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OTAVA has extensive experience in the synthesis of highly valuable products for biotech and pharmaceutical applications around the world.

Our company offers a number of NOTEWORTHY compounds displaying inhibitory activity against distinct targets. These compounds are available in milligram and gram quantities. We also sell intermediates on route to the synthesis of these compounds. Custom and bulk quotes for final products and intermediates are available too.

*If you do not see a compound you are looking for, we offer Custom Synthesis Services. For quotes and details, contact our **Customer Service Department***

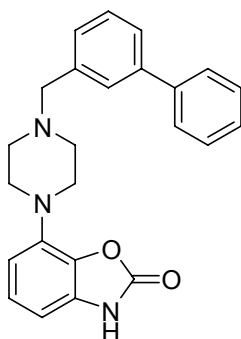
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OTAVA, North American Division, 55 Eglerslie Ave., Suite 524, Toronto, ON, M2N 1X9, CANADA

Tel.: 1-416-305-9979, Fax: 1-866-881-9921 (Toll-free in US & Canada)

7-[4-([1,1'-Biphenyl]-3-ylmethyl)-1-piperazinyl]-2(3H)-benzoxazolone (Bifeprunox) - a novel atypical antipsychotic agent which is under development as a treatment for schizophrenia and potentially conditions such as bipolar disorder. It is a partial agonist at D(2)-like receptors and is an efficacious agonist at 5-HT(1A) receptors



Chemical Formula: C₂₄H₂₃N₃O₂
Molecular Weight: 385.46

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7070707030	350992-10-8	1 mg 5 mg 25 mg 100 mg 250 mg	In-stock In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR

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 extrapyramidal side effects.

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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/>

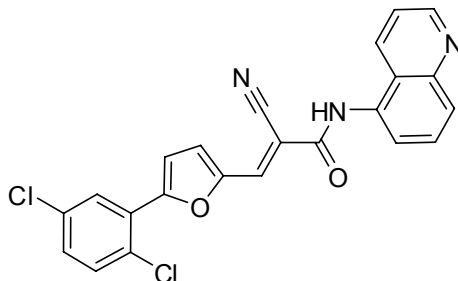
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2-Cyano-3-[5-(2,5-dichlorophenyl)-2-furanyl]-N-5-quinolinyl-2-propenamide - a potent inhibitor of sirtuin 2 (SIRT2)



Chemical Formula: C₂₃H₁₃Cl₂N₃O₂
Molecular Weight: 434.27

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
0117392020	304896-28-4	1 mg 5 mg 25 mg 1 gram	In-stock In-stock In-stock In-stock	≥ 95% by HPLC & ¹ H NMR

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.

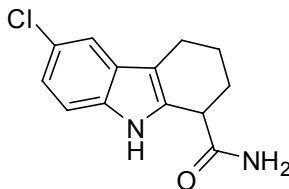
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6-Chloro-2,3,4,9-tetrahydro-1H-carbazole-1-carboxamide (*racemic*) - a selective inhibitor of the deacetylase SIRT1



Chemical Formula: C₁₃H₁₃ClN₂O
Molecular Weight: 248.71

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7020402314	49843-98-3	1 mg 5 mg 25 mg 1 gram 5 grams	In-stock In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR

- 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 IC₅₀ 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

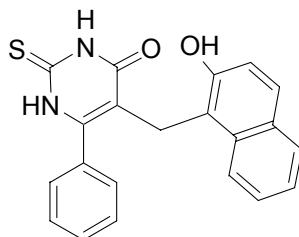
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5-(2-Hydroxy-naphthalen-1-ylmethyl)-6-phenyl-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (NSC-112546) - SIRT1/2 Inhibitor IV, Cambinol



C₂₁H₁₆N₂O₂S
Mol. Wt.: 360.43

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7020402315	14513-15-6	1 mg 5 mg 25 mg 1 gram 5 grams	In-stock In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR

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.

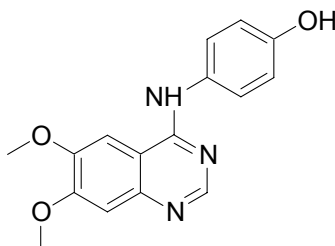
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4-[(6,7-Dimethoxy-4-quinazolinyl)amino]-phenol (4-(4'-Hydroxyphenyl)amino-6,7-dimethoxyquinazoline; **JANEX-1**; **WHI-P131**) - Janus kinase 3 inhibitor



$C_{16}H_{15}N_3O_3$
Mol. Wt.: 297.31

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7015070103	202475-60-3	1 mg 5 mg 25 mg 1 gram	In-stock In-stock In-stock In-stock	≥ 97% by HPLC & ¹ H NMR

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.

