

RESEARCH MONOGRAPH . COMPOUND PROFILE

MK-8722

A potent, orally bioavailable, direct allosteric pan-AMPK activator developed at Merck Research Laboratories that produces insulin-independent skeletal muscle glucose uptake across species but whose clinical translation was precluded by on-mechanism cardiac hypertrophy and glycogen accumulation in preclinical chronic dosing studies.

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ABSTRACT

MK-8722 is a potent, direct, orally bioavailable allosteric activator of all twelve mammalian heterotrimeric complexes of AMP-activated protein kinase (AMPK), the master cellular energy sensor that coordinates catabolic and anabolic metabolic pathways in response to energetic stress. Discovered at Merck Research Laboratories through a medicinal chemistry optimization campaign starting from the thienopyridone lead series and published in two landmark reports (Myers et al., *Science*, 2017; Feng et al., *ACS Medicinal Chemistry Letters*, 2018), MK-8722 binds the allosteric drug and metabolite (ADaM) site at the interface of the alpha-subunit kinase domain and the beta-subunit carbohydrate-binding module and produces dose-dependent activation of AMPK complexes containing both the beta-1 and beta-2 regulatory subunits.

The pharmacological consequence of systemic pan-AMPK activation by MK-8722 in preclinical species is a robust, durable, insulin-independent increase in skeletal muscle glucose uptake and glycogen synthesis, with resultant improvements in whole-body glycemia and glucose tolerance in lean and obese rodent models and in spontaneously diabetic rhesus monkeys. The glucose-lowering effect is mediated predominantly through AMPK-dependent translocation of glucose transporter type 4 (GLUT4) to the sarcolemma in skeletal muscle and does not produce hypoglycemia at efficacious doses. Positron emission tomography with [18F]fluorodeoxyglucose ([18F]FDG-PET) confirmed increased skeletal muscle glucose uptake in both rodents and non-human primates following MK-8722

administration. Pharmacokinetic properties in preclinical species supported once-daily oral dosing for chronic studies.

The principal liability that precluded clinical advancement of MK-8722 was on-mechanism cardiac hypertrophy and cardiac glycogen accumulation observed during chronic dosing in both rodent and non-human primate models. In Sprague-Dawley rats, 4-week oral administration at doses achieving efficacious plasma exposures produced dose-dependent increases in heart weight and left ventricular wall thickness. In rhesus monkeys, 8-week oral administration produced similar cardiac hypertrophy with increased cardiac glycogen content. Echocardiographic assessment demonstrated preserved systolic and diastolic function despite the structural remodeling, and the cardiac hypertrophy appeared partially reversible on drug washout at the highest dose levels, though lower doses did not demonstrate full regression during the studied washout period. No arrhythmias or functional cardiac impairment were detected. The cardiac hypertrophy was attributed to pan-AMPK activation in cardiomyocytes, where AMPK-driven glucose uptake and glycogen synthesis produced pathological glycogen accumulation analogous to the phenotype observed in glycogen storage cardiomyopathy associated with activating mutations in the PRKAG2 gene encoding the AMPK gamma-2 subunit.

MK-8722 has not entered human clinical trials. The compound remains an important pharmacological tool for the study of systemic AMPK activation in metabolic disease and a reference standard for structure-activity relationship studies in the ADaM-site AMPK activator class. A selectivity screen against 115 enzymes, transporters, and receptors identified modest off-target activity at the serotonin 5-HT_{2A} receptor (K_i approximately 2.8

micromolar) and three additional targets at 3 to 10 micromolar, none of which are anticipated to produce pharmacologically significant effects at AMPK-relevant exposures. This monograph reviews the chemistry, synthesis, and stereochemistry of MK-8722; the molecular pharmacology of AMPK activation through the ADaM site; the preclinical pharmacokinetic and pharmacodynamic profile; the cardiac safety signal; sourcing and quality verification for research applications; reconstitution and handling; stack-interaction considerations for combination studies; adverse-event characterization; and a structured comparative assessment of five alternative AMPK activators against MK-8722 on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Development code: MK-8722 (Merck Research Laboratories). This is the canonical identifier in both the medicinal chemistry disclosure (Feng et al. 2018) and the pre-clinical pharmacology report (Myers et al. 2017) [1, 2].

Chemical Abstracts Service registry number: 1394371-71-1.

International Union of Pure and Applied Chemistry name: (3R,3aR,6R,6aR)-6-((6-([1,1'-biphenyl]-4-yl)-7-chloro-3H-imidazo[4,5-b]pyridin-2-yl)oxy)hexahydrofuro[3,2-b]furan-3-ol.

Other designations: The compound is referenced in the literature as a pan-AMPK activator, a direct AMPK activator, and an ADaM-site AMPK activator. It is distinct from indirect AMPK activators (metformin, AICAR, thiazolidinediones) and from beta-1-selective direct activators (A-769662, salicylate).

1.2 Structural class and chemistry

MK-8722 is a synthetic small molecule belonging to the imidazo[4,5-b]pyridine structural class. The compound features three principal structural domains: (a) a 7-chloro-6-(biphenyl-4-yl)-3H-imidazo[4,5-b]pyridine heterocyclic core that occupies the alpha-beta interface at the ADaM binding site of AMPK; (b) a biphenyl substituent at the 6-position of the pyridine ring that extends into a hydrophobic pocket on the alpha-subunit kinase domain; and (c) a hexahydrofuro[3,2-b]furan-3-ol (a bicyclic tetrahydrofuranyl sugar mimic) linked through an ether bond at the 2-position of the imidazole that makes hydrogen-bonding contacts with conserved residues on the alpha-2 subunit backbone [1, 2].

Molecular formula: C₂₄H₂₀ClN₃O₄.

Molecular weight: 449.89 g/mol.

Physical properties: White to off-white crystalline solid. Soluble in dimethyl sulfoxide (DMSO); sparingly soluble in aqueous buffers at neutral pH. The compound is typically supplied as the free base for research applications.

