulfonyl]phenyl]-4-methyl-2-thiazolyl]-acetamide (PIK-93)**

- *PI4KIIIβ inhibitor with IC_{50} = 19 nM*



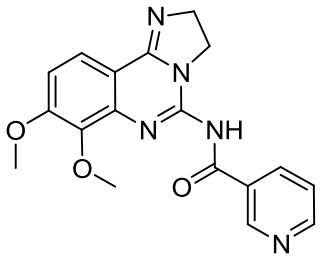
Chemical Formula: $C_{14}H_{16}ClN_3O_4S_2$
Molecular Weight: 389.88

OTAVA Catalogue Number: 7070707029
CAS Registry Number: 593960-11-3
Purity: 97%+

PI3K Inhibitor

N-(2,3-Dihydro-7,8-dimethoxyimidazo[1,2-*c*]quinazolin-5-yl)-3-pyridinecarboxamide (PIK-90)

- *PIK-90 is a potent and cell permeable PI3K inhibitor, with IC_{50} values of 11 nM, 350 nM, 18 nM, and 58 nM for p110 α, β, γ and δ isoforms*



Chemical Formula: $C_{18}H_{17}N_5O_3$
Molecular Weight: 351.36

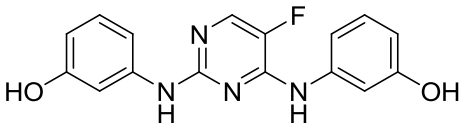
OTAVA Catalogue Number: 7070707028
CAS Registry Number: 677338-12-4
Purity: 97%+

Ref. 1: Weiss et al. **A dual PI3 kinase/mTOR inhibitor reveals emergent efficacy in glioma.** *Cancer Cell* (**2006**), *9*, 341-349
The PI3 kinase family of lipid kinases promotes cell growth and survival by generating the second messenger phosphatidylinositol-3,4,5-*tris*phosphate. To define targets critical for cancers driven by activation of PI3 kinase, we screened a panel of potent and structurally diverse drug-like molecules that target this enzyme family. Surprisingly, a single agent (PI-103) effected proliferative arrest in glioma cells, despite the ability of many compounds to block PI3 kinase signaling through its downstream effector, Akt. The unique cellular activity of PI-103 was traced directly to its ability to inhibit both PI3 kinase α and mTOR. PI-103 showed significant activity in xenografted tumors with no observable toxicity. These data demonstrate an emergent efficacy due to combinatorial inhibition of mTOR and PI3 kinase α in malignant glioma.

Ref. 2: Shokat et al. **A pharmacological map of the PI3-K family defines a role for p110α in insulin signaling.** *Cell (Cambridge, MA, United States)* (**2006**), *125*, 733-747
Phosphoinositide 3-kinases (PI3-Ks) are an important emerging class of drug targets, but the unique roles of PI3-K isoforms remain poorly defined. We describe here an approach to pharmacologically interrogate the PI3-K family. A chemically diverse panel of PI3-K inhibitors was synthesized, and their target selectivity was biochemically enumerated, revealing cryptic homologies across targets and chemotypes. Crystal structures of three inhibitors bound to p110γ identify a conformationally mobile region that is uniquely exploited by selective compounds. This chemical array was then used to define the PI3-K isoforms required for insulin signaling. We find that p110α is the primary insulin-responsive PI3-K in cultured cells, whereas p110β is dispensable but sets a phenotypic threshold for p110α activity. Compounds targeting p110α block the acute effects of insulin treatment in vivo, whereas a p110β inhibitor has no effect. These results illustrate systematic target validation using a matrix of inhibitors that span a protein family.

Syk kinase inhibitor

3,3'-[(5-Fluoro-2,4-pyrimidinediyl)diimino]bis-phenol (R112)



Chemical Formula: $C_{16}H_{13}FN_4O_2$
Molecular Weight: 312.30

OTAVA Catalogue Number: 7070707049
CAS Registry Number: 575474-82-7
Purity: 97%+

Ref.: Rossi et al. **Identification of the Syk kinase inhibitor R112 by a human mast cell screen.** *Journal of Allergy and Clinical Immunology* (**2006**), *118*, 749-755

Background

Activation of the IgE receptor, FcεRI, in mast cells is the key mechanism initiating and propagating pathophysiological responses in allergic rhinitis.

Objective

Identify and characterize a small molecule inhibitor of IgE-dependent mast cell activation for the treatment of allergic diseases.

Methods

A cell-based high-throughput screen for small molecules that block IgE signaling was performed in cultured human mast cells. A potent inhibitor, referred to as **R112**, was selected and characterized by using biochemical and cell-based assays. **R112** effects on IgE-dependent degranulation and cytokine production was measured in mast cells and basophils and compared with other mast cell inhibitors.