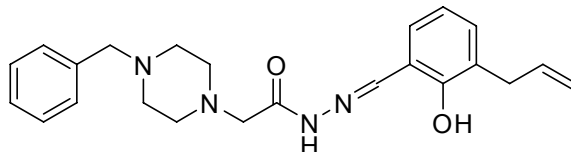
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2-[[2-Hydroxy-3-(2-propen-1-yl)phenyl]methylene]hydrazide 4-(phenylmethyl)-1-piperazineacetic acid (PAC-1) - antitumor agent activating procaspase-3 to caspase-3



Chemical Formula: C₂₃H₂₈N₄O₂
Molecular Weight: 392.49

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7210801533	315183-21-2	1 mg 5 mg 25 mg 1 gram 5 grams	In-stock In-stock In-stock In-stock In-stock	≥ 95% by HPLC, ¹³ C NMR & ¹ H NMR

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>

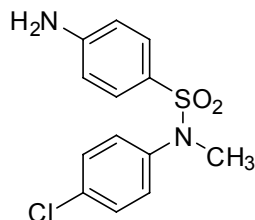
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4-Amino-N-(4-chlorophenyl)-N-methyl-benzenesulfonamide - benzenesulfonamide-type cyclooxygenase-1-selective inhibitor



Chemical Formula: C₁₃H₁₃ClN₂O₂S
Molecular Weight: 296.77

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7070707001	304913-22-2	1 mg 5 mg 25 mg 1 gram	In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR

Ref.: Zheng et al. **Analgesic agents without gastric damage: Design and synthesis of structurally simple benzenesulfonamide-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.

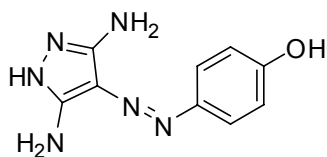
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Tel.: 1-416-305-9979, Fax: 1-866-881-9921 (Toll-free in US & Canada)

4-(3,5-Diamino-1H-pyrazol-4-ylazo)-phenol (CAN508)- CDK9 Inhibitor II



Chemical Formula: C₉H₁₀N₆O
Molecular Weight: 218.22

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7020402317	140651-18-9	1 mg 5 mg 25 mg 1 gram	In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR

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-1H-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.

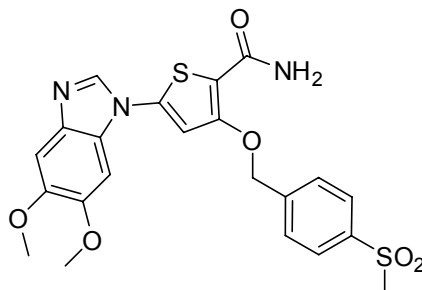
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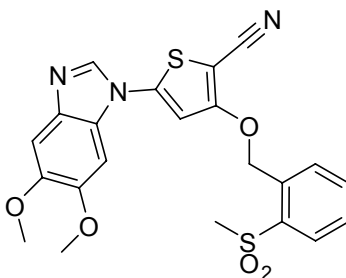
5-(5,6-Dimethoxy-1H-benzimidazol-1-yl)-3-[[4-(methylsulfonyl)phenyl]methoxy]-2-thiophenecarboxamide - potent and selective inhibitor of IKK-ε kinase



Chemical Formula: C₂₂H₂₁N₃O₆S₂
Molecular Weight: 487.55

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7020402323	916985-21-2	1 mg 5 mg 25 mg 100 mg	In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR

5-(5,6-Dimethoxy-1H-benzimidazol-1-yl)-3-[[2-(methylsulfonyl)phenyl]methoxy]-2-thiophenecarbonitrile - potent and selective inhibitor of IKK-ε kinase



Chemical Formula: C₂₂H₁₉N₃O₅S₂
Molecular Weight: 469.53

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OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7020402324	862812-98-4	1 mg 5 mg 25 mg 100 mg	In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR

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 pIC₅₀ 7.4, and has a highly encouraging wider selectivity profile, including selectivity within the IKK kinase family.

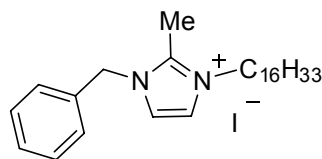
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1-Hexadecyl-2-methyl-3-(phenylmethyl)-1*H*-imidazolium iodide (NH125) - eEF-2 Kinase Inhibitor (inhibitor of eukaryotic elongation factor 2 kinase against human cancer cell lines & potent antibacterial agent against drug-resistant bacteria)



Chemical Formula: C₂₇H₄₅IN₂
Molecular Weight: 524.56

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

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7070707012	278603-08-0	1 mg 5 mg 25 mg 1 gram 5 grams	In-stock In-stock In-stock In-stock In-stock	≥ 97% by 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 (IC₅₀ = 60 nM) in vitro, blocked the phosphorylation of eEF-2 in intact cells, and showed relative selectivity over other protein kinases: protein kinase C (IC₅₀ = 7.5 mM), protein kinase A (IC₅₀ = 80 mM), and calmodulin-dependent kinase II (IC₅₀ > 100 mM). **NH125** decreased the viability of 10 cancer cell lines with IC₅₀s 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**.