Stereochemistry: MK-8722 contains four stereocenters within the hexahydrofuro[3,2-b]furan-3-ol moiety, with the (3R,3aR,6R,6aR) absolute configuration. The stereochemistry is critical for ADaM-site binding; the mannitol-derived sugar mimic positions hydroxyl groups for backbone hydrogen bonding with alpha-2 subunit residues that are absent in the corresponding diastereomers [1]. Investigators should confirm stereochemical integrity on acquisition through chiral chromatography or optical rotation measurement.

1.3 Synthesis

The medicinal chemistry route to MK-8722 was disclosed by Feng et al. (2018) in ACS Medicinal Chemistry Letters [1]. The synthesis proceeds from the imidazo[4,5-b]pyridine core, constructed through condensation of the appropriately substituted 2,3-diaminopyridine with cyanogen bromide or equivalent C1 electrophile, followed by N-alkylation or O-alkylation with the protected hexahydrofuro[3,2-b]furanyl alcohol under Mitsunobu or displacement conditions. The biphenyl group at the 6-position is introduced through Suzuki-Miyaura cross-coupling of a 6-halopyridine intermediate with a phenylboronic acid derivative. Chlorination at the 7-position is achieved through directed electrophilic or radical halogenation. The sugar mimic is synthesized from D-mannitol through a series of acetonide protection, cyclization, and selective deprotection steps that establish the (3R,3aR,6R,6aR) stereochemistry. Final global deprotection and purification by silica gel chromatography or reverse-phase preparative HPLC yield the target compound. The published route achieves the compound in multi-step sequences with overall yields in the range typical of medicinal chemistry optimization (exact overall yield not disclosed). Process-scale synthesis details are not publicly available.

2. Abstract

MK-8722 is a potent, orally bioavailable, direct allosteric activator of all twelve heterotrimeric AMP-activated protein kinase (AMPK) complexes, developed at Merck Research Laboratories as a candidate therapeutic for type 2 diabetes mellitus [1, 2]. The compound binds the allosteric drug and metabolite (ADaM) site at the interface of the AMPK alpha-subunit kinase domain and the beta-subunit carbohydrate-binding module, producing conformational stabilization of the active kinase state and dose-dependent phosphorylation of downstream substrates including acetyl-CoA carboxylase (ACC).

The principal pharmacological activity of MK-8722 is the induction of insulin-independent glucose uptake in skeletal muscle through AMPK-dependent translocation of GLUT4 to the plasma membrane [2]. In diet-induced obese mice, ob/ob mice, and spontaneously diabetic rhesus monkeys, oral administration of MK-8722 produced dose-dependent reductions in blood glucose, improvements in oral glucose tolerance, and increases in skeletal muscle glycogen content without evidence of hypoglycemia. [18F]FDG-PET imaging confirmed increased skeletal muscle glucose disposal in both rodent and non-human primate models [3]. The glucose-lowering effect was durable over chronic dosing periods of 4 to 8 weeks and was not accompanied by changes in body weight or food intake at efficacious doses.

The development-limiting liability was cardiac hypertrophy and cardiac glycogen accumulation observed during chronic dosing in rodent and non-human primate studies [2]. In Sprague-Dawley rats, 4-week oral dosing produced dose-dependent increases in heart weight, left ventricular wall thickness, and cardiac glycogen content. In rhesus monkeys, 8-week dosing produced comparable cardiac structural changes. Echocardiographic assessment demonstrated preserved systolic and diastolic function, and no arrhythmias were detected. The cardiac hypertrophy was partially reversible at the highest dose following drug washout but did not fully regress at lower doses during the studied recovery period. The cardiac phenotype is consistent with the glycogen storage cardiomyopathy observed in patients with activating mutations in the PRKAG2 gene (encoding the AMPK gamma-2 subunit), supporting an on-mechanism etiology.

MK-8722 did not advance to human clinical trials. The compound is available as a research-grade preparation from multiple chemical suppliers and serves as a reference standard for the ADaM-site AMPK activator class, as a pharmacological tool for the study of pan-AMPK activation in metabolic disease models, and as a structural basis for next-generation selective AMPK activators designed to avoid cardiac activation.

3. Discovery and Development History

3.1 Origin

The discovery of MK-8722 originated from a medicinal chemistry program at Merck Research Laboratories (Kenilworth, New Jersey and Rahway, New Jersey) directed at the identification of orally bioavailable, systemically active, direct AMPK activators for the treatment of type 2 diabetes mellitus. AMPK had long been recognized as a therapeutic target in metabolic disease based on its role as a master energy sensor that stimulates glucose uptake, fatty acid oxidation, and mitochondrial biogenesis while suppressing lipogenesis and gluconeogenesis [4, 5]. The indirect AMPK activator metformin, the most widely prescribed glucose-lowering agent globally, provided clinical proof of concept for AMPK-mediated metabolic improvement, though metformin activates AMPK through indirect mechanisms involving mitochondrial complex I inhibition rather than through direct kinase binding [6].

3.2 Lead optimization

The Merck program built on the structural characterization of the ADaM (allosteric drug and metabolite) binding site on AMPK, a druggable pocket at the interface of the alpha-subunit kinase domain and the beta-subunit carbohydrate-binding module first characterized with the tool compound 991 (ex229) and with the beta-1-selective activator A-769662 [7, 8]. The medicinal chemistry starting point was a thienopyridone series identified through high-throughput screening; optimization through iterative rounds of structure-activity relationship exploration, guided by X-ray crystallographic structures of AMPK-ligand complexes, led to the imidazo[4,5-b]pyridine chemotype and ultimately to MK-8722 [1].

Critical design decisions in the optimization campaign included the introduction of the biphenyl group at the 6-position for hydrophobic complementarity with the alpha-subunit, the 7-chloro substituent for potency enhancement, and the hexahydrofuro[3,2-b]furanyl sugar mimic (derived from D-mannitol) at the 2-position of the imidazole for hydrogen-bonding contacts with the alpha-2 subunit backbone [1]. This last modification was essential for achieving pan-AMPK activation

(activity at both beta-1 and beta-2 containing complexes), as prior ADaM-site activators such as A-769662 showed strong beta-1 selectivity that limited their utility in skeletal muscle, where the beta-2 subunit predominates.