Results

R112 inhibited degranulation induced by anti-IgE cross-linking in mast cells (tryptase release, effective concentration for 50% inhibition [EC_{50}] = 353 nmol/L) or basophils (histamine release, EC_{50} = 280 nmol/L), and by allergen (dust mite) in basophils (histamine release, EC_{50} = 490 nmol/L). **R112** also blocked leukotriene C4 production and all proinflammatory cytokines tested. Subsequent molecular characterization indicated that R112 is an ATP-competitive spleen tyrosine kinase (Syk) inhibitor (inhibitory constant [K_i] = 96 nmol/L). Its onset of action was immediate, and the inhibition was reversible. Incubation of mast cells with **R112** showed that cytokine production in mast cells was dependent on sustained activation of the FcεRI-Lyn–spleen tyrosine kinase pathway. Unlike other mast cell inhibitors, **R112** was able to completely inhibit all three IgE-induced mast cell functions: degranulation, lipid mediator production, and cytokine production.

Conclusion

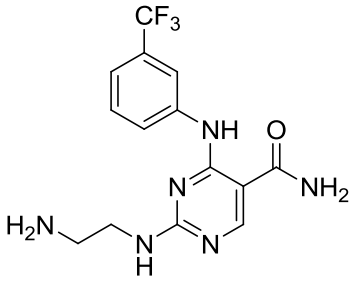
R112 potently, completely, and rapidly abrogated all mast cell activation cascades triggered by IgE receptor cross-linking.

Clinical implications

R112 and its analogues offer a new modality in the treatment of allergic rhinitis.

Syk kinase inhibitor

2-[(2-Aminoethyl)amino]-4-[[3-(trifluoromethyl)phenyl]amino]-5-pyrimidinecarboxamide



Chemical Formula: $C_{14}H_{15}F_3N_6O$
Molecular Weight: 340.30

OTAVA Catalogue Number: 7070707056
CAS Registry Number: 726695-51-8
Purity: 97%+

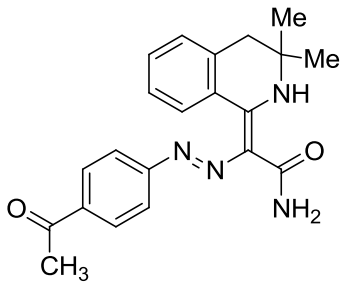
Ref.: Hisamichi et al. **Synthetic studies on novel Syk inhibitors. Part 1: Synthesis and structure-activity relationships of pyrimidine-5-carboxamide derivatives.** *Bioorganic and Medicinal Chemistry* (**2005**), *13*, 4936-4951

Spleen tyrosine kinase (Syk) is a non-receptor-type tyrosine kinase which mediates diverse responses in haematopoietic cells. Therefore, Syk is an attractive therapeutic target, and in a study of Syk inhibitors as potentially new therapeutic agents, we discovered the 4-anilinopyrimidine-5-carboxamides. Enzyme screening indicated that an aminoethylamino moiety at the 2-position of the pyrimidine ring was important for Syk inhibitory activity, and an investigation of the substituents at the 4-position revealed that an anilino moiety substituted at the meta position was preferred. These compounds showed high selectivity for Syk, compared to other kinases, such as ZAP-70, c-Src, and PKC, and exhibited good inhibitory activities against 5-HT release from RBL-cells. Among them, compound 9a inhibited the passive cutaneous anaphylaxis reaction in mice, with an ID50 of 13 mg/kg following subcutaneous administration. These results suggest that our compounds are worthy of further evaluation as new anti-allergic agents.

Stem Cell Reagent; Wnt Pathway Activator III

2-[(4-Acetylphenyl)azo]-2-(3,4-dihydro-3,3-dimethyl-1(2*H*)-isoquinolinylidene)-acetamide (IQ-1)

- *A cell-permeable tetrahydroisoquinolinylidene compound that modulates Wnt/b-catenin signaling by targeting the PR72/130 subunit of PP2A and thereby blocking PP2A/Nkd complex formation, resulting in diminished b-catenin/p300 interaction and a concomitant increase in b-catenin/CBP usage. Co-adminitration of IQ-1 (4 µg/ml) and Wnt3a (100 ng/ml), but neither reagent alone, has been shown to be sufficient in maintaining long-term (>48 days) murine ESCs (Embryonic Stem Cells) pluripotency in the absence of serum.*