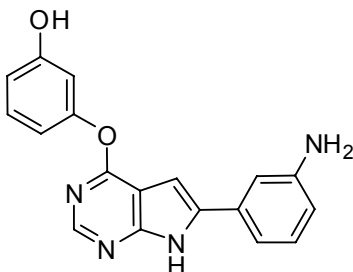
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3-[[6-(3-aminophenyl)-1H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy]-phenol (TWS119) - glycogen synthase kinase-3 (GSK-3) inhibitor



Chemical Formula: C₁₈H₁₄N₄O₂
Molecular Weight: 318.33

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7070707013	601514-19-6	1 mg 5 mg 25 mg 100 mg	In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR

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.

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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-3 β (GSK-3 β) by both affinity-based and biochemical methods. This study provides evidence that GSK-3 β 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.

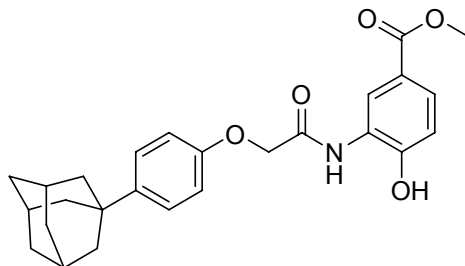
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4-Hydroxy-3-[[2-(4-tricyclo[3.3.1.1^{3,7}]dec-1-ylphenoxy)acetyl]amino]-benzoic acid methyl ester - Hypoxia-Inducible Factor-1 Inhibitor



Chemical Formula: C₂₆H₂₉NO₅
Molecular Weight: 435.51

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7070707015	934593-90-5	1 mg 5 mg 25 mg 1 gram	In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR

Ref.: Lee et al. **(Aryloxyacetyl)amino)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-1 α protein accumulation and its target gene expression under hypoxic conditions in human hepatocellular carcinoma Hep3B cells.

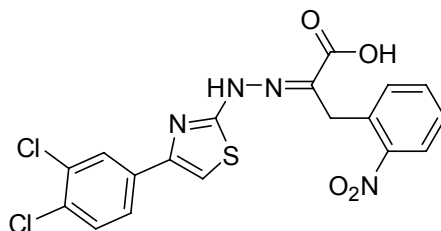
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α -[2-[4-(3,4-Dichlorophenyl)-2-thiazolyl]hydrazinylidene]-2-nitro-benzenepropanoic acid (4EGI-1) - inhibitor of interaction between the translation initiation factors eIF4E and eIF4G



Chemical Formula: C₁₈H₁₂Cl₂N₄O₄S
Molecular Weight: 451.28

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7070707011	315706-13-9	1 mg 5 mg 25 mg 1 gram	In-stock In-stock In-stock In-stock	≥ 95% by HPLC & ¹ H NMR

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.

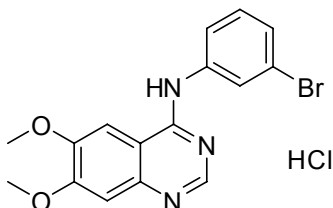
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Tel.: 1-416-305-9979, Fax: 1-866-881-9921 (Toll-free in US & Canada)

N-(3-Bromophenyl)-6,7-dimethoxy-4-quinazolinamine hydrochloride (AG 1517; NSC 669364; PD 153035; SU 5271; WHI-P79) - an extremely potent inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase, with an IC₅₀ of 25 pM. Inhibits other purified tyrosine kinases only at micromolar or higher concentrations



Chemical Formula: C₁₆H₁₅BrClN₃O₂
Molecular Weight: 396.67

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7020540711	153436-54-5	1 mg 5 mg 25 mg 1 gram	In-stock In-stock In-stock In-stock	≥ 95% by HPLC & ¹ H NMR

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.