3.3 Key publications

The preclinical pharmacology of MK-8722 was disclosed in a landmark publication by Myers et al. in *Science* in July 2017 [2]. This report described the in vitro AMPK activation profile, the in vivo efficacy in rodent and non-human primate diabetic models, the insulin-independent glucose uptake mechanism, and the cardiac hypertrophy finding. The medicinal chemistry discovery was subsequently published by Feng et al. in *ACS Medicinal Chemistry Letters* in January 2018 [1]. Together, these two publications established MK-8722 as the most thoroughly characterized systemic pan-AMPK activator in the literature and defined both the therapeutic promise and the safety limitation of the ADaM-site activation approach.

3.4 Clinical development status

MK-8722 did not advance to clinical trials. The cardiac hypertrophy observed across species in chronic dosing studies, combined with the lack of full reversibility at lower doses and the mechanistic consistency with PRKAG2 cardiomyopathy, presented a safety liability that precluded initiation of first-in-human studies [2]. The compound remains in the public domain as a research tool and as a basis for next-generation AMPK activator design focused on tissue-selective or isoform-selective approaches that might avoid cardiac activation.

4. Mechanism of Action

4.1 AMPK structure and function

AMP-activated protein kinase (AMPK) is a heterotrimeric serine/threonine kinase consisting of a catalytic alpha subunit, a scaffolding beta subunit, and a regulatory gamma subunit [4, 5]. In mammals, two alpha isoforms (alpha-1, alpha-2), two beta isoforms (beta-1, beta-2), and three gamma isoforms (gamma-1, gamma-2, gamma-3) combine to form twelve possible heterotrimeric complexes with tissue-specific expression patterns. AMPK functions as a cellular energy sensor: the gamma subunit binds AMP and ADP (produced during energetic stress) at CBS domains, inducing conformational changes that promote alpha-subunit phosphorylation at Thr172 by upstream kinases (principally LKB1 and CaMKKbeta), protect against Thr172 dephosphorylation, and allosterically activate the phosphorylated kinase [4].

Activation of AMPK switches on ATP-generating catabolic pathways (glucose uptake, fatty acid oxidation, autophagy) and switches off ATP-consuming anabolic pathways (fatty acid and cholesterol synthesis, gluconeogenesis, protein synthesis) through phosphorylation of key metabolic substrates including acetyl-CoA carboxylase (ACC1 and ACC2), HMG-CoA reductase, TSC2 (tuberin), ULK1, and TBC1D1/TBC1D4 (regulators of GLUT4 trafficking) [5].

4.2 The ADaM binding site

The allosteric drug and metabolite (ADaM) site is located at the interface of the alpha-subunit kinase domain small lobe and the beta-subunit carbohydrate-binding module (CBM) [7, 8]. This site was first characterized structurally with the compound 991 (also known as ex229), a potent direct AMPK activator identified at Genentech/Roche, and is distinct from the nucleotide-binding CBS domains on the gamma subunit [7]. Compounds binding the ADaM site stabilize the interaction between the alpha-kinase domain and the beta-CBM, producing allosteric activation and protection of Thr172 from dephosphorylation. The ADaM site is the target for MK-8722, PF-739, A-769662, 991, and SC4 [1, 7, 8, 9].

4.3 MK-8722 activation mechanism

MK-8722 binds the ADaM site of AMPK and produces dose-dependent allosteric activation of all twelve heterotrimeric complexes [1, 2]. In cell-free kinase assays, MK-8722 activates alpha-1/beta-1/gamma-1, alpha-2/beta-1/gamma-1, alpha-1/beta-2/gamma-1, and alpha-2/beta-2/gamma-1 complexes with EC50 values in the low nanomolar range. The compound activates both beta-1-containing and beta-2-containing complexes, though, like other ADaM-site ligands, it exhibits modestly higher potency at beta-1-containing complexes [1, 9].

The pan-AMPK activation profile of MK-8722 is critical to its pharmacological activity in skeletal muscle, where the predominant AMPK complexes contain the beta-2 subunit (alpha-2/beta-2/gamma-3 in glycolytic fibers, alpha-2/beta-2/gamma-1 in oxidative fibers). Prior ADaM-site activators with strong beta-1 selectivity (A-769662) failed to produce glucose uptake in skeletal muscle because beta-1-containing complexes represent a minor fraction of total AMPK in this tissue [2, 10]. Data obtained with MK-8722 demonstrated that beta-2 activation is required for AMPK-mediated modulation of glycemic control [2].

4.4 Downstream signaling and glucose uptake

MK-8722-mediated AMPK activation produces phosphorylation of the Rab-GTPase-activating proteins TBC1D1 and TBC1D4 (also known as AS160), which control the trafficking and exocytosis of GLUT4-containing vesicles to the sarcolemma [2, 11]. The resulting insulin-independent GLUT4 translocation increases glucose uptake into skeletal muscle fibers. Simultaneously, AMPK activation phosphorylates and inactivates glycogen synthase kinase 3 (GSK3), relieving inhibition of glycogen synthase and promoting glycogen synthesis from the imported glucose. The combined effect is robust glucose disposal from plasma into skeletal muscle glycogen stores, producing the observed glycemia reduction without hypoglycemia (because the mechanism is additive to, rather than a replacement for, insulin-mediated glucose disposal) [2].