Chemical Formula: $C_{21}H_{22}N_4O_2$
Molecular Weight: 362.42

OTAVA Catalogue Number: 7070707017
CAS Registry Number: 331001-62-8
Purity: 97%+

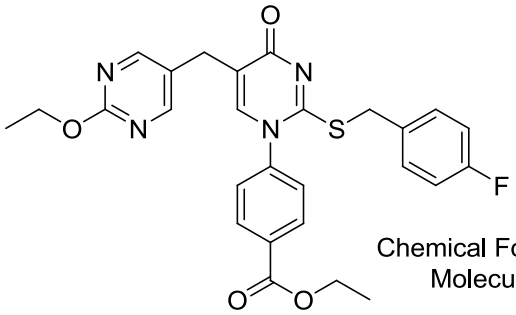
Ref.: Miyabayashi et al. **Wnt/β-catenin/CBP signaling maintains long-term murine embryonic stem cell pluripotency.** *Proceedings of the National Academy of Sciences of the United States of America* (**2007**), *104*, 5668-5673

Embryonic stem cells (ESCs) represent an important research tool and a potential resource for regenerative medicine. Generally, ESCs are cocultured with a supportive feeder cell layer of murine embryonic fibroblasts, which maintain the ESCs' capacity for self-renewal and block spontaneous differentiation. These cumbersome conditions, as well as the risk of xenobiotic contamination of human ESCs grown on murine embryonic fibroblasts, make it a priority to develop chemically defined methods that can be safely used for the expansion of ESCs. Using a high-throughput, cell-based assay, we identified the small molecule **IQ-1** that allows for the Wnt/β-catenin-driven long-term expansion of mouse ESCs and prevents spontaneous differentiation. We demonstrate that **IQ-1**, by targeting the PR72/130 subunit of the serine/threonine phosphatase PP2A, prevents β-catenin from switching coactivator usage from CBP to p300. The increase in β-catenin/CBP-mediated transcription at the expense of β-catenin/p300-mediated transcription is critical for the maintenance of murine stem cell pluripotency.

GPR40 antagonist

1-(4-Ethoxycarbonylphenyl)-2-(4-fluorobenzylthio)-5-(2-ethoxy-5-pyrimidinylmethyl)-4-pyrimidinone (GW1100)

- *An inhibitor of the phospholipase A2 enzyme Lp-PLA2 for the treatment of atherosclerosis*
- *A selective GPR40 antagonist*



Chemical Formula: $C_{27}H_{25}FN_4O_4S$
Molecular Weight: 520.58

OTAVA Catalogue Number: 7070707009
CAS Registry Number: 306974-70-9
Purity: 97%+

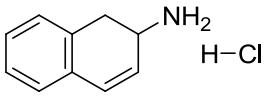
Ref.: Briscoe et al. **Pharmacological regulation of insulin secretion in MIN6 cells through the fatty acid receptor GPR40: identification of agonist and antagonist small molecules.** *Br J Pharmacol* (**2006**), *148*, 619-628

1. Long chain fatty acids have recently been identified as agonists for the G protein-coupled receptors GPR40 and GPR120. Here, we present the first description of GW9508, a small-molecule agonist of the fatty acid receptors GPR40 and GPR120. In addition, we also describe the pharmacology of **GW1100**, a selective GPR40 antagonist. These molecules were used to further investigate the role of GPR40 in glucose-stimulated insulin secretion in the MIN6 mouse pancreatic beta-cell line.
2. GW9508 and linoleic acid both stimulated intracellular Ca^{2+} mobilization in human embryonic kidney (HEK)293 cells expressing GPR40 (pEC_{50} values of 7.32+/-0.03 and 5.65+/-0.06, respectively) or GPR120 (pEC_{50} values of 5.46+/-0.09 and 5.89+/-0.04, respectively), but not in the parent HEK-293 cell line.
3. **GW1100** dose dependently inhibited GPR40-mediated Ca^{2+} elevations stimulated by GW9508 and linoleic acid (pIC_{50} values of 5.99+/-0.03 and 5.99+/-0.06, respectively). **GW1100** had no effect on the GPR120-mediated stimulation of intracellular Ca^{2+} release produced by either GW9508 or linoleic acid.
4. GW9508 dose dependently potentiated glucose-stimulated insulin secretion in MIN6 cells, but not in primary rat or mouse islets. Furthermore, GW9508 was able to potentiate the KCl-mediated increase in insulin secretion in MIN6 cells. The effects of GW9508 on insulin secretion were reversed by **GW1100**, while linoleic acid-stimulated insulin secretion was partially attenuated by **GW1100**.
5. These results add further evidence to a link between GPR40 and the ability of fatty acids to acutely potentiate insulin secretion and demonstrate that small-molecule GPR40 agonists are glucose-sensitive insulin secretagogues

Antagonist of NMDA receptor

1,2-Dihydro-2-naphthalenamine hydrochloride

- *potent antagonist of the modulatory glycine site of the N-methyl-D-aspartate (NMDA) receptor*