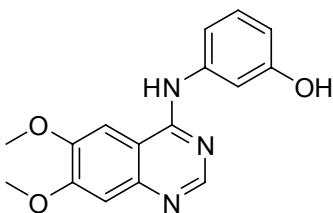
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Tel.: 1-416-305-9979, Fax: 1-866-881-9921 (Toll-free in US & Canada)

3-[(6,7-Dimethoxy-4-quinazoliny]amino]-phenol (Janex 3; WHI-P180) - a potent inhibitor of IgE-mediated mast cell responses to allergens in vitro and in vivo. Also inhibits cyclin-dependent kinase 2 (CDK2; $IC_{50} = 1\mu M$) by blocking the ATP site



Chemical Formula: $C_{16}H_{15}N_3O_3$

Molecular Weight: 297.31

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7015070102	211555-08-7	1 mg 5 mg 25 mg 1 gram	In-stock In-stock In-stock In-stock	≥ 95% by HPLC & 1H NMR

- 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.

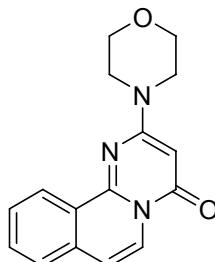
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Tel.: 1-416-305-9979, Fax: 1-866-881-9921 (Toll-free in US & Canada)

2-(4-Morpholinyl)-4H-Pyrimido[2,1-a]isoquinolin-4-one (Compound 401) - a synthetic inhibitor of DNA-dependent protein kinase (DNA-PK); inhibitor of mammalian target of rapamycin signalling



Chemical Formula: C₁₆H₁₅N₃O₂
Molecular Weight: 281.31

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7070707024	168425-64-7	1 mg 5 mg 25 mg 1 gram	In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR

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-

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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 (p110 α). 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.

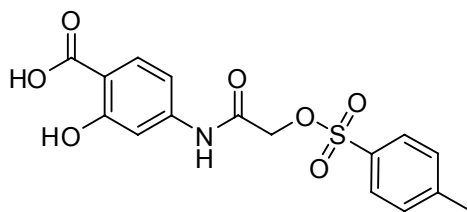
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2-Hydroxy-4-[[[(4-methylphenyl)sulfonyl]oxy]acetyl]amino]-benzoic acid (NSC 74859) - inhibitor of STAT3 with anti-tumor activity; **NSC 74859** in inhibition of STAT3 dimerization assays demonstrated an IC₅₀ of < 500 μM



Chemical Formula: C₁₆H₁₅NO₇S
Molecular Weight: 365.36

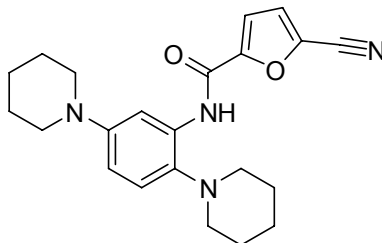
OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7070707021	501919-59-1	1 mg 5 mg 25 mg 1 gram	In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR

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Tel.: 1-416-305-9979, Fax: 1-866-881-9921 (Toll-free in US & Canada)

5-Cyano-N-(2,5-di-1-piperidinylphenyl)-2-furancarboxamide – cFMS Receptor Tyrosine Kinase Inhibitor

Chemical Formula: C₂₂H₂₆N₄O₂
Molecular Weight: 378.47

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7070707032	959626-45-0	1 mg 5 mg 25 mg 1 gram	In-stock In-stock In-stock In-stock	≥ 97% by HPLC, ¹³ C NMR & ¹ H NMR

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.

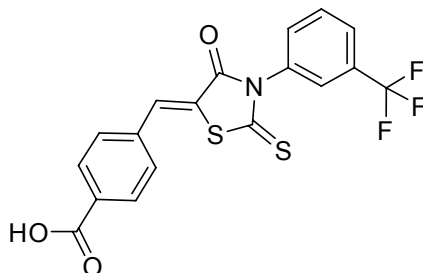
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4-[[4-Oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]-benzoic acid - CFTR_{inh}-172 (It blocks CFTR-dependent Cl⁻ currents in airway cells with KI ~ 300 nM, nearly 500-fold more potent than that of the reference CFTR blocker glibenclamide)



Chemical Formula: C₁₈H₁₀F₃NO₃S₂
Molecular Weight: 409.40

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
0129690030	307510-92-5	25 mg 500 mg 1 gram	In-stock In-stock In-stock	≥ 95% by HPLC & ¹ H NMR

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.

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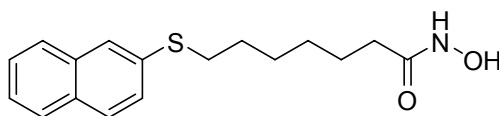
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Bulk quotes are also available.

N-Hydroxy-7-(2-naphthalenylthio)-heptanamide (HNHA) - a novel histone deacetylase (HDAC) inhibitor



Chemical Formula: C₁₇H₂₁NO₂S

Molecular Weight: 303.42

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7070707016	926908-04-5	1 GRAM (minimum package size)	4-6 weeks	≥ 95% by HPLC, ¹³ C NMR & ¹ H NMR

Ref.: Kim et al. **Anti-tumor activity of N-hydroxy-7-(2-naphthylthio)heptanamide, 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.

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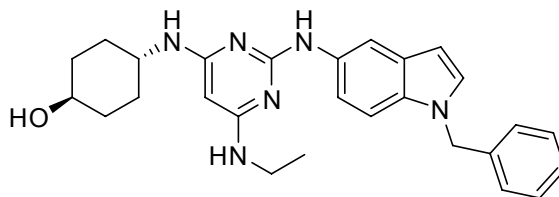
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trans-4-[[6-(Ethylamino)-2-[[1-(phenylmethyl)-1H-indol-5-yl]amino]-4-pyrimidinyl]amino]-cyclohexanol (CINK4) - inhibitor of cyclin-dependent kinase 4

Relative stereochemistry



Chemical Formula: C₂₇H₃₂N₆O
Molecular Weight: 456.58

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
OTV-CINK4	359886-84-3	500 mg (minimum package size)	6-8 weeks	≥ 95% by HPLC, ¹³ C NMR & ¹ H NMR

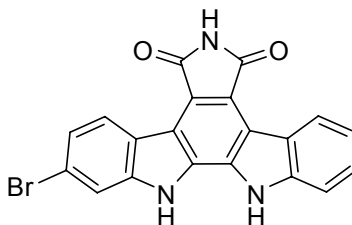
Ref.: Soni et al. **Selective in vivo and in vitro effects of a small molecule inhibitor of cyclin-dependent kinase 4.** *Journal of the National Cancer Institute* (2001), 93, 436-446
Like p16, the natural inhibitor of Cdk4, **CINK4** inhibits Cdk4 activity in vitro and slows tumor growth in vivo.

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2-Bromo-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione - Cyclin D1-CDK4 Inhibitor

Chemical Formula: C₂₀H₁₀BrN₃O₂
Molecular Weight: 404.22

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7070707035	546102-60-7	500 mg (minimum package size)	6-8 weeks	≥ 95% by HPLC, ¹³ C NMR & ¹ H NMR

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 (IC₅₀ values of 76 and 42 nM). Two compounds 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.

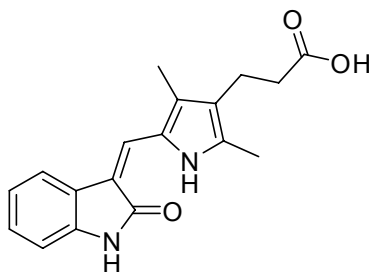
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5-[(1,2-Dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-propanoic acid (NSC 702827; SU 6668; TSU 6) - an inhibitor of VEGF, FGF, and PDGF Receptor Tyrosine Kinases



Chemical Formula: C₁₈H₁₈N₂O₃
Exact Mass: 310.13

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
OTV- SU-6668	252916-29-3	500 mg <i>(minimum package size)</i>	6-8 weeks	≥ 95% by HPLC, ¹³ C NMR & ¹ H NMR

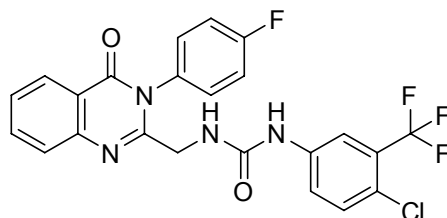
Ref. 1: Fabbro & Manley. **SU-6668, SUGEN**. *Current Opinion in Investigational Drugs* (2001), 2, 1142-1148
SUGEN is developing **SU-6668**, a tyrosine kinase inhibitor that inhibits three distinct growth factor receptor targets, for the potential treatment of cancer.

Ref. 2: Sun et al. **Design, Synthesis, and Evaluations of Substituted 3-[(3- or 4-Carboxyethylpyrrol-2-yl)methylidene]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 IC₅₀ values at nanomolar level.

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N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-[[3-(4-fluorophenyl)-3,4-dihydro-4-oxo-2-quinazolinyl]methyl]-urea - an inhibitor of the Hedgehog Signalling Pathway (IC₅₀ = 70 nM)



Chemical Formula: C₂₃H₁₅ClF₄N₄O₂
Molecular Weight: 490.84

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
OTV-Hh	330796-24-2	500 mg (minimum package size)	6-8 weeks	≥ 95% by HPLC, ¹³ C NMR & ¹ H NMR

Ref.: Brunton et al. **Potent Inhibitors of the Hedgehog Signaling Pathway.** *Journal of Medicinal Chemistry* (2008), ASAP Article, 10.1021/jm070694n
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.

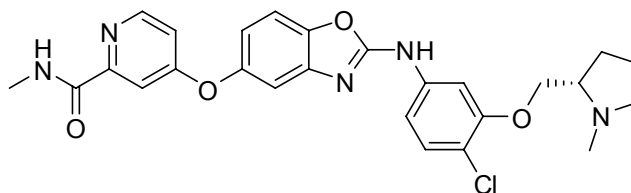
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4-((2-((4-Chloro-3-(((2S)-1-methyl-2-pyrrolidiny)methyl)oxy)-phenyl)amino)-1,3-benzoxazol-5-yl)oxy)-N-methyl-2-pyridinecarboxamide - a selective VEGFR-2 inhibitor



Chemical Formula: C₂₆H₂₆ClN₅O₄
Molecular Weight: 507.97

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
OTV-VEGFR-2-Inh	769960-39-6	500 mg (minimum package size)	6-8 weeks	≥ 95% by HPLC, ¹³ C NMR & ¹ H NMR

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 (ED₅₀ = 16.3 mg/kg).

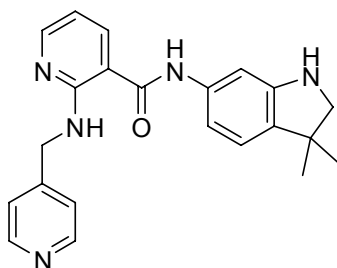
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***N*-(2,3-Dihydro-3,3-dimethyl-1*H*-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide (**AMG 706**; **Motesanib**) - multi kinase inhibitor with anti-angiogenic and anti-tumor activity achieved by selectively targeting all known VEGF, PDGF, Kit and Ret receptors**



Chemical Formula: C₂₂H₂₃N₅O
Molecular Weight: 373.45

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
OTV- AMG706	453562-69-1	500 mg (<i>minimum package size</i>)	6-8 weeks	≥ 95% by HPLC, ¹³ C NMR & ¹ H NMR

Ref. 1: Polverino et al. **AMG 706, an oral, multikinase inhibitor that selectively targets vascular endothelial growth factor, platelet-derived growth factor, and Kit receptors, potently inhibits angiogenesis and induces regression in tumor xenografts.** *Cancer Research* (2006), 66, 8715-8721

The growth of solid tumors is dependent on the continued stimulation of endothelial cell proliferation and migration resulting in angiogenesis. The angiogenic process is controlled by a variety of factors of which the vascular endothelial growth factor (VEGF) pathway and its receptors play a pivotal role. Small-molecule inhibitors of VEGF receptors (VEGFR) have been shown to inhibit angiogenesis and tumor growth in preclinical models and in clinical trials. A novel nicotinamide, **AMG 706**, was identified as a potent, orally bioavailable inhibitor of the VEGFR1/Flt1, VEGFR2/kinase domain receptor/Flk-1, VEGFR3/Flt4, platelet-derived growth factor receptor, and Kit receptors in preclinical models. **AMG 706** inhibited human endothelial cell proliferation induced by VEGF, but not by basic fibroblast growth factor in vitro, as well as vascular permeability induced by VEGF in mice. Oral administration of **AMG 706** potently inhibited VEGF-induced angiogenesis in the rat corneal model and induced regression of established A431 xenografts. **AMG 706** was well tolerated and had no significant effects on body

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weight or on the general health of the animals. Histologic analysis of tumor xenografts from **AMG 706**-treated animals revealed an increase in endothelial apoptosis and a reduction in blood vessel area that preceded an increase in tumor cell apoptosis. In summary, **AMG 706** is an orally bioavailable, well-tolerated multikinase inhibitor that is presently under clinical investigation for the treatment of human malignancies.

Ref. 2:

Rosen et al. **Safety, pharmacokinetics, and efficacy of AMG 706, an oral multikinase inhibitor, in patients with advanced solid tumors.** *Journal of Clinical Oncology* (2007), 25, 2369-2376

PURPOSE: **AMG 706** is an investigational, orally bioavailable inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, platelet-derived growth factor receptor, and stem-cell factor receptor. This phase I, dose-finding study evaluated the safety, pharmacokinetics, and pharmacodynamics of **AMG 706** in patients with refractory advanced solid tumors. **PATIENTS AND METHODS:** **AMG 706** was administered at escalating doses of 50 to 175 mg once daily or 25 mg bid for the first 21 days of a 28-day cycle. The 125-mg once-daily dose was also administered continuously. The maximum-tolerated dose (MTD), safety, pharmacokinetics, tumor response, and serum levels of proangiogenic markers were determined. **RESULTS:** Seventy-one patients received **AMG 706**. The MTD was 125 mg once daily administered continuously. The most frequent adverse events were fatigue (55%), diarrhea (51%), nausea (44%), and hypertension (42%). Plasma **AMG 706** concentrations increased in a dose-proportional manner with no accumulation after multiple doses. Five patients (7%) had a partial response, 35 patients (49%) had stable disease (at least through day 50), and 31 patients (44%) had progressive disease. Changes in tumor size correlated significantly with an increase in placental growth factor ($P = .003$) and a decrease in soluble kinase domain receptor ($P = .001$). **CONCLUSION:** In this study of patients with advanced refractory solid tumors, **AMG 706** was well tolerated and displayed favorable pharmacokinetics and evidence of antitumor activity. Additional studies of **AMG 706** as monotherapy and in combination with various agents are ongoing.

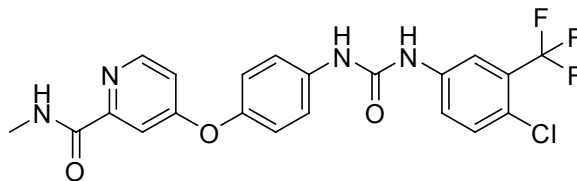
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4-[4-[[[4-Chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-2-pyridinecarboxamide (BAY 43-9006; Sorafenib) - an inhibitor of Raf kinase, PDGF (platelet-derived growth factor), VEGF receptor 2 & 3 kinases and c Kit the receptor for Stem cell factor



Chemical Formula: $C_{21}H_{16}ClF_3N_4O_3$
Molecular Weight: 464.82

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
OTV- BAY-43-9006	284461-73-0	500 mg (<i>minimum package size</i>)	6-8 weeks	≥ 95% by HPLC, ¹³ C NMR & ¹ H NMR

Ref.: Stein & Flaherty. **CCR drug updates: Sorafenib and sunitinib in renal cell carcinoma.** *Clinical Cancer Research* (2007), 13, 3765-3770
A review. The role of **sorafenib** and sunitinib antagonize VEGF receptor tyrosine kinases of these agents as VEGFR inhibitors in renal cell carcinoma and their unique spectra of activity are discussed.

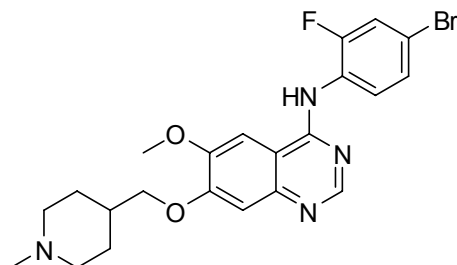
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***N*-(4-Bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-4-quinazolinamine (Vandetanib; ZD6474; Zactima)** - a potent and selective inhibitor of VEGFR (vascular endothelial growth factor receptor), EGFR (epidermal growth factor receptor) and RET (REarranged during Transfection) tyrosine kinases



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

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
OTV- ZD-6474	443913-73-3	500 mg (<i>minimum package size</i>)	6-8 weeks	≥ 95% by HPLC, ¹³ C NMR & ¹ H NMR

VEGFR- and EGFR-dependent signalling are both clinically validated pathways in cancer, including non-small-cell lung cancer. RET activity is important in some types of thyroid cancer, and early data with **vandetanib** in medullary thyroid cancer has led to orphan-drug designation by the regulatory authorities in the USA and EU.

- 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

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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.

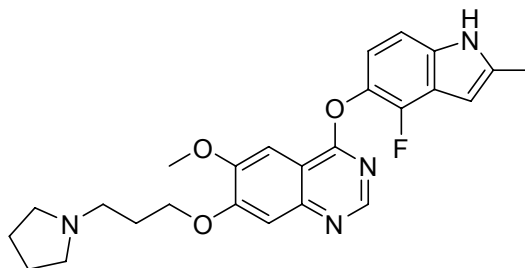
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4-[(4-Fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline (AZD2171; Cediranib) - an oral tyrosine kinase inhibitor of all of the VEGF receptors (VEGFR1, VEGFR2, VEGFR3), as well as KIT and (less potently) PDGFRA and PDGFRB



Chemical Formula: C₂₅H₂₇FN₄O₃
Molecular Weight: 450.51

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
OTV- AZD2171	288383-20-0	500 mg (<i>minimum package size</i>)	6-8 weeks	≥ 95% by HPLC, ¹³ C NMR & ¹ H NMR

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 (IC₅₀ <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 IC₅₀ 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

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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.