4.5 Cardiac AMPK activation

The same AMPK activation mechanism operates in cardiomyocytes, where AMPK complexes containing alpha-1, alpha-2, beta-1, beta-2, and gamma-2 subunits are expressed [12]. Pan-AMPK activation in the heart produces increased glucose up-

take and glycogen synthesis in cardiomyocytes, leading to glycogen accumulation. Chronic glycogen overload in cardiomyocytes produces cellular hypertrophy through mechanisms that may involve mTOR pathway activation secondary to AMPK-independent glycogen signaling, and through direct physical expansion of the glycogen-laden cells [2, 12]. This phenotype closely recapitulates the glycogen storage cardiomyopathy observed in patients with gain-of-function mutations in the PRKAG2 gene encoding the gamma-2 subunit of AMPK, confirming the on-mechanism nature of the cardiac liability [13].

4.6 Selectivity profile

In a screen of 115 enzymes, transporters, and receptors, MK-8722 demonstrated off-target activity at four targets in the 3 to 10 micromolar range [2]. The most potent off-target activity was at the serotonin 5-HT_{2A} receptor (K_i approximately 2.8 micromolar). None of these off-target activities are anticipated to produce pharmacologically meaningful effects at the plasma exposures required for AMPK-mediated glycemic efficacy, which are substantially lower than the off-target K_i values.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

MK-8722 is orally bioavailable in all preclinical species tested [1, 2]. In rodents (mice and rats), the compound demonstrates adequate oral absorption to support once-daily dosing regimens that achieve sustained plasma concentrations above the in vitro AMPK activation EC50. In rhesus monkeys, oral bioavailability is sufficient for chronic once-daily dosing at doses that produce pharmacologically relevant plasma exposures [2]. Specific oral bioavailability values (F%) have not been disclosed in the published literature.

5.2 Distribution

Volume of distribution data for MK-8722 are consistent with distribution beyond the plasma compartment, as expected for a small molecule with moderate lipophilicity targeting an intracellular kinase expressed in multiple tissues [1]. The compound distributes to skeletal muscle, liver, heart, and adipose tissue, as demonstrated by the pharmacodynamic effects (AMPK substrate phosphorylation, glycogen accumulation) observed in these tissues. [18F]FDG-PET imaging studies confirmed pharmacologically relevant tissue exposure in skeletal muscle and heart in both rodent and non-human primate models [3].

Plasma protein binding has not been explicitly reported but is inferred to be moderate based on the relationship between total plasma concentration and free-fraction-dependent pharmacodynamic effects.

5.3 Metabolism

Metabolic characterization of MK-8722 in preclinical species has not been fully disclosed in the public literature. The compound was designed for metabolic stability sufficient to support once-daily oral dosing, and the observed plasma concentration-time profiles in chronic studies are consistent with moderate hepatic clearance [1, 2].

5.4 Elimination

Plasma half-life in rodents and non-human primates supports once-daily oral dosing [1, 2]. The published pharmacokinetic profiles demonstrate a plasma concentration-time course consistent with an effective half-life of several hours in rodents, adequate for sustained AMPK activation over a 24-hour dosing interval. Specific half-life values, clearance rates, and routes of elimination (renal versus biliary versus metabolic) have not been disclosed in the published literature. Investigators should consult the Merck patent literature for additional pharmacokinetic detail.

5.5 Routes of administration

The published preclinical studies exclusively used the oral route, administered as a suspension or solution in standard pharmaceutical vehicles (typically polyethylene glycol-based or cyclodextrin-based formulations) [1, 2]. Parenteral formulations have not been reported but are feasible given the compound's solubility in DMSO and in PEG-based vehicles. For in vitro studies, the compound is dissolved in DMSO at 10 to 50 mM stock concentrations and diluted into aqueous media.

5.6 Dose-exposure-response relationships

In diet-induced obese mice, MK-8722 at 3, 10, and 30 mg/kg oral once daily for 4 weeks produced dose-dependent reductions in blood glucose and oral glucose tolerance test AUC, with maximal efficacy at the 30 mg/kg dose [2]. In spontaneously diabetic rhesus monkeys, once-daily oral dosing for 8 weeks at doses producing efficacious plasma exposures produced significant reductions in fasting blood glucose and glycated hemoglobin (HbA1c) [2]. The relationship between plasma exposure and cardiac hypertrophy was also dose-dependent, with higher exposures producing greater cardiac glycogen accumulation and heart weight increases.

6. Preclinical Pharmacology

6.1 In vitro AMPK activation

MK-8722 activates all twelve mammalian AMPK heterotrimeric complexes in cell-free kinase assays with EC₅₀ values in the low nanomolar range [1, 2]. Activation is allosteric and does not require prior Thr172 phosphorylation, though the magnitude of activation is greater when the kinase is pre-phosphorylated. In cellular assays (HEK293, C2C12 myotubes, primary hepatocytes), MK-8722 produces dose-dependent phosphorylation of ACC at Ser79 (the canonical AMPK substrate site) with EC₅₀ values in the submicromolar to low micromolar range, reflecting the cellular context including endogenous phosphatase activity and competing regulatory inputs [2].

6.2 Skeletal muscle glucose uptake

In isolated mouse extensor digitorum longus (EDL) muscle and in C2C12 differentiated myotubes, MK-8722 produces dose-dependent, insulin-independent glucose uptake that is AMPK-dependent (blocked by the AMPK inhibitor compound C and by genetic ablation of AMPK alpha subunits) [2]. The glucose uptake is mediated by GLUT4 translocation to the plasma membrane and is additive to insulin-stimulated glucose uptake, consistent with a parallel, non-redundant signaling pathway.

6.3 Rodent efficacy models

In diet-induced obese (DIO) C57BL/6 mice, oral MK-8722 at 3 to 30 mg/kg once daily for 4 weeks produced dose-dependent reductions in fed and fasted blood glucose concentrations, improved oral glucose tolerance (reduced glucose AUC), and increased skeletal muscle glycogen content without changes in body weight, food intake, or plasma insulin concentration [2]. In ob/ob mice (leptin-deficient genetic obesity model), MK-8722 produced similar glucose-lowering effects.

The glucose-lowering effect was confirmed to be AMPK-dependent through the use of skeletal-muscle-specific AMPK beta-1/beta-2 double knockout mice, in which MK-8722 failed to stimulate glucose uptake or improve glycemia, confirming that

the therapeutic mechanism requires skeletal muscle AMPK activation [2].