Chemical Formula: $C_{10}H_{12}ClN$
Molecular Weight: 181.66

OTAVA Catalogue Number: 7070707014
CAS Registry Number: 81094-64-6
Purity: 97%+

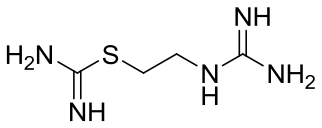
Ref.: Hathaway et al. **A new, potent, conformationally-restricted analog of amphetamine: 2-amino-1,2-dihydronaphthalene.** *Journal of Medicinal Chemistry* (**1982**), *25*, 535-538

A new stimulant was prepared as an analog of amphetamine and of 2-aminotetralin. The optical isomers of this amine were obtained by chemical resolution, and the absolute configuration was determined to be (R)-(+) and (S)-(-). (±)-1,2-Dihydro-2-naphthalenamine is approximately one-fourth as potent as (+)-amphetamine as a stimulant in mice. (S)-(-)-1,2-Dihydro-2-naphthalenamine is solely responsible for the stimulant effects of the racemate.

Histamine H_4 receptor agonist

2-[(Aminoiminomethyl)amino]ethyl carbamimidothioic acid ester (*S*-(2-guanidylethyl)-isothiourea; VUF 8430 dihydrobromide)

- *Potent histamine H_4 receptor agonist, with a 33-fold selectivity over the histamine H_3 receptor and negligible affinity for the other histamine receptor*



H–Br H–Br

Chemical Formula: $C_4H_{13}Br_2N_5S$
Molecular Weight: 323.05

OTAVA Catalogue Number: 7070707134
CAS Registry Number: 100130-32-3
CAS Registry Number: 98021-17-1 (free base)
Purity: 97%+

Ref. 1: Sterk et al. **Studies on histaminergic compounds. IV. Non-isosterism between the imidazole, guanidino and isothiourea moieties at the H_2-receptor.** *Archiv der Pharmazie (Weinheim, Germany)* (**1986**), *319*, 1057-1064
S,S'-Alkylenediisothioureas were found to show only weak agonistic or antagonistic H_2-activity, depending on the length of the alkylene chain.
Introduction of a substituent in the amidino parts of both isothiourea groups resulted in a complete loss of the agonistic activity; only inactive compounds or weakly active H_2-antagonists were obtained.
Replacing one of the isothiourea groups of the alkylenediisothioureas with n = 2, 3 or 4 by a guanidino group has hardly any or no effect at all on the histamine H_2-activity on the guinea-pig right atrium. However, extending the alkylene chain of these guanidylalkylisothioureas to n = 5 and 6 results in a strong increase in the H_2-agonistic activity

Ref. 2: Lim et al. **Pharmacological characterization of the new histamine H_4 receptor agonist VUF 8430.** *British Journal of Pharmacology* (**2009**), *157*, 34-43
Background and purpose: We compare the pharmacological profiles of a new histamine H4 receptor agonist 2-(2-guanidinoethyl)isothiourea (VUF 8430) with that of a previously described H4 receptor agonist, 4-methylhistamine.
Experimental approach: Radioligand binding and functional assays were performed using histamine H4 receptors expressed in mammalian cell lines. Compounds were also evaluated ex vivo in monocyte-derived dendritic cells endogenously expressing H4 receptors and in vivo in anaesthetized rats for gastric acid secretion activity.
Key results: Both VUF 8430 and 4-methylhistamine were full agonists at human H4 receptors with lower affinity at rat and mouse H4 receptors. Both compounds induced chemotaxis of monocyte-derived dendritic cells. VUF 8430 also showed reasonable affinity and was a full agonist at the H3 receptor. Agmatine is a metabolite of arginine, structurally related to VUF 8430, and was a H4 receptor agonist with micromolar affinity. At histamine H3 receptors, agmatine was a full agonist, whereas 4-methylhistamine was an agonist

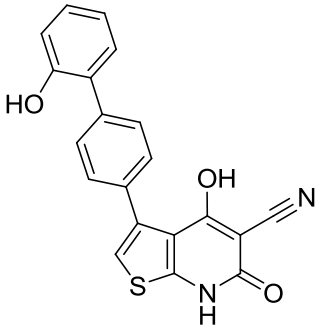
only at high concentrations. Both VUF 8430 and agmatine were inactive at H1 and H2 receptors, whereas 4-methylhistamine is as active as histamine at H2 receptors. In vivo, VUF 8430 only caused a weak secretion of gastric acid mediated by H2 receptors, whereas 4-methylhistamine, dimaprit, histamine and amthamine, at equimolar doses, induced 2.5- to 6-fold higher output than VUF 8430.
Conclusions and implications: Our results suggest complementary use of 4-methylhistamine and VUF 8430 as H4 receptor agonists. Along with H4 receptor antagonists, both agonists can serve as useful pharmacological tools in studies of histamine H4 receptors.

Ref. 3: Lim et al. **Discovery of *S*-(2-guanidylethyl)-isothiourea (VUF 8430) as a potent nonimidazole histamine H_4 receptor agonist.** *Journal of Medicinal Chemistry* (**2006**), *49*, 6650-6651
During an inhouse database screen, the authors identified *S*-(2-guanidylethyl)-isothiourea as a high affinity agonist for the histamine H_4 receptor, with a 33-fold selectivity over the histamine H_3 receptor and negligible affinity for the other histamine receptor subtypes. This nonimidazole ligand is introduced as a useful and complementary pharmacol. tool that enables further unraveling of the physiol. roles of the H_4 receptor.

AMPK activator

6,7-Dihydro-4-hydroxy-3-(2'-hydroxy[1,1'-biphenyl]-4-yl)-6-oxo-thieno[2,3-*b*]pyridine-5-carbonitrile (A-769662)

- *Potent, reversible AMP-activated protein kinase (AMPK) activator (EC_{50} = 0.8 μM) that displays selectivity towards β1 subunit-containing heterotrimers. Inhibits fatty acid synthesis (IC_{50} = 3.2 μM) and decreases plasma glucose and triglyceride levels in vivo.*



Chemical Formula: $C_{20}H_{12}N_2O_3S$
Molecular Weight: 360.39

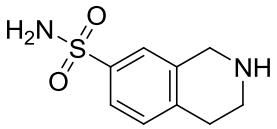
OTAVA Catalogue Number: 7070707027
CAS Registry Number: 844499-71-4
Purity: 97%+

Ref.:

Cool et al. **Identification and characterization of a small molecule AMPK activator that treats key components of type 2 diabetes and the metabolic syndrome.** *Cell Metabolism* (**2006**), *3*, 403-416
AMP-activated protein kinase (AMPK) is a key sensor and regulator of intracellular and whole-body energy metabolism. We have identified a thienopyridone family of AMPK activators. **A-769662** directly stimulated partially purified rat liver AMPK (EC_{50} = 0.8 microM) and inhibited fatty acid synthesis in primary rat hepatocytes (IC_{50} = 3.2 microM). Short-term treatment of normal Sprague Dawley rats with **A-769662** decreased liver malonyl CoA levels and the respiratory exchange ratio, VCO2/VO2, indicating an increased rate of whole-body fatty acid oxidation. Treatment of ob/ob mice with 30 mg/kg b.i.d. **A-769662** decreased hepatic expression of PEPCK, G6Pase, and FAS, lowered plasma glucose by 40%, reduced body weight gain and significantly decreased both plasma and liver triglyceride levels. These results demonstrate that small molecule-mediated activation of AMPK in vivo is feasible and represents a promising approach for the treatment of type 2 diabetes and the metabolic syndrome

Inhibitor of Phenylethanolamine *N*-Methyl-Transferase

1,2,3,4-Tetrahydro-7-isoquinolinesulfonamide (SK&F 29661)



Chemical Formula: $C_9H_{12}N_2O_2S$
Molecular Weight: 212.27

OTAVA Catalogue Number: 1183326
CAS Registry Number: 31404-61-2
Purity: 97%+

Ref. 1: Pendleton et al. **Studies on SK&F 29661, an organ-specific inhibitor of phenylethanolamine *N*-methyltransferase.** *Journal of Pharmacology and Experimental Therapeutics* (**1979**), *208*, 24-30
SK&F 29661 is an effective, reversible inhibitor of both central nervous system and adrenal phenylethanolamine *N*-methyl-transferase in vitro; its Ki values in our standard assay systems were 6 X 10(-7) M (central nervous system) and 3 X 10(-7) M (adrenal), respectively. In vivo, the drug inhibited the conversion of [3H]norepinephrine to [3H]epinephrine in the rat adrenal gland and upon chronic administration decreased the endogenous adrenal epinephrine/norepinephrine ratio in both the rat and squirrel monkey. SK&F 29661 did not, however, reduce rat brain stem PNMT activity after systemic administration; subsequent radioautographic studies indicated that the compound did not enter the central nervous system, presumably because of its high polarity. This drug may be useful in defining the physiological importance of peripheral phenylethanolamine N- methyltransferase inhibition.

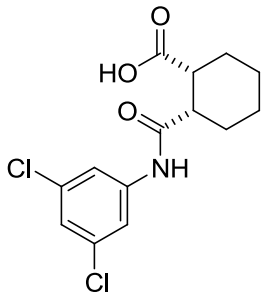
Ref. 2: Grunewald et al. **Examination of the Role of the Acidic Hydrogen in Imparting Selectivity of 7-(Aminosulfonyl)-1,2,3,4-tetrahydroisoquinoline (SK&F 29661) Toward Inhibition of Phenylethanolamine N-Methyltransferase vs the α2-Adrenoceptor.** *Journal of Medicinal Chemistry* (**1997**), *40*, 3997-4005

Potent and positive allosteric $mGlu_4$ agonist

(±)-*cis*-2-{[(3,5-dichlorophenyl)amino]carbonyl}cyclohexanecarboxylic acid ((1*R*,2*S*)-*rel*-2-[[(3,5-dichlorophenyl)amino]carbonyl]-cyclohexanecarboxylic acid; **VU0155041)**

- *Positive allosteric selective modulator at $mGluR_4$ (EC_{50} values are 798 nM and 693 nM at human and rat $mGluR_4$ receptors respectively). It has advantages over PHCCC (Asc-043) as it is water soluble and more potent. Active in behavioural models of Parkinsons Disease*

Relative stereochemistry



Chemical Formula: $C_{14}H_{15}Cl_2NO_3$
Molecular Weight: 316.18

OTAVA Catalogue Number: 7114471128
CAS Registry Number: 1093757-42-6
CAS Registry Number: 1259372-69-4 (sodium salt)
Purity: 97%+

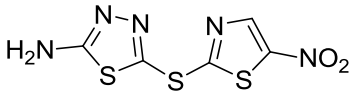
Ref.: Niswender et al. **Discovery, characterization, and antiparkinsonian effect of novel positive allosteric modulators of metabotropic glutamate receptor 4.** *Molecular Pharmacology* (**2008**), *74*, 1345-1358
Parkinson's disease (PD) is caused by the death of dopamine neurons in the basal ganglia and results in motor symptoms such as tremor and bradykinesia. Activation of metabotropic glutamate receptor 4 (mGluR4) has been shown to modulate neurotransmission in the basal ganglia and results in antiparkinsonian effects in rodent PD models. *N*-Phenyl-7-(hydroxyimino)cyclopropa[*b*]chromen-1a-carboxamide (PHCCC) is a positive allosteric modulator (PAM) of $mGluR_4$ that has been used to further validate the role of $mGluR_4$ in PD, but the compound suffers from a lack of selectivity, relatively low potency, and poor solubility. Via high-throughput screening, we discovered more than 400 novel PAMs of $mGluR_4$. Compounds derived from a novel chemical scaffold were characterized in vitro at both rat and human $mGluR_4$ using two distinct assays of $mGluR_4$ function. The lead compound was approximately 8-fold more potent than PHCCC, enhanced the potency of glutamate at $mGluR_4$ by 8-fold, and did not show any significant potentiator or antagonist activity at other mGluR subtypes. Resolution of the regioisomers of the lead revealed that the *cis* regioisomer, (±)-*cis*-2-(3,5-dichlorphenylcarbamoyl)cyclohexanecarboxylic acid (**VU0155041**), contained the majority of the $mGluR_4$ PAM activity and also exhibited partial agonist activity at

$mGluR_4$ at a site that was distinct from the glutamate binding site, suggesting that this compound is a mixed allosteric agonist/PAM of $mGluR_4$. **VU0155041** was soluble in an aqueous vehicle, and intracerebroventricular administration of 31 to 316 nmol of **VU0155041** dose-dependently decreased haloperidol-induced catalepsy and reserpine-induced akinesia in rats. These exciting results provide continued support for $mGluR_4$ as a therapeutic target in PD.

Selective inhibitor of c-Jun N-terminal kinase

5-[(5-Nitro-2-thiazolyl)thio]-1,3,4-thiadiazol-2-amine (SU 3327)

- *Selective inhibitor of c-Jun N-terminal kinase (JNK) (IC_{50} = 0.7 μM). Inhibits the protein-protein interaction between JNK and JIP (IC_{50} = 239 nM). Displays selectivity over p38 MAPK and Akt. Restores insulin sensitivity in a mouse model of type-2 diabetes*



Chemical Formula: $C_5H_3N_5O_2S_3$
Molecular Weight: 261.30

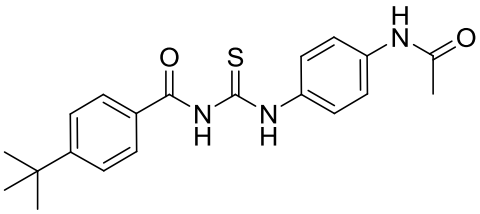
OTAVA Catalogue Number: 7070707069
CAS Registry Number: 40045-50-9
Purity: 97%+

Ref.: Pellecchia et al. **Design, Synthesis, and Structure-Activity Relationship of Substrate Competitive, Selective, and in Vivo Active Triazole and Thiadiazole Inhibitors of the c-Jun N-Terminal Kinase.** *Journal of Medicinal Chemistry* (**2009**), *52,* 1943-1952
Comprehensive structure-activity relationship studies on a novel series of c-Jun N-terminal kinase(JNK) inhibitors is reported. The compounds are substrate competitive inhibitors that bind to the docking site of the kinase. The reported medicinal chemistry and structure-based optimizations studies resulted in the discovery of selective and potent thiadiazole JNK inhibitors that display promising in vivo activity in mouse models of insulin insensitivity.

p53 activator

N-[[[4-(Acetylamino)phenyl]amino]thioxomethyl]-4-(1,1-dimethylethyl)-benzamide (Tenovin 1)

- *p53 activator that protects against MDM2-mediated p53 degradation. Elevates levels of p53 and p21$^{CIP/WAF1}$ and induces expression from an endogenous p53-dependent promoter. Exhibits potent antiproliferative activity in vitro*



Chemical Formula: $C_{20}H_{23}N_3O_2S$
Molecular Weight: 369.48

OTAVA Catalogue Number: 7215270035
CAS Registry Number: 380315-80-0
Purity: 99%+

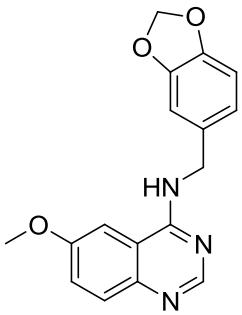
Ref.: Lain et al. **Discovery, in vivo activity, and mechanism of action of a small-molecule p53 activator.** *Cancer Cell* (**2008**), *13*, 454-463

We have carried out a cell-based screen aimed at discovering small molecules that activate p53 and have the potential to decrease tumor growth. Here, we describe one of our hit compounds, tenovin-1, along with a more water-soluble analog, tenovin-6. Via a yeast genetic screen, biochemical assays, and target validation studies in mammalian cells, we show that tenovins act through inhibition of the protein-deacetylating activities of SirT1 and SirT2, two important members of the sirtuin family. Tenovins are active on mammalian cells at one-digit micromolar concentrations and decrease tumor growth in vivo as single agents. This underscores the utility of these compounds as biological tools for the study of sirtuin function as well as their potential therapeutic interest.

Inhibitor of cGMP-specific phosphodiesterase

N-(1,3-Benzodioxol-5-ylmethyl)-6-methoxy-4-quinazolinamine

- *Potent and specific inhibitor of cGMP-specific phosphodiesterase with IC_{50} = 230 nM. It levates the intracellular cGMP level without causing any change in the cAMP level in isolated porcine coronary arteries and it has no effect on other PDE isozymes*



Chemical Formula: $C_{17}H_{15}N_3O_3$
Molecular Weight: 309.32

OTAVA Catalogue Number: 7020540496
CAS Registry Number: 150450-42-3
Purity: 97%+

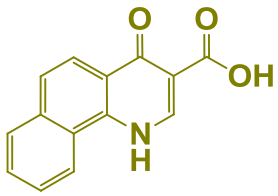
Ref.: Takase et al. **Cyclic GMP Phosphodiesterase Inhibitors. 2. Requirement of 6-Substitution of Quinazoline Derivatives for Potent and Selective Inhibitory Activity.** *Journal of Medicinal Chemistry* (**1994**), *37*, 2106-2111

4-[3,4-Methylenedioxybenzylamino]quinazolines were prepared and evaluated their inhibitory activities toward cyclic GMP phosphodiesterase (cGMP-PDE) from porcine aorta. Monosubstitution at the 6-position was essential for inhibitory activity, and the preferred substituents were compact and hydrophobic, i.e. **I** (R and IC_{50} given: OMe 0.23, Me 0.10, Cl 0.019, SMe 0.031, CN 0.090). **I** lacked inhibitory activity toward other phosphodiesterase isoenzymes (all IC_{50} values > 100 μM), and their relaxing activities in porcine coronary arteries were well correlated with the inhibitory activities toward cGMP-PDE ($r = 0.88$, $p < 0.05$). **I** (R = OMe) elevated the intracellular cGMP level in isolated porcine coronary arteries without causing any change in the cAMP level. This series of compounds dilates coronary arteries via potent and specific inhibition of cGMP-PDE.