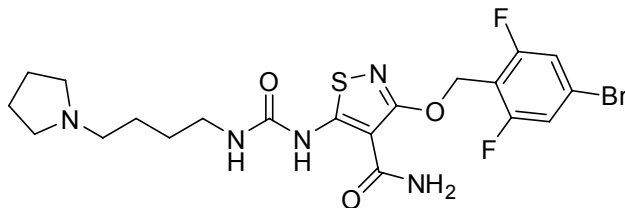
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3-[(4-Bromo-2,6-difluorophenyl)methoxy]-5-[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-4-isothiazolecarboxamide (CP-547632) - a potent inhibitor of the VEGFR-2 and basic fibroblast growth factor (FGF) kinases (IC_{50} = 11 and 9 nM, respectively). It is selective relative to epidermal growth factor receptor, platelet-derived growth factor β , 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 catalog no.	CAS RN	Amount	Delivery time	Purity
OTV- CP-547632	252003-65-9	500 mg (<i>minimum package size</i>)	6-8 weeks	$\geq 95\%$ by HPLC, ^{13}C NMR & 1H NMR

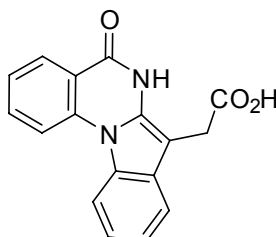
Ref.: Beebe et al. **Pharmacological Characterization of CP-547,632, a Novel Vascular Endothelial Growth Factor Receptor-2 Tyrosine Kinase Inhibitor for Cancer Therapy.** *Cancer Research* (2003), 63, 7301-7309
CP-547,632 is a well-tolerated, orally-bioavailable inhibitor presently under clinical investigation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

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

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5,6-Dihydro-5-oxo-indolo[1,2-a]quinazoline-7-acetic acid (IQA; CGP029482) - a potent and selective CK2 inhibitor; $K_i = 0.17 \mu\text{M}$



Chemical Formula: $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_3$
Molecular Weight: 292.29

OTAVA catalog no.	CAS RN	Amount	Delivery time	Purity
7020402316	391670-48-7	500 mg (<i>minimum package size</i>)	8-12 weeks	$\geq 95\%$ by HPLC, ^{13}C NMR & ^1H NMR

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

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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 ($K_i = 0.4 \mu\text{M}$), the TBB derivative 2-dimethylamino-4,5,6,7-tetrabromo-1H-benzimidazole, DMAT ($K_i = 0.040 \mu\text{M}$), the emodin related coumarinic compound 8-hydroxy-4-methyl-9-nitrobenzo[g]chromen-2-one, NBC ($K_i = 0.22 \mu\text{M}$) and the indoloquinazoline derivative (**[5-oxo-5,6-dihydroindolo-(1,2a)quinazolin-7-yl]acetic acid**), IQA ($K_i = 0.17 \mu\text{M}$). 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.

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HUMAN PROTEIN KINASE CK2 INHIBITORS DEVELOPED BY

OTAVA SCIENTISTS

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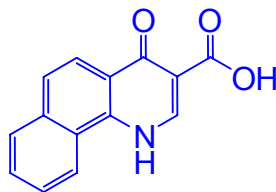
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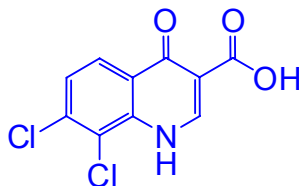
1,4-Dihydro-4-oxo-benzo[*h*]quinoline-3-carboxylic acid (NSC 210902) - a new CK2 inhibitor from OTAVA with $IC_{50} = 1 \mu M$



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 1 gram	In-stock In-stock In-stock	≥ 95% by CHN analysis & 1H NMR

7,8-Dichloro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid - a new CK2 inhibitor from OTAVA with $IC_{50} = 0.8 \mu M$



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 1 gram	In-stock In-stock In-stock	≥ 95% by CHN analysis & 1H NMR

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Ref.: Golub et al. **Evaluation of 3-Carboxy-4(1H)-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(1H)-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 ($IC_{50} = 0.3 \mu M$) and 4-oxo-1,4-dihydrobenzo[h]quinoline-3-carboxylic acid ($IC_{50} = 1 \mu M$), are ATP competitive (K_i 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.*

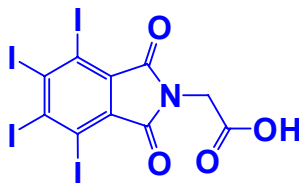
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4,5,6,7-Tetraiodo-1,3-dioxo-2-isoindolineacetic acid - a new CK2 inhibitor from OTAVA
with $IC_{50} = 0.3 \mu M$



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 1 gram	In-stock In-stock In-stock	$\geq 95\%$ by CHN analysis & 1H NMR

Ref.: Golub et al. **Evaluation of 4,5,6,7-tetrahalogeno-1H-isoindole-1,3(2H)-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-1H-isoindole-1,3(2H)-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 $0.15 \mu M$ and $0.3 \mu M$, 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.

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