6.4 Non-human primate efficacy

In spontaneously diabetic rhesus monkeys, oral MK-8722 administered once daily for 8 weeks produced statistically significant reductions in fasting blood glucose and HbA1c compared to vehicle control [2]. The effect was durable over the treatment period, and no hypoglycemia was observed. [18F]FDG-PET imaging demonstrated increased glucose uptake specifically in skeletal muscle (bicep) after 2 and 4 weeks of treatment, with the signal returning to baseline after 5 weeks of drug washout [3].

6.5 Cardiac findings in preclinical studies

In Sprague-Dawley rats, 4-week oral administration of MK-8722 at efficacious doses produced dose-dependent increases in absolute and relative heart weight (heart weight to body weight ratio), increases in left ventricular wall thickness on echocardiographic assessment, and increased cardiac glycogen content on histological examination [2]. Echocardiographic function was preserved: left ventricular ejection fraction, fractional shortening, and diastolic filling parameters were not significantly different from vehicle-treated controls. No arrhythmias were detected on continuous electrocardiographic monitoring.

In rhesus monkeys, 8-week oral administration produced comparable cardiac hypertrophy and glycogen accumulation [2]. Cardiac functional parameters were preserved. On drug washout, cardiac hypertrophy showed partial reversibility at the highest dose level but did not fully regress at lower dose levels during the studied recovery period, raising concern about cumulative or incompletely reversible cardiac structural changes [2, 14].

In human induced pluripotent stem cell-derived cardiomyocyte (hiPSC-CM) monolayer and microtissue models, MK-8722 produced concentration-dependent increases in cellular glycogen content and in cardiomyocyte size, recapitulating the in vivo cardiac findings in a human-relevant in vitro system [15].

6.6 FDG-PET pharmacodynamic imaging

A 2025 publication by Merck investigators described the use of [18F]FDG-PET as a pharmacodynamic biomarker for MK-8722-mediated AMPK activation [3]. In rats, acute MK-8722 dosing produced significant increases in forelimb skeletal muscle FDG uptake. In rhesus monkeys, chronic oral administration produced significantly higher FDG uptake in bicep skeletal muscle after 2 and 4 weeks of treatment, with no difference observed after 5 weeks of drug washout. Cardiac muscle FDG uptake was significantly reduced with MK-8722 treatment in rats but did not change significantly in rhesus monkeys, suggesting species-specific differences in cardiac metabolic adaptation to chronic AMPK activation [3].

7. Clinical Evidence Base

MK-8722 has not been evaluated in human clinical trials. The compound did not advance to first-in-human studies because of the cardiac hypertrophy observed in chronic preclinical dosing across rodent and non-human primate species [2]. No investigator-initiated trials, compassionate-use programs, or expanded-access protocols have been reported.

The clinical relevance of MK-8722 is therefore entirely indirect, derived from its contribution to the understanding of AMPK biology and from its role as a pharmacological tool that informed the design of subsequent AMPK activator candidates. The cardiac hypertrophy finding with MK-8722 has been influential in directing the AMPK activator field toward tissue-selective or isoform-selective approaches that aim to achieve skeletal muscle AMPK activation without cardiac activation [16, 17].

The most clinically advanced direct AMPK activator is O304 (Betagenon AB), which operates through a distinct mechanism (synergistic activation with endogenous AMP rather than direct ADaM-site binding) and has completed a Phase IIa proof-of-concept trial in type 2 diabetes patients with positive glucose-lowering results and without cardiac safety signals [18]. The design and interpretation of the O304 clinical program were informed in part by the MK-8722 preclinical cardiac findings.

8. Sourcing and Quality Verification

MK-8722 is available as a research-grade preparation from multiple chemical and pharmaceutical research suppliers. The compound is not available as a pharmaceutical-grade clinical preparation, as it was never advanced to clinical development.

Commercial suppliers: Selleckchem, Cayman Chemical, MedChemExpress, MedKoo Biosciences, BOC Sciences, Alfa Chemistry, Tocris, Sigma-Aldrich/MilliporeSigma, and several additional specialty chemical suppliers offer MK-8722 at stated purities of greater than 98 percent by HPLC. Supply quantities range from milligram to gram scale. Pricing is moderate, in the range of \$100 to \$500 per 50 mg of research-grade material at the time of monograph preparation.

Quality verification: Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity (target: greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (450.89 [M+H]⁺ for C₂₄H₂₁ClN₃O₄)
- Nuclear magnetic resonance spectroscopy (¹H and ¹³C) for structural confirmation
- Chiral chromatography or optical rotation for stereochemical integrity of the (3R,3aR,6R,6aR) configuration
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis (gas chromatography) for common synthesis solvents

Third-party analytical confirmation (Janoshik Analytical or equivalent) is recommended for studies where dose-response precision is critical. The research-grade MK-8722 market is well established given the compound's importance as a pharmacological tool; counterfeit material is uncommon, but lot-to-lot variability in stereochemical purity is a potential concern given the four stereocenters in the sugar mimic moiety.

9. Reconstitution and Handling

MK-8722 as a free base is sparingly soluble in aqueous buffers at neutral pH. For in vitro applications, the compound is dissolved in DMSO to prepare stock solutions at 10 to 50 mM concentration. DMSO stock solutions are stable at -20 degrees Celsius for at least 6 months when protected from light and moisture; aliquoting into single-use volumes is recommended to avoid freeze-thaw degradation.

For in vivo applications in rodents, the compound is formulated as a suspension or solution in standard pharmaceutical vehicles. Published formulations include polyethylene glycol 400/Tween 80/water mixtures, hydroxypropyl methylcellulose (HPMC) suspensions, and hydroxypropyl-beta-cyclodextrin (HP-beta-CD) solutions [1, 2]. The specific vehicle composition should be selected based on the target dose volume and route of administration.

Storage of the solid compound is recommended at -20 degrees Celsius in a sealed container protected from light and moisture. The compound is stable as a solid under these conditions for at least 2 years (manufacturer stated stability). Room-temperature storage of the solid for short periods (days to weeks) during active research use is acceptable but prolonged room-temperature storage is not recommended.

For cell-based assays, final DMSO concentration in the assay medium should not exceed 0.1 to 0.5 percent (v/v) to avoid solvent-mediated cytotoxicity or confounding effects on cellular metabolism. Vehicle controls matched for DMSO concentration are essential.

10. Stack Interactions and Combinations

MK-8722 has been studied primarily as a monotherapy in preclinical models. Combination studies are limited but the following interactions are pharmacologically relevant for research design.

Metformin: Metformin activates AMPK indirectly through mitochondrial complex I inhibition, raising the intracellular AMP:ATP ratio [6]. Combination of metformin with MK-8722 produces additive or potentially synergistic AMPK activation, as the two agents engage different activation mechanisms (nucleotide-dependent versus ADaM-site allosteric). The combination has not been formally characterized in published studies but is a rational experimental design for maximizing AMPK pathway activation. Investigators should monitor for excessive hypoglycemia in combination studies, though MK-8722 alone does not produce hypoglycemia.

Insulin and insulin sensitizers: MK-8722-mediated glucose uptake is insulin-independent and additive to insulin-stimulated glucose uptake [2]. Combination with exogenous insulin or with insulin sensitizers (thiazolidinediones, which also activate AMPK indirectly) could produce additive glucose lowering and increase hypoglycemia risk.

AICAR (5-aminoimidazole-4-carboxamide ribonucleoside): AICAR is converted intracellularly to ZMP, an AMP mimetic that activates AMPK through the gamma-subunit nucleotide sites [19]. Combination with MK-8722 produces dual-site AMPK activation (ADaM site plus gamma-subunit nucleotide site) and is expected to be synergistic; this combination is a useful experimental tool for maximal AMPK pathway engagement.

Other ADaM-site activators: Concurrent administration with other ADaM-site AMPK activators (991, A-769662, PF-739, SC4) is pharmacologically redundant, as these compounds compete for the same binding site. The combination is not recommended for in vivo studies but may be informative for binding competition assays.

CYP enzyme modulators: Metabolic drug-drug interactions have not been formally characterized for MK-8722. Investigators combining MK-8722 with known CYP inhibitors or inducers should monitor for altered MK-8722 exposure through pharmacokinetic sampling.

Cardiac-relevant combinations: Given the cardiac hypertrophy liability, combinations of MK-8722 with other agents known to produce cardiac hypertrophy (anabolic steroids, growth hormone, chronic catecholamine exposure) should be approached with caution in chronic studies.

11. Adverse Events and Safety Signal

11.1 Principal safety finding: cardiac hypertrophy

The dose-limiting adverse finding for MK-8722 is cardiac hypertrophy and cardiac glycogen accumulation observed in chronic dosing studies across rodent and non-human primate species [2]. The finding is characterized by:

- Dose-dependent increase in absolute and relative heart weight (up to approximately 15 to 20 percent increase over vehicle control in rats at the highest efficacious dose)
- Increased left ventricular wall thickness on echocardiography
- Increased cardiac glycogen content on periodic acid-Schiff (PAS) histochemical staining
- Preserved systolic and diastolic cardiac function on echocardiographic assessment
- No detected arrhythmias on continuous electrocardiographic monitoring
- Partial reversibility at the highest dose on drug washout; incomplete regression at lower doses during the studied washout period

The mechanistic basis for the cardiac hypertrophy is on-target AMPK activation in cardiomyocytes, producing AMPK-driven glucose uptake and glycogen synthesis analogous to the therapeutic effect in skeletal muscle but pathological in the cardiac context [2, 12]. The phenotype closely resembles the glycogen storage cardiomyopathy associated with activating mutations in PRKAG2 (encoding the gamma-2 subunit of AMPK), in which constitutive AMPK activation in cardiomyocytes produces glycogen accumulation, cellular hypertrophy, conduction abnormalities, and progressive cardiomyopathy [13].

11.2 Incomplete reversibility concern

The claimed reversibility of cardiac hypertrophy after interruption of MK-8722 treatment is nuanced [14]. Regression of cardiac hypertrophy was documented at the highest dose level but not at lower doses during the studied washout period. Residual cardiac hypertrophy following pharmacological interventions has been

associated with increased risk of adverse cardiac events in multiple clinical contexts. The incomplete reversibility at lower doses increases the concern about long-term cardiac safety of chronic systemic pan-AMPK activation.

11.3 Absence of hypoglycemia

MK-8722 did not produce hypoglycemia in any preclinical species at efficacious doses [2]. This finding reflects the insulin-independent, additive nature of AMPK-mediated glucose uptake, which supplements rather than replaces normal glucose homeostatic mechanisms.

11.4 Off-target findings

No significant off-target toxicological findings were reported in the published pre-clinical studies beyond the cardiac hypertrophy [2]. General toxicology parameters (clinical chemistry, hematology, organ weights other than heart, histopathology of non-cardiac tissues) were unremarkable at efficacious doses.

11.5 Genotoxicity and reproductive toxicity

Genotoxicity and reproductive toxicity data for MK-8722 have not been disclosed in the published literature. These studies may have been conducted internally at Merck but were not reported given the decision not to advance the compound to clinical development.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative AMPK activators against MK-8722, evaluated on five competency standards: novelty, effect size, promising potential (current development status and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal direct or near-direct AMPK activators with substantive pharmacological characterization, with priority given to compounds that have been evaluated in vivo and that address the same therapeutic hypothesis (glucose lowering through AMPK activation in metabolic disease).

12.1 991 (ex229)

Mechanism: Direct, potent ADaM-site AMPK activator. Binds the same allosteric site as MK-8722 at the alpha-beta interface with pan-AMPK activity across beta-1 and beta-2 containing complexes. Originally identified at Genentech/Roche [7].

Development trajectory: 991 was the first compound for which the ADaM-site binding mode was crystallographically resolved, providing the structural foundation for the entire ADaM-site activator class including MK-8722 [7]. The compound is a research tool and has not been advanced to clinical development. It has been extensively used as a reference standard for in vitro AMPK activation studies.

Novelty: High at the time of disclosure (2013). The crystallographic characterization of the ADaM site with 991 was a foundational discovery for the field. The novelty is now diminished by the availability of multiple ADaM-site activators with superior pharmacological properties.

Effect size: Potent in vitro activation of AMPK across isoform combinations. In vivo pharmacodynamic data are limited; the compound has not been extensively characterized in chronic metabolic disease models due to suboptimal pharmacokinetic properties for oral dosing.

Promising potential: Low as a drug candidate. The compound persists as an essential research tool for AMPK pharmacology.

Side-effect profile: Not systematically characterized in chronic in vivo studies. As a pan-AMPK activator binding the same site as MK-8722, cardiac hypertrophy would be predicted with chronic systemic exposure.

Overall validation: Moderate to high as a research tool. The compound is the structural reference standard for the ADaM-site class.

Comparison to MK-8722: 991 and MK-8722 share the same binding site and pan-AMPK activation mechanism. MK-8722 is the superior compound for in vivo studies due to its optimized oral bioavailability and pharmacokinetic profile. 991 retains value as the structural reference compound with the most complete crystallographic dataset.

12.2 A-769662

Mechanism: Direct ADaM-site AMPK activator with strong selectivity for beta-1-containing AMPK complexes [8, 10]. Essentially inactive at beta-2-containing complexes at pharmacologically relevant concentrations.

Development trajectory: Discovered at Abbott Laboratories as one of the first direct small-molecule AMPK activators [10]. Extensively characterized in vitro and in vivo as a research tool. Not advanced to clinical development due to beta-1 selectivity, limited oral bioavailability, and the consequent inability to produce skeletal muscle glucose uptake (which requires beta-2 AMPK activation).

Novelty: Moderate at the time of disclosure (2006); now low given the availability of pan-AMPK activators. Historical importance as one of the first direct AMPK activators.

Effect size: Strong activation of beta-1-containing AMPK complexes in vitro and in vivo. Produces hepatic AMPK activation and lipid-lowering effects in rodent models. Does not produce skeletal muscle glucose uptake due to beta-1 selectivity, limiting its utility for the glucose-lowering therapeutic hypothesis [2, 10].

Promising potential: Low as a drug candidate. Substantial as a research tool for dissecting beta-1-dependent versus beta-2-dependent AMPK biology.

Side-effect profile: Cardiac hypertrophy has not been systematically studied but would not be expected to the same degree as MK-8722, because beta-1-containing complexes are a smaller fraction of cardiac AMPK than beta-2-containing

complexes.

Overall validation: Moderate. Extensive research tool literature. No clinical validation.

Comparison to MK-8722: A-769662 and MK-8722 demonstrate the critical importance of beta-2 AMPK activation for skeletal muscle glucose uptake. MK-8722 is the superior compound for metabolic disease research because of its pan-AMPK profile. A-769662 is the superior compound for dissecting beta-1-selective AMPK biology (hepatic lipid metabolism, macrophage inflammatory responses).

12.3 PF-739

Mechanism: Direct ADaM-site pan-AMPK activator with a structural profile similar to MK-8722, including a mannitol-derived sugar mimic that enables hydrogen bonding with alpha-2 subunit residues and consequent beta-2 AMPK activation [9]. Developed at Pfizer.

Development trajectory: Published by Pfizer investigators as part of the characterization of the structural determinants of beta-2 AMPK activation [9]. Demonstrated glucose lowering in rodent and non-human primate models similar to MK-8722. Like MK-8722, produced cardiac hypertrophy in chronic studies, confirming that the cardiac liability is a class effect of systemic pan-AMPK activation rather than an MK-8722-specific finding.

Novelty: Low. The compound is mechanistically and structurally related to MK-8722 and was developed contemporaneously.

Effect size: Comparable to MK-8722 in rodent glucose-lowering models and in non-human primate glucose homeostasis studies [9]. The two compounds are pharmacological near-equivalents.

Promising potential: Low. Not in clinical development; cardiac hypertrophy observed as with MK-8722.

Side-effect profile: Cardiac hypertrophy and glycogen accumulation similar to MK-8722, confirming the on-mechanism class effect [9].

Overall validation: Moderate. The PF-739 data are valuable precisely because they replicate the MK-8722 efficacy and safety findings with an independent compound from an independent research group, strengthening the conclusion that car-

diac hypertrophy is an intrinsic consequence of systemic pan-AMPK activation rather than an idiosyncratic feature of a single chemotype.

Comparison to MK-8722: PF-739 and MK-8722 are functionally interchangeable for most research applications. MK-8722 has a more extensive published preclinical dataset and is more widely available from commercial suppliers.

12.4 O304

Mechanism: Pan-AMPK activator operating through a mechanism distinct from ADaM-site binding [18]. O304 protects AMPK from dephosphorylation at Thr172 and acts synergistically with endogenous AMP to maintain the activated kinase state. The compound does not bind the ADaM site and is structurally unrelated to MK-8722, 991, A-769662, or PF-739.

Development trajectory: Developed by Betagenon AB (Sweden) with European Commission Horizon 2020 funding. O304 is the most clinically advanced direct AMPK activator, having completed a Phase IIa proof-of-concept randomized, double-blind, placebo-controlled 28-day trial (TELLUS study) in 65 type 2 diabetes patients on metformin background therapy [18]. The trial reported statistically significant reduction in fasting plasma glucose (mean reduction 0.60 mM versus 0.10 mM on placebo, $p = 0.0096$), reduction in HOMA-IR, reduction in diastolic blood pressure, and improvement in peripheral microvascular perfusion. No cardiac hypertrophy or other cardiac safety signals were observed.

Novelty: High. The mechanism of action is distinct from ADaM-site activation, and the clinical advancement beyond MK-8722 and PF-739 represents meaningful translational progress.

Effect size: Moderate in Phase IIa. Fasting glucose reduction of 0.5 mM over placebo is clinically modest but statistically significant in a 28-day study with 65 patients [18]. The effect size on insulin resistance (HOMA-IR) was also significant. The cardiovascular effects (blood pressure reduction, microvascular perfusion improvement) may contribute additional clinical value beyond glucose lowering.

Promising potential: Moderate to high. The Phase IIa data support advancement to larger Phase IIb/III trials. The absence of cardiac hypertrophy signal distinguishes O304 from MK-8722 and PF-739, though longer-duration studies will be required to definitively exclude chronic cardiac effects. Development status beyond Phase IIa has not been publicly disclosed as of the monograph revision date.

Side-effect profile: Well tolerated in Phase IIa with no safety signals [18]. No cardiac hypertrophy. The distinct mechanism of action (protection from dephosphorylation rather than ADaM-site allosteric activation) may explain the absence of the cardiac liability, though this has not been conclusively demonstrated.

Overall validation: Moderate to high. O304 is the only direct AMPK activator with positive human clinical data. The Phase IIa dataset is small and short-duration but represents a meaningful clinical proof of concept for pharmacological AMPK activation in type 2 diabetes.

Comparison to MK-8722: O304 is the most clinically relevant comparator to MK-8722. The two compounds address the same therapeutic hypothesis (AMPK activation for glucose lowering in type 2 diabetes) but through distinct molecular mechanisms. O304 has the critical advantages of clinical advancement and absence of cardiac hypertrophy signal. MK-8722 has the advantages of a more thoroughly characterized molecular mechanism, a more extensive preclinical dataset, and broader commercial availability as a research tool. The clinical trajectory of O304 was informed by the MK-8722 cardiac findings, making MK-8722 historically important even in the absence of its own clinical development.

12.5 SC4

Mechanism: Direct ADaM-site AMPK activator classified as a "glucose importagog" [20]. SC4 exhibits mild beta-1 selectivity but retains activity at beta-2-containing complexes. Structurally, SC4 differs from MK-8722 and PF-739 in the replacement of the mannitol-derived sugar mimic with a 2'-o-toluic acid group, which reduces the backbone hydrogen-bonding contacts with alpha-2 residues that drive beta-2 AMPK potency.

Development trajectory: SC4 was characterized in academic and industrial research settings as part of the structure-function analysis of the ADaM site [9, 20]. The compound demonstrated glucose importation activity in skeletal muscle in vitro and in vivo but has not been advanced to clinical development. It serves principally as a research tool for understanding the structural determinants of AMPK isoform selectivity.

Novelty: Low. The compound is structurally related to the ADaM-site activator class and was characterized as part of the broader structure-activity relationship program.

Effect size: Moderate glucose-lowering activity in rodent models, less potent than MK-8722 at beta-2-containing complexes due to the structural differences at the sugar mimic position [9, 20].

Promising potential: Low. Research tool without clinical development trajectory.

Side-effect profile: Not systematically characterized in chronic studies. Cardiac hypertrophy would be predicted with chronic systemic exposure given the pan-AMPK activation profile, though the reduced beta-2 potency might attenuate the cardiac signal.

Overall validation: Low. Principally valuable as a structural comparator for understanding the molecular determinants of ADaM-site AMPK isoform selectivity.

Comparison to MK-8722: SC4 is less potent than MK-8722 at beta-2 AMPK complexes and produces correspondingly less robust skeletal muscle glucose uptake. The structural comparison between SC4 (o-toluic acid at the sugar mimic position) and MK-8722 (mannitol-derived furanyl sugar at the same position) is the key dataset demonstrating that the sugar mimic backbone hydrogen bonds are critical for beta-2 AMPK potency [9, 20].

12.6 Comparator summary

The five comparators occupy distinct positions in the AMPK activator landscape. **991** is the structural reference compound for the ADaM site, with the most complete crystallographic dataset but limited pharmacokinetic utility. **A-769662** is the beta-1-selective reference, valuable for isoform dissection but unable to engage the skeletal muscle glucose uptake mechanism. **PF-739** is the closest mechanistic and pharmacological equivalent to MK-8722, independently confirming both the efficacy and the cardiac liability of systemic pan-AMPK activation. **O304** is the most clinically advanced comparator, with a distinct mechanism, positive Phase IIa clinical data, and the critical absence of cardiac hypertrophy signal. **SC4** is the structural comparator that illuminates the molecular determinants of beta-2 AMPK potency.

MK-8722 occupies a central position in this comparator landscape. It is the most thoroughly characterized systemic pan-AMPK activator in the published literature, with the most complete preclinical efficacy and safety dataset across rodent and non-human primate species. Its principal contribution is dual: (a) the demonstration that pharmacological AMPK activation can produce clinically meaningful in-

sulin-independent glucose lowering across species, validating the therapeutic hypothesis; and (b) the identification of on-mechanism cardiac hypertrophy as the dose-limiting liability of systemic pan-AMPK activation, defining the safety boundary for the field.

The cardiac hypertrophy finding with MK-8722 (and its independent replication with PF-739) has been the primary driver of the field's evolution toward tissue-selective approaches (intestinal-selective AMPK activators), isoform-selective approaches (beta-2-selective activators for skeletal muscle without cardiac beta-1/beta-2 activation), and mechanistically distinct approaches (O304-type dephosphorylation inhibitors). MK-8722 therefore remains scientifically important despite the absence of its own clinical development, as the reference compound that defined both the opportunity and the boundary of pharmacological AMPK activation in metabolic disease.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. MK-8722 has not been evaluated in human clinical trials and is not approved by any regulatory authority for

any indication. The compound produced cardiac hypertrophy in chronic preclinical studies across species; investigators should consider this safety signal when designing chronic dosing protocols. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.