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RESEARCH COMPOUND MONOGRAPH · SERIES 1 · NO. 015

AOD-9604

Tyrosine-extended C-terminal fragment of human growth hormone (Tyr-hGH 177-191) — engineered at Monash University by Ng, Heffernan and colleagues to isolate the lipolytic and antilipogenic activity of the parent GH molecule without engaging the growth hormone receptor or producing the IGF-1 elevation characteristic of full-length GH.

CAS REGISTRY	CATALOG REFERENCE	CLASS	DATE OF ISSUE
221231-10-3	BM-LYO-015	Synthetic peptide fragment · 16 a.a.	May 2026

AOD-9604 (Anti-Obesity Drug 9604) is a 16-residue synthetic peptide corresponding to the C-terminal fragment of human growth hormone (hGH) residues 177–191 with an additional tyrosine residue at the N-terminus. The molecule was engineered at Monash University by Frank Ng, Michael Heffernan and colleagues as a chemistry-optimised version of the earlier AOD-9401 fragment (hGH 177-191 without the N-terminal tyrosine extension), designed to isolate the lipolytic and antilipogenic activity of the parent GH molecule without engaging the growth hormone receptor or producing the IGF-1 elevation, insulin resistance, or somatic growth effects characteristic of full-length GH. Preclinical animal studies have documented effects on fat metabolism in obese rodents through what published mechanistic work attributes to β3-adrenergic-receptor pathways and direct adipose-tissue lipolysis activation. Human clinical trial efficacy results have been inconsistent. ***This monograph summarises published preclinical findings for laboratory research reference only.***

01 Compound Profile

COMMON DESIGNATION	AOD-9604 · Tyr-hGH(177-191) · Advanced Obesity Drug 9604
PRIMARY SEQUENCE	Tyr-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe (Tyr-hGH residues 177-191)
DISULFIDE BOND	Cys7-Cys14 intramolecular disulfide (the native hGH 182-189 disulfide is retained in the fragment)
CAS REGISTRY	221231-10-3
MOLECULAR FORMULA	$C_{78}H_{123}N_{23}O_{23}S_2$
AVERAGE MOLECULAR MASS	1815.08 g · mol^{-1}
PARENT MOLECULE	Human growth hormone (191 residues, ~22 kDa); AOD-9604 corresponds to the C-terminal lipolytic-domain residues with N-terminal Tyr extension
PROPOSED MOLECULAR TARGETS	β3-adrenergic receptor pathway engagement (preclinical mechanism); receptor-independent direct adipose tissue activity; does not engage the growth hormone receptor[2]
PHYSICAL FORM	White lyophilised solid
SOLUBILITY (LAB RECONSTITUTION)	Soluble in sterile water and bacteriostatic water; **gelling behaviour has been reported** on rapid reconstitution at high concentration — reconstitute slowly with gentle mixing
STORAGE (RESEARCH HANDLING)	Lyophilised solid: −18 °C, desiccated; reconstituted solution refrigerated 2–8 °C short-term; aliquoted long-term at −18 °C; the Cys7-Cys14 disulfide must be preserved — reducing agents must be avoided
ANALYTICAL SPECIFICATION	≥ 98 % purity by HPLC (BIOMOD Labs internal release specification)

02 Origin and Chemistry

The hGH C-terminal lipolytic domain was identified during structure–function studies of growth hormone in the 1980s and 1990s. Wu and colleagues (1993) demonstrated that the 176-191 fragment of native hGH retained antilipogenic activity in rat adipose tissue preparations despite lacking the full somatotrophic activity of the parent molecule. Subsequent chemistry work at Monash University and Metabolic Pharmaceuticals (Australia), led by

Frank Ng and Michael Heffernan, characterised the synthetic fragment chemistry and optimised the molecule for stability and synthesis: AOD-9401 corresponds to hGH 177-191, and AOD-9604 extends this with an N-terminal tyrosine residue that improves chemical stability and synthesis tractability.[1]

Chemically, AOD-9604 retains the native Cys7-Cys14 disulfide bond (corresponding to the Cys182-Cys189 disulfide in full-length hGH) — this disulfide is essential for the fragment's adoption of the receptor-relevant conformation. Reducing agents must therefore be excluded from buffers, vehicles, and laboratory glassware. The molecule has been reported to exhibit gelling behaviour at high reconstitution concentrations — slow reconstitution with gentle mixing is the recommended laboratory practice.[2]

03 Proposed Mechanisms in Preclinical Models

The Heffernan et al. 2001 study published in *Endocrinology* (PMID 11713213) examined AOD-9604 in obese mice and β3-adrenergic-receptor knockout mice, reporting that the lipolytic effects of the fragment are substantially attenuated in β3-AR null animals — implicating the β3-adrenergic receptor pathway as a principal mediator of the molecule's preclinical fat-metabolism effects. Cell-culture studies have additionally reported direct effects of AOD-9604 on adipocyte lipolytic enzyme activity (hormone-sensitive lipase activation) and lipogenic enzyme suppression (acetyl-CoA carboxylase inhibition) in rat adipose tissue preparations.[1,3]

Critically, AOD-9604 does not engage the growth hormone receptor (GHR) — the receptor responsible for the IGF-1 elevation, insulin resistance, and somatic growth effects of full-length GH. The fragment's selective lipolytic profile, without these off-target somatotrophic effects, was the central pharmacological motivation for its development.[4] PRECLINICAL · MOUSE

04 Preclinical Findings

SYSTEM	ANIMAL MODEL / PREPARATION	REPORTED OBSERVATION	REF.
Adipose lipolysis	Rat adipose tissue preparations	Hormone-sensitive lipase activation; acetyl-CoA carboxylase inhibition	3
Body weight in obese mice	Zucker rats and ob/ob mice	Body weight reduction without IGF-1 elevation or glycaemic disturbance	1
β3-AR dependence	β3-adrenergic receptor knockout mice	Lipolytic effects substantially attenuated in β3-AR null animals	2
Lipid metabolism	Indirect calorimetry & plasma lipid panels in obese rodents	↑ fat oxidation; ↑ plasma glycerol/FFA in lipolysis assays	2
GH receptor engagement	Cell-line receptor binding studies	No significant engagement of GHR; no IGF-1 elevation	4
Joint preparations	Rabbit osteoarthritis model (Kwon 2015)	Anti-inflammatory effects in intra-articular preparations with or without hyaluronic acid	5

05 Research Synthesis & Limitations

METHODOLOGICAL NOTES

AOD-9604 occupies a distinctive position in the published peptide literature: relatively well-characterised preclinically with consistent rodent-model lipolytic findings, but with inconsistent human clinical trial efficacy results that led to the discontinuation of the original Phase 2 development programme. For researchers, the principal considerations are (a) the Cys7-Cys14 disulfide must be preserved — reducing agents (DTT, β-mercaptoethanol, TