ALEXIS® BIOCHEMICALS

Cannabinoid Receptors & Ligands Endocannabinoids

highlight

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International Version

Cannabinoid Receptors & Ligands – Introduction

The discovery in the early 1990s of specific membrane receptors of the psychoactive compound (-)-Δ^9-tetrahydrocannabinol (THC) opened the way to the revelation of a whole endogenous signalling system now known as the endocannabinoid system. For a review see [1]. This system comprises the cannabinoid (CB) receptors and their endogenous ligands (the endocannabinoids) as well as related proteins and molecular targets.

Two cannabinoid G protein-coupled receptors have been cloned so far, central CB_1 receptors (rat: [2], human: [3], mouse: [4]), expressed in the brain primarily by neurons, and peripheral CB_2 receptors (human: [5], mouse: [6], rat: [7]), expressed primarily by immune and hematopoietic tissues. For a review see [8]. Aside from these two receptors, evidence exists supporting the presence of yet uncloned cannabinoid receptors, a hypothesis predominantly based on pharmacological activity of cannabinoid compounds in CB_1 and CB_2 receptor-deficient mice or following the administration of 'selective' CB_1 and CB_2 receptor antagonists [9].

Extensive molecular and pharmacological studies have demonstrated that cannabinoid receptors are Gi/o-protein-coupled receptors that signal inhibition of adenylyl cyclase and activation of the extracellular signal-regulated kinase (ERK) cascade. Furthermore, the CB_1 receptor modulates ion channels, inducing, for example, inhibition of N- and P/Q-type voltage-sensitive Ca^{2+} channels and activation of G-protein-activated inwardly rectifying K^+ channels [10].

Following the cloning of CB_1 and CB_2 receptors two endocannabinoid ligands were identified and characterized: anandamide (N-arachidonoylethanolamine; AEA) [11] and 2-arachidonoylglycerol (2-AG) [12, 13]. For reviews see [14, 15].

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Cannabinoid Receptors Modulators

AM 251

ALX-270-239-M001 1 mg
ALX-270-239-M005 5 mg

Structurally related to the cannabinoid receptor (CB) antagonist SR 141716A. Binds with high affinity to cannabinoid receptor CB_1 (K_i=7.49nM; 306-fold selective over CB_2 receptors).

LIT: Binding of the non-classical cannabinoid CP 55, 940, and the diarylpyrazole AM251 to rodent brain cannabinoid receptors: S.J. Gatley, et al.; Life Sci. **61,** PL 191 (1997) ▪ Structure-activity relationships of pyrazole derivatives as cannabinoid receptor antagonists: R. Lan, et al.; J. Med. Chem. **42,** 769 (1999)

AM 281

ALX-270-240-M001 1 mg
ALX-270-240-M005 5 mg

Analog of the cannabinoid receptor (CB) antagonist SR 141716A. Potent CB_1 receptor antagonist/inverse agonist (K_i=14nM).

LIT: Effect of the cannabinoid receptor SPECT agent, AM 281, on hippocampal acetylcholine release from rat brain slices: A.N. Gifford, et al.; Neurosci. Lett. **238,** 84 (1997)

AM 630 BULK

ALX-270-241-M001 1 mg
ALX-270-241-M005 5 mg

Competitive CB_1 receptor antagonist in guinea-pig brain. Shows also agonist properties. CB_2 antagonist/inverse agonist (K_i=31.2nM; 165-fold selective over CB_1 receptors).

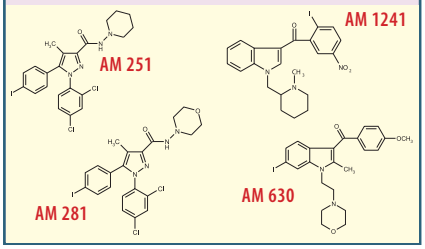
LIT: AM630, a competitive cannabinoid receptor antagonist: R. Pertwee, et al.; Life Sci. **56,** 1949 (1995)

AM 1241 BULK

ALX-550-383-M001 1 mg
ALX-550-383-M005 5 mg

Potent and selective CB_2 receptor agonist (K_i=3.4nM (mouse), K_i=280nM (rat)) also *in vivo.*

LIT: CB2 cannabinoid receptor-mediated peripheral antinociception: T.P. Malan, Jr., et al.; Pain **93,** 239 (2001) ▪ Activation of CB2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: pain inhibition by receptors not present in the CNS: M.M. Ibrahim, et al.; PNAS **100,** 10529 (2003)



Cannabinoid Receptors Antibodies

PAb to Cannabinoid Receptor 1

ALX-210-316-R100 100 µl

From rabbit. **IMMUNOGEN:** Recombinant rat CB_1 (cannabinoid receptor 1) fusion protein (aa 1-77). **SPECIFICITY:** Recognizes human, non-human primate, mouse, rat, amphibian, chicken and fish CB_1. Detects a band of ~60kDa by Western blot representing CB_1; also detects less intense bands of ~23kDa, ~72kDa and ~180kDa from rat brain homogenate. **APPLICATION:** IHC (PS), ICC, WB.

PAb to Cannabinoid Receptor 1

ALX-210-314-R100 100 µl

From rabbit. **IMMUNOGEN:** Recombinant human CB_1 (cannabinoid receptor 1) fusion protein (aa 1-99). **SPECIFICITY:** Recognizes human and rat CB_1. Detects a band of ~60kDa by Western blot. **APPLICATION:** IHC (FS), ICC, WB.

PAb to Cannabinoid Receptor 2

ALX-210-317-R100 100 µl

From rabbit. **IMMUNOGEN:** Recombinant rat CB_2 (cannabinoid receptor 2) fusion protein (aa 1-32). **SPECIFICITY:** Recognizes human and rat CB_2. **APPLICATION:** ICC.

PAb to Cannabinoid Receptor 2

ALX-210-198-1 1 Vial

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 20-33 (N^{20}PMKDYMILSGPQK^{33}) of N-terminal human CB_2 (cannabinoid receptor 2). **SPECIFICITY:** Recognizes human and mouse CB_2. Detects a band of ~45kDa by Western blot. Does not cross-react with CB1. **APPLICATION:** IHC (PS), WB.

LIT: Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors: M.L. Casanova, et al.; J. Clin. Invest. **111,** 43 (2003)

PAb to Cannabinoid Receptor 2 (human)

ALX-210-315-R100 100 µl

From rabbit. **IMMUNOGEN:** Recombinant human CB_2 (cannabinoid receptor 2) fusion protein (aa 1-33). **SPECIFICITY:** Recognizes human CB_2. Detects a band of ~60kDa by Western blot. **APPLICATION:** FC, IHC (FS, PS), ICC, WB.

LIT: Distinct expression profiles of the peripheral cannabinoid receptor in lymphoid tissues depending on receptor activation status: N. Rayman, et al.; J. Immunol. **172,** 2111 (2004) ▪ The peripheral cannabinoid receptor Cb2, frequently expressed on AML blasts, either induces a neutrophilic differentiation block or confers abnormal migration properties in a ligand-dependent manner: M. Alberich Jorda, et al.; Blood **104,** 526 (2004)

Introduction *continued*

In just a couple of years, four more candidates to the role of cannabinoid receptor agonists have been proposed: 2-arachidonoylglyceryl ether (noladin ether; 2-AGE) [16], O-arachidonoylethanolamine (virodhamine) [17], N-arachidonoyldopamine (NADA) [18] and oleamide [19].

Although the biosynthetic route underlying the formation of anandamide has been extensively studied, the enzyme NAPE-PLD responsible for release of anandamide from its precursor N-arachidonoylphosphatidylethanolamine has only been cloned, purified and characterized recently [20].

LIT: [1] The endocannabinoid system: a general view and latest additions: L. De Petrocellis, et al.; Br. J. Pharmacol. **141,** 765 (2004) ▪ **[2]** Structure of a cannabinoid receptor and functional expression of the cloned cDNA: L.A. Matsuda, et al.; Nature **346,** 561 (1990) ▪ **[3]** Molecular cloning of a human cannabinoid receptor which is also expressed in testis: C.M. Gerard, et al.; Biochem. J. **279,** 129 (1991) ▪ **[4]** Cloning and sequencing of a cDNA encoding the mouse brain-type cannabinoid receptor protein: A. Chakrabarti, et al.; DNA Seq. **5,** 385 (1995) ▪ **[5]** Molecular characterization of a peripheral receptor for cannabinoids: S. Munro, et al.; Nature **365,** 61 (1993) ▪ **[6]** Molecular cloning, expression and function of the murine CB2 peripheral cannabinoid receptor: D. Shire, et al.; Biochim. Biophys. Acta **1307,** 132 (1996) ▪ **[7]** Cloning and pharmacological characterization of the rat CB(2) cannabinoid receptor: G. Griffin, et al.; J. Pharmacol. Exp. Ther. **292,** 886 (2000) ▪ **[8]** Pharmacology of cannabinoid CB1 and CB2 receptors: R.G. Pertwee; Pharmacol. Ther. **74,** 129 (1997) ▪ **[9]** Evidence for novel cannabinoid receptors: M. Begg, et al.; Pharmacol. Ther. **106,** 133 (2005) ▪ **[10]** Pharmacology of cannabinoid receptor ligands: R.G. Pertwee; Curr. Med. Chem. **6,** 635 (1999) ▪ **[11]** Isolation and structure of a brain constituent that binds to the cannabinoid receptor: W.A. Devane, et al.; Science **258,** 1946 (1992) ▪ **[12]** Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors: R. Mechoulam, et al.; Biochem. Pharmacol. **50,** 83 (1995) ▪ **[13]** 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain: T. Sugiura, et al.; BBRC **215,** 89 (1995) ▪ **[14]** Metabolism of anandamide and 2-arachidonoylglycerol: an historical overview and some recent developments: V. Di Marzo, et al.; Lipids **34,** S319 (1999) ▪ **[15]** Biosynthesis and degradation of anandamide and 2-arachidonoylglycerol and their possible physiological significance: T. Sugiura, et al.; Prostaglandins Leukot. Essent. Fatty Acids **66,** 173 (2002) ▪ **[16]** 2-arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor: L. Hanus, et al.; PNAS **98,** 3662 (2001) ▪ **[17]** Characterization of a novel endocannabinoid, virodhamine, with antagonist activity at the CB1 receptor: A.C. Porter, et al.; J. Pharmacol. Exp. Ther. **301,** 1020 (2002) ▪ **[18]** N-acyl-dopamines: novel synthetic CB(1) cannabinoid-receptor ligands and inhibitors of anandamide inactivation with cannabimimetic activity in vitro and in vivo: T. Bisogno, et al.; Biochem. J. **351,** 817 (2000) ▪ **[19]** Oleamide is a selective endogenous agonist of rat and human CB1 cannabinoid receptors: J.D. Leggett, et al.; Br. J. Pharmacol. **141,** 253 (2004) ▪ **[20]** Molecular characterization of a phospholipase D generating anandamide and its congeners: Y. Okamoto, et al.; J. Biol. Chem. **279,** 5298 (2004)