Human Protein Kinase CK2 Inhibitors Developed by OTAVA Scientists

1,4-Dihydro-4-oxo-benzo[*h*]quinoline-3-carboxylic acid (NSC 210902)

- *new CK2 inhibitor from OTAVA with IC_{50} = 1 μM*

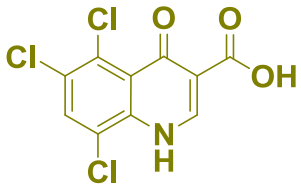


Chemical Formula: $C_{14}H_9NO_3$
Molecular Weight: 239.23

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
0107830116	51726-83-1	**5 mg** **25 mg**	**In-stock** **In-stock**	≥ 95% by CHN analysis & ^{1}H NMR

5,6,8-Trichloro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

- *new CK2 inhibitor from OTAVA with IC_{50} = 0.3 μM*

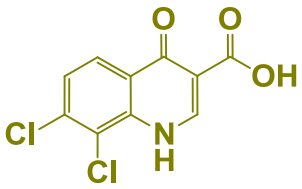


Chemical Formula: $C_{10}H_4Cl_3NO_3$
Molecular Weight: 292.50

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
0107830108	302553-01-1	**5 mg** **25 mg**	**In-stock** **In-stock**	≥ 95% by CHN analysis, HPLC & ^{1}H NMR

7,8-Dichloro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

- *new CK2 inhibitor from OTAVA with IC_{50} = 0.8 μM*



Chemical Formula: $C_{10}H_5Cl_2NO_3$
Molecular Weight: 258.06

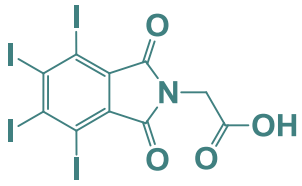
OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
0107830107	300675-28-9	**5 mg** **25 mg**	**In-stock** **In-stock**	≥ 95% by CHN analysis & ^{1}H NMR

Ref.: Golub et al. **Evaluation of 3-Carboxy-4(1*H*)-quinolones as Inhibitors of Human Protein Kinase CK2.** *Journal of Medicinal Chemistry* (**2006**), *49*, 6443-6450

A new class of CK2 inhibitors, **3-carboxy-4(1*H*)-quinolones**, has been selected via receptor-based virtual screening of the **OTAVA** compound library. It was revealed that the most active compounds, 5,6,8-trichloro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (IC_{50} = 0.3 μM) and 4-oxo-1,4-dihydrobenzo[h]quinoline-3-carboxylic acid (IC_{50} = 1 μM), are ATP competitive (Ki values are 0.06 and 0.28 μM, resp.). Evaluation of the inhibitors on seven protein kinases shows considerable selectivity toward CK2. *According to theoretical calculations and experimental data, a **structural** model describing the key features of 3-carboxy-4(1H)-quinolones responsible for tight binding to CK2 active site has been developed*.

4,5,6,7-Tetraiodo-1,3-dioxo-2-isoindolineacetic acid

- *new CK2 inhibitor from OTAVA with IC_{50} = 0.3 μM*



Chemical Formula: $C_{10}H_3I_4NO_4$
Molecular Weight: 708.75

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7015980251	19231-60-8	**5 mg** **25 mg**	**In-stock** **In-stock**	≥ 95% by CHN analysis & ^{1}H NMR

Ref.: Golub et al. **Evaluation of 4,5,6,7-tetrahalogeno-1*H*-isoindole-1,3(2*H*)-diones as inhibitors of human protein kinase CK2.** *Biochimica et Biophysica Acta* (**2008**), *1784*, 143-149

Protein kinase CK2 (Casein Kinase 2) is an extremely pleiotropic Ser/Thr kinase with high constitutive activity. The observation of CK2 deregulations in various pathological processes suggests that CK2 inhibitors may have a therapeutic value, particularly as anti-neoplastic and antiviral drugs. The 4,5,6,7-tetrahalogeno-1*H*-isoindole-1,3(2*H*)-diones as a novel potent class of CK2 inhibitors is presented. This class of inhibitors was identified by high-throughput docking of the **OTAVA** compound collection in the ATP-binding site of human CK2. The most active compounds are 2-(4,5,6,7-tetraiodo-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoic acid and 2-(4,5,6,7-tetraiodo-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl) acetic acid with IC_{50} values of 0.15 μM and 0.3 μM, respectively. These inhibitors are ATP-competitive and they only minimally inhibit the activities of protein kinases DYRK1a, MSK1, GSK3 and CDK5. Binding modes for the most active inhibitors are proposed.

Compounds covered by valid patents are solely for research use and are offered under research exemption in accordance with 35 USC 271(e) + A13(1) in the US, section 69.1 of the Japanese Patent Law in Japan, Section 11, No. 2 of the German Patent Law and Section 60 Par 5b of the UK Patents Act. Some compounds may therefore not be available in some countries, to some institutions and for some uses. Please enquire on availability in your country. Any patent infringement issue and resulting liability is solely at buyer's risk.

Compounds will be shipped only to corporations, universities, research institutes or governmental organisations.