Selected Latest Review Articles

The endocannabinoid system: a general view and latest additions: L. De Petrocellis, et al.; Br. J. Pharmacol. **141,** 765 (2004) ▪ The endocannabinoid system and its therapeutic exploitation: V. Di Marzo, et al.; Nat. Rev. Drug Discov. **3,** 771 (2004) ▪ Pharmacology of cannabinoids: F. Grotenhermen; Neuroendocrinol. Lett. **25,** 14 (2004) ▪ Cannabinoid physiology and pharmacology: 30 years of progress: A.C. Howlett, et al.; Neuropharmacology 47 Suppl. **1,** 345 (2004) ▪ Evidence for novel cannabinoid receptors: M. Begg, et al.; Pharmacol. Ther. **106,** 133 (2005) ▪ The endocannabinoid signaling system: biochemical aspects: T. Bisogno, et al.; Pharmacol. Biochem. Behav. **81,** 224 (2005) ▪ The endocannabinoid signaling system: pharmacological and therapeutic aspects: C.J. Fowler, et al.; Pharmacol. Biochem. Behav. **81,** 248 (2005) ▪ Recent developments in cannabinoid ligands: L.W. Padgett; Life Sci. **77,** 1767 (2005) ▪ The endocannabinoid system: drug targets, lead compounds, and potential therapeutic applications: D.M. Lambert & C.J. Fowler; J. Med. Chem. **48,** 5059 (2005) ▪ Design, synthesis, and binding studies of new potent ligands of cannabinoid receptors: A. Brizzi, et al.; J. Med. Chem. **48,** 7343 (2005) ▪ The therapeutic potential of drugs that target cannabinoid receptors or modulate the tissue levels or actions of endocannabinoids: R.G. Pertwee; AAPS J. **7,** E625 (2005) ▪ The endocannabinoid system: physiology and pharmacology: F. Rodriguez de Fonseca, et al.; Alcohol Alcohol. **40,** 2 (2005) ▪ Endocannabinoid metabolic pathways and enzymes: A. Ligresti, et al.; Curr. Drug Targets CNS Neurol. Disord. **4,** 615 (2005) ▪ Cannabinoid signalling: D.G. Demuth & A. Molleman; Life Sci. **78,** 549 (2006) ▪ Cannabinoid Receptors as Therapeutic Targets: K. Mackie; Annu. Rev. Pharmacol. Toxicol. **46,** 101 (2006)

Endocannabinoids

Anandamide — BULK

ALX-340-029-M005 5 mg

Endogenous ligand for the CB_1 receptor (CB_1: K_i=52nm; CB_2: K_i=1930nm) and TRPV1 (K_i=5.78µM). Inhibits NF-κB activation through direct binding to IKKβ and induces apoptosis independently of cannabinoid or vanilloid receptors. Activates the MAP kinase (MAPK/ERK) signalling pathway

LIT: Isolation and structure of a brain constituent that binds to the cannabinoid receptor: W.A. Devane, et al.; Science **258,** 1946 (1992)

Selected Latest Review Articles

Anandamide transport: M.J. McFarland & E.L. Barker; Pharmacol. Ther. **104,** 117 (2004) ▪ Anandamide as an intracellular messenger regulating ion channel activity: M. van der Stelt & V. Di Marzo; Prostaglandins Other Lipid Mediat. **77,** 111 (2005)

N-Arachidonoyldopamine — BULK

ALX-340-049-M001 1 mg
ALX-340-049-M005 5 mg

Endogenous, specific ligand for the CB_1 receptor (CB_1: K_i=250nM; CB_2: K_i=12µM) and TRPV1 (EC_{50}=50nM) found in nervous tissues [3, 4]. Immunosuppressant inhibiting T cell proliferation and phosphorylation of the NF-κB p65 subunit. Potent vasorelaxant and inhibitor of HIV-1.

LIT: N-acyl-dopamines: novel synthetic CB(1) cannabinoid-receptor ligands and inhibitors of anandamide inactivation with cannabimimetic activity in vitro and in vivo: T. Bisogno, et al.; Biochem. J. **351,** 817 (2000) ▪ Synthesis and biological evaluation of novel amides of polyunsaturated fatty acids with dopamine: V. Bezuglov, et al.; Bioorg. Med. Chem. Lett. **11,** 447 (2001)

2-Arachidonoylglycerol

ALX-340-036-M005 5 mg

Endogenous ligand for the CB_1 receptor (CB_1: K_i=58.3nM); CB_2: K_i>3µM) present in high levels in the CNS.

LIT: A second endogenous cannabinoid that modulates long-term potentiation: N. Stella, et al.; Nature **388,** 773 (1997)

Noladin ether

ALX-340-052-M005 5 mg

Endogenous specific ligand for the CB_1 and CB_2 receptor. Chemically stable, but less potent than 2-AG (Prod. No. ALX-340-052) with an endogenous half-life time of hours rather than minutes.

LIT: 2-arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor: L. Hanus, et al.; PNAS **98,** 3662 (2001)

cis-9,10-Octadecenamide

ALX-550-121-M010 10 mg

Sleep-inducing brain lipid. Shown to be a full CB_1 but not CB_2 receptor agonist.

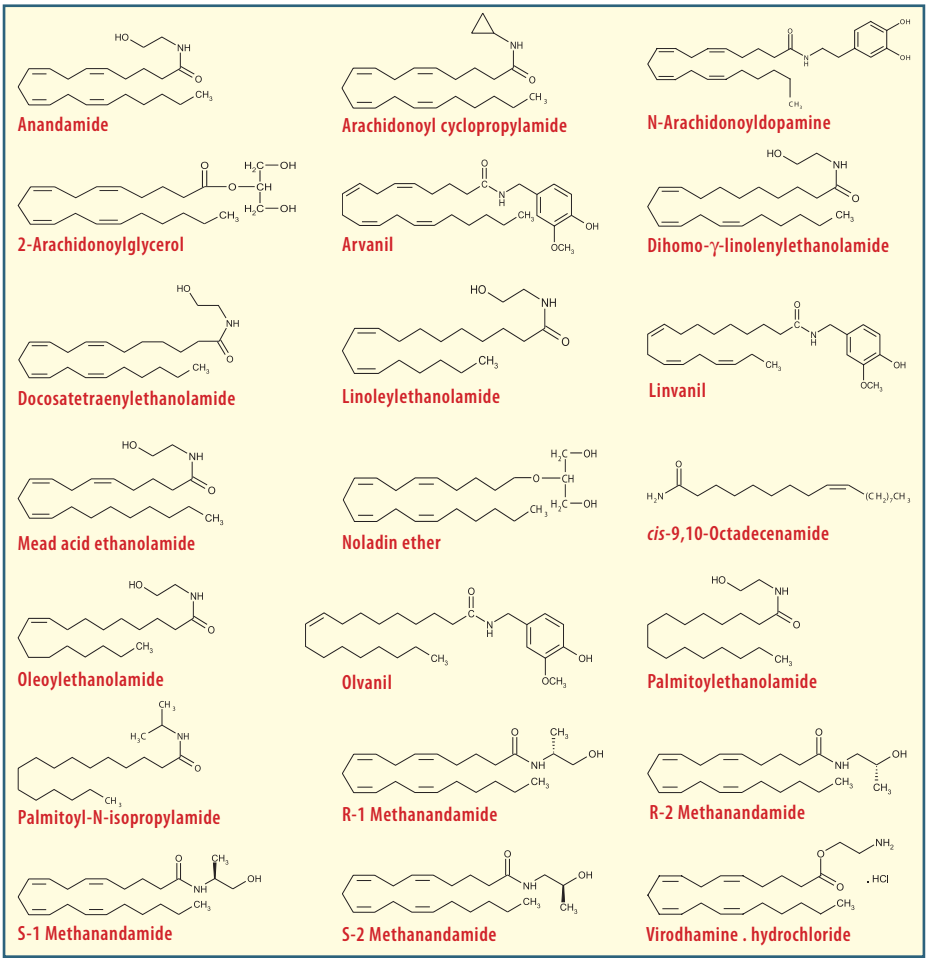
LIT: Chemical characterization of a family of brain lipids that induce sleep: B.F. Cravatt, et al.; Science **268,** 1506 (1995) ▪ Oleamide is a selective endogenous agonist of rat and human CB1 cannabinoid receptors: J.D. Leggett, et al.; Br. J. Pharmacol. **141,** 253 (2004)

Virodhamine . hydrochloride

ALX-340-051-M005 5 mg

Endogenous endocannabinoid. Partial agonist with *in vivo* antagonist activity at the CB_1 receptor (EC_{50}=1.9µM; 61% efficacy), full agonist for the CB_2 receptor (100% efficacy).

LIT: Characterization of a novel endocannabinoid, virodhamine, with antagonist activity at the CB1 receptor: A.C. Porter, et al.; J. Pharmacol. Exp. Ther. **301,** 1020 (2002)



Anandamide Related Products

N-Arachidonoyl-γ-aminobutyric acid
ALX-340-050-M005 5 mg

Arachidonoyl 2'-chloroethylamide
ALX-340-053-M005 5 mg

Arachidonoyl cyclopropylamide
ALX-340-054-M005 5 mg

Potent and selective CB_1 agonist (K_i=2.2nM). Displays 325-fold selectivity over CB_2 receptors (K_i=0.7μM). Active *in vivo*.

LIT: Synthesis and characterization of potent and selective agonists of the neuronal cannabinoid receptor (CB1): C.J. Hillard, et al.; J. Pharmacol. Exp. Ther. **289,** 1427 (1999) ▪ Arachidonylcyclopropylamide increases microglial cell migration through cannabinoid CB2 and abnormal-cannabidiol-sensitive receptors: A. Franklin, et al.; Eur. J. Pharmacol. **474,** 195 (2003) ▪ The interaction of cannabinoids and opioids on pentylenetetrazole-induced seizure threshold in mice: H. Shafaroodi, et al.; Neuropharmacology **47,** 390 (2004)

Arachidonoyl 2'-fluoroethylamide
ALX-340-061-M005 5 mg

N-Arachidonoyl glycine
ALX-340-055-M005 5 mg

Arvanil BULK
ALX-340-042-M005 5 mg

„Hybrid" activator of CB_1 receptor (CB_1: K_i=0.5μM; CB_2: K_i=>15μM) and TRPV1 (K_i=0.3μM). Also inhibits anandamide uptake (IC_{50}=3.6μM) and fatty acid amide hydrolase (FAAH) (IC_{50}=3μM). Analgesic, vasodilatory and anti-inflammatory *in vivo*. Apoptosis inducer.

LIT: Unsaturated long-chain N-acyl-vanillyl-amides (N-AVAMs): vanilloid receptor ligands that inhibit anandamide-facilitated transport and bind to CB1 cannabinoid receptors: D. Melck, et al.; BBRC **262,** 275 (1999) ▪ Neurobehavioral activity in mice of N-vanillyl-arachidonyl-amide: V. Di Marzo, et al.; Eur. J. Pharmacol. **406,** 363 (2000)

Dihomo-γ-linolenylethanolamide
ALX-300-147-M005 5 mg

Docosatetraenylethanolamide
ALX-300-148-M005 5 mg

Linoleylethanolamide
ALX-300-149-M005 5 mg

Linvanil
ALX-340-044-M005 5 mg

Mead acid ethanolamide
ALX-300-151-M001 1 mg

R-1 Methanandamide
ALX-340-030-M005 5 mg

Amidase resistant cannabinoid receptor (CB) agonist (CB_1: K_i=20nM; CB_2: K_i=815nM). The most potent of the series of methyl-anandamides. About 4-fold higher binding affinity for cannabinoid receptor CB_1 than anandamide (Prod. No. ALX-340-029) in the presence of PMSF. Does also bind to TRPV1 (K_i=4.67μM).

LIT: (R)-methanandamide: a chiral novel anandamide possessing higher potency and metabolic stability: V. Abadji, et al.; J. Med. Chem. **37,** 1889 (1994) ▪ Head group analogs of arachidonylethanolamide, the endogenous cannabinoid ligand: A.D. Khanolkar, et al.; J. Med. Chem. **39,** 4515 (1996)

S-1 Methanandamide
ALX-340-031-M005 5 mg

CB_1 receptor agonist (K_i=175nM). About one-third as potent as anandamide (Prod. No. ALX-340-029).

LIT: (R)-methanandamide: a chiral novel anandamide possessing higher potency and metabolic stability: V. Abadji, et al.; J. Med. Chem. **37,** 1889 (1994)

R-2 Methanandamide
ALX-340-033-M005 5 mg

S-2 Methanandamide
ALX-340-034-M005 5 mg

Oleoylethanolamide
ALX-300-150-M005 5 mg

Olvanil BULK
ALX-340-041-M005 5 mg
ALX-340-041-M010 10 mg

„Hybrid" activator of CB_1 receptor (CB_1: K_i=1.6μM; CB_2: K_i=15μM) and TRVP1 (K_i=0.4μM; EC_{50}=33nM (human); EC_{50}=6.71nM (rat)). Also inhibits anandamide uptake (IC_{50}=9μM, K_i=14.1μM) and fatty acid amide hydrolase (FAAH) (IC_{50}=20μM).

LIT: NE-19550: a novel, orally active anti-inflammatory analgesic: L. Brand, et al.; Drugs Exp. Clin. Res. **13,** 259 (1987) ▪ The antinociceptive effect and pharmacokinetics of olvanil following oral and subcutaneous dosing in the mouse: W.K. Sietsema, et al.; Life Sci. **43,** 1385 (1988) ▪ Olvanil: more potent than capsaicin at stimulating the efferent function of sensory nerves: S.R. Hughes, et al.; Eur. J. Pharmacol. **219,** 481 (1992)

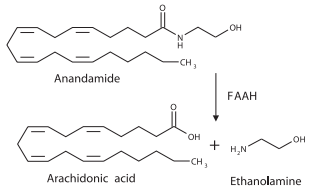
Palmitoylethanolamide BULK
ALX-300-146-M010 10 mg

Endogenous cannabinoid. Weak ligand of CB_1 (K_i=23.8μM) and CB_2 (K_i=13.9μM) receptor. Inhibits fatty acid amide hydrolase (FAAH) (IC_{50}=5.1μM). Immunosuppressant, anti-inflammatory, anti-nociceptive and anti-convulsant *in vivo*. The exact mode of action has not yet been revealed. It has been suggested that PEA: i) binds to a yet to be discovered cannabinoid receptor similar to CB_2; ii) administered *in vivo* elicits the synthesis of endogenous agonists of CB_2; iii) acts as an „entourage" compound by enhancing the activity and/or by influencing the turnover of endogenous agonists of CB_2, possibly but not uniquely, by inhibiting their degradation.

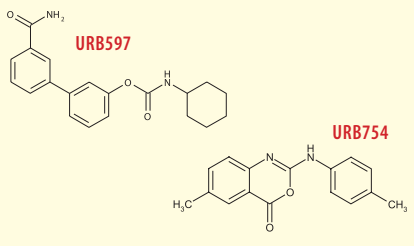
LIT: Mast cells express a peripheral cannabinoid receptor with differential sensitivity to anandamide and palmitoylethanolamide: L. Facci, et al.; PNAS **92,** 3376 (1995)

Palmitoyl-N-isopropylamide
ALX-300-302-M005 5 mg

For a comprehensive bibliography please visit our website
www.axxora.com



Fatty acid amide hydrolase (FAAH) is the enzyme responsible for hydrolysis and inactivation of fatty acid amides.



FAAH & Related Products

Fatty Acid Amide Hydrolase [FAAH] Inhibitors

URB597 BULK
ALX-550-382-M005 5 mg
ALX-550-382-M050 50 mg

Potent inhibitor of fatty acid amide hydrolase (FAAH) (IC_{50}=4.6nM). Exhibits both anti-nociceptive and anxiolytic effects *in vivo* without evoking other symptoms associated with cannabinoid-like compounds.

LIT: Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides: B.F. Cravatt, et al.; Nature **384,** 83 (1996) ▪ Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase: B.F. Cravatt, et al.; PNAS **98,** 9371 (2001) ▪ Modulation of anxiety through blockade of anandamide hydrolysis: S. Kathuria, et al.; Nat. Med. **9,** 76 (2003) ▪ Monoglyceride lipase-like enzymatic activity is responsible for hydrolysis of 2-arachidonoylglycerol in rat cerebellar membranes: S.M. Saario, et al.; Biochem. Pharmacol. **67,** 1381 (2004) ▪ Actions of the FAAH inhibitor URB597 in neuropathic and inflammatory chronic pain models: A. Jayamanne, et al.; Br. J. Pharmacol. , In press (2005) ▪ Characterization of the fatty acid amide hydrolase inhibitor cyclohexyl carbamic acid 3'-carbamoyl-biphenyl-3-yl ester (URB597): effects on anandamide and oleoylethanolamide deactivation: D. Fegley, et al.; J. Pharmacol. Exp. Ther. **313,** 352 (2005)

AEBSF . hydrochloride BULK
ALX-270-022-M050 50 mg
ALX-270-022-M250 250 mg
ALX-270-022-G001 1 g

Arachidonoyl serotonin
ALX-340-060-M005 5 mg

Arachidonyl trifluoromethylketone
ALX-340-001-M005 5 mg
ALX-340-001-M010 10 mg
ALX-340-001-M050 50 mg

Methylarachidonyl fluorophosphonate
ALX-340-017-M001 1 mg
ALX-340-017-M005 5 mg

Phenylmethylsulfonyl fluoride BULK
ALX-270-184-G001 1 g
ALX-270-184-G005 5 g
ALX-270-184-G025 25 g

Related Products

PAb to Fatty Acid Amide Hydrolase
ALX-210-418-1 1 Vial

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 561-579 (C^{561}LRFMREVEQLMTPQKQPS^{579}) of rat C-terminal FAAH (fatty acid amide hydrolase). **SPECIFICITY:** Recognizes human, mouse, rat and ferret FAAH. Detects a band of ~53kDa by Western blot. **APPLICATION:** IHC, WB. **BP:** ALX-156-005.

LIT: Fatty acid amide hydrolase is located preferentially in large neurons in the rat central nervous system as revealed by immunohistochemistry: K. Tsou, et al.; Neurosci. Lett. **254,** 137 (1998) ▪ Cannabinoids inhibit emesis through CB1 receptors in the brainstem of the ferret: M.D. Van Sickle, et al.; Gastroenterology **121,** 767 (2001)

NEW URB754 BULK
ALX-550-410-M001 1 mg
ALX-550-410-M005 5 mg

Potent, noncompetitive inhibitor of monoacylglycerol lipase (MGL), which hydrolyzes 2-arachidonoylglycerol (2-AG) to arachidonic acid and glycerol. IC_{50}=200nM for the recombinant rat brain enzyme. Inhibits rat brain fatty acid amide hydrolase (FAAH) less effectively (IC_{50}=32μM) and binds weakly to the rat CB_1 receptor (IC_{50}=3.8μM).

LIT: Selective inhibition of 2-AG hydrolysis enhances endocannabinoid signaling in hippocampus: J. K. Makara, et al.; Nat. Neurosci. **8,** 1139 (2005)

Leading the Cannabinoid Receptor & Vanilloid Receptor TRPV1 Research!

The TRP (Transient Receptor Potential) Superfamily

TRPV4 & Related Products

The relevance of anandamide as an endovanilloid is further highlighted by its identification as an endogenous activator of TRPV4 (OTRPC4; VRL-2; VR-OAC; TRP12) [1-4], an observation which adds to the growing receptor promiscuity of this important endogenous lipid. The activation of TRPV4 by anandamide is indirect and mediated by oxidative metabolites of arachidonic acid. TRPV4 was originally characterised as an osmotically regulated ion channel sensing changes in cell volume, but was later discovered to be activated not only by physical stimuli, such as cell swelling or heat. It is basically a thermosensor similar to TRPV1 but insensitive to capsaicin. TRPV4 is activated under physiological conditions by the non-tumor promoter phorboid 4α-phorbol didecanoate (4α-PDD) [2]. 4α-PDD does not activate TRPV1 like phorbol 12,13-didecanoate 20-homovanillate (PDDHV), another resiniferatoxin-type phorboid vanilloid. TRPV4 is an interesting new pharmacological target whose potential is just beginning to surface.

LIT: [1] Anandamide and arachidonic acid use epoxyeicosatrienoic acids to activate TRPV4 channels: H. Watanabe, et al.; Nature **424,** 434 (2003) ▪ **[2]** Activation of TRPV4 channels (hVRL-2/mTRP12) by phorbol derivatives: H. Watanabe, et al.; J. Biol. Chem. **277,** 13569 (2002) ▪ **[3]** The TRPV4 channel: structure-function relationship and promiscuous gating behaviour: B. Nilius, et al.; Pflugers Arch. **446,** 298 (2003) ▪ **[4]** TRPV4 calcium entry channel: a paradigm for gating diversity: B. Nilius, et al.; Am. J. Physiol. Cell Physiol. **286,** C195 (2004)

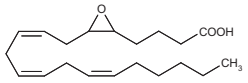
TRPV4 Agonist

5',6'-Epoxyeicosatrienoic acid

ALX-340-059-C025	25 µg
ALX-340-059-C050	50 µg

Endogenous TRPV4 agonist (K_i=150nM).

LIT: Anandamide and arachidonic acid use epoxyeicosatrienoic acids to activate TRPV4 channels: H. Watanabe, et al.; Nature **424,** 434 (2003)



TRPV4 Activator

4α-Phorbol 12,13-didecanoate — **BULK**

ALX-445-006-M001	1 mg
ALX-445-006-M005	5 mg

Activator of TRPV4. Negative control for phorbol 12,13-didecanoate (PDD) (Prod. No. ALX-445-002).

LIT: Activation of TRPV4 channels (hVRL-2/mTRP12) by phorbol derivatives: H. Watanabe, et al.; J. Biol. Chem. **277,** 13569 (2002) ▪ TRPV4 calcium entry channel: a paradigm for gating diversity: B. Nilius, et al.; Am. J. Physiol. Cell Physiol. **286,** C195 (2004)

Activator of TRPV1, V2 & V3

2-Aminoethoxydiphenyl borate

ALX-400-045-M100	100 mg

Cell permeable modulator of Ins(1,4,5)-P_3-induced Ca^{2+} release. A prototype drug for a group of structurally related calcium channel blockers in human platelets. Has been shown, in the absence of other stimuli, to activate TRPV1, V2 and V3, but not TRPV4, V5 and V6 expressed in HEK293 cells.

LIT: 2APB, 2-aminoethoxydiphenyl borate, a membrane-penetrable modulator of Ins(1,4,5)P3-induced Ca2+ release: T. Maruyama, et al.; J. Biochem. **122,** 498 (1997)

Potent TRPV1 Antagonist

SB366791 — **BULK**

ALX-550-388-M001	1 mg
ALX-550-388-M005	5 mg
ALX-550-388-M025	25 mg

Potent and selective TRPV1 antagonist.

LIT: Identification of SB-366791, a potent and selective antagonist of vanilloid receptor-1: H.K. Rami, et al.; Drugs Fut. **27** (Supply A), 411 (2002) ▪ Identification and charakterisation of SB-366791, a potent and selective vanilloid receptor (VR1/TRPV1) antagonist: M.J. Gunthorpe, et al.; Neuropharmacology **46,** 133 (2004) ▪ Effects of the novel TRPV1 receptor antagonist SB366791 in vitro and in vivo in the rat: A. Varga, et al.; Neurosci. Lett. **385,** 137 (2005)

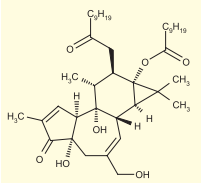
TRPM8 [CMR1]/TRPA1 Activator

NEW Icilin — **BULK**

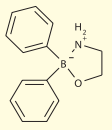
ALX-420-037-M001	1 mg
ALX-420-037-M005	5 mg
ALX-420-037-M025	25 mg

Cooling agent. Strongly activates TRPM8 (cold menthanol receptor 1 (CMR1)) and TRPA1 (at 10- to 100-fold higher concentration). Induces currents in TRPM8 expressing HEK 293 cells (EC_{50}=0.36mM) more potently than menthol or low temperatures.

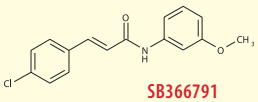
LIT: AG-3-5: a chemical producing sensations of cold: E.T. Wei and D.A. Seid; J. Pharm. Pharmacol. **35,** 110 (1983) ▪ TRPM8 activation by menthol, icilin, and cold is differentially modulated by intracellular pH: D.A. Andersson, et al.; J. Neurosci. **24,** 5364 (2004)



4α-Phorbol 12,13-didecanoate



2-Aminoethoxydiphenyl borate



Resiniferatoxin-type Phorboid Vanilloids

PDDHV

ALX-550-371-M001	1 mg
ALX-550-371-M005	5 mg

PDNHV

ALX-550-372-M001	1 mg
ALX-550-372-M005	5 mg

PPAHV — **BULK**

ALX-550-355-M001	1 mg
ALX-550-355-M005	5 mg

Non-pungent resiniferatoxin-type phorboid vanilloid. Agonist at rat TRPV1 (EC_{50} between 3 and 10µM) but virtually inactive at human TRPV1 (EC_{50}>10µM). Induces apoptosis through a TRPV-independent mechanism.

LIT: Synthesis and evaluation of phorboid 20-homovanillates: discovery of a class of ligands binding to the vanilloid (capsaicin) receptor with different degrees of cooperativity: G. Appendino, et al.; J. Med. Chem. **39,** 3123 (1996) ▪ For comprehensive bibliography please visit our website.

Product Highlight

LY2183240 – New Potent & Competitive Inhibitor of Anandamide Uptake

S.A. Moore, et al. report the identification of a potent, competitive small molecule inhibitor of anandamide uptake (IC_{50}=270 ± 29.4pM) to characterize a high-affinity, saturable anandamide transporter binding site that is distinct from fatty acid amide hydrolase (FAAH).

LIT: Identification of a high-affinity binding site involved in the transport of endocannabinoids: S.A. Moore, et al.; PNAS **102,** 17852 (2005) ▪ Commented in: Toward an anandamide transporter: R. Mechoulam and D.G. Deutsch; PNAS **102,** 17541 (2005)

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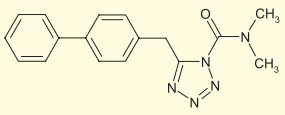

Selected Latest Review Articles

The role of TRP channels in sensory neurons: M. Koltzenburg; Novartis Found. Symp. **260,** 206 (2004) ▪ Diversity of TRP channel activation: B. Nilius & T. Voets; Novartis Found. Symp. **258,** 140 (2004) ▪ Thermosensation and pain: M. Tominaga & M.J. Caterina; J. Neurobiol. **61,** 3 (2004) ▪ Senisng with TRP channels: T. Voets, et al.; Nat. Chem. Biol. **1,** 85 (2005) ▪ Recent developments in vascular endothelial cell transient receptor potential channels: X. Yao & C.J. Garland; Circ. Res. **97,** 853 (2005)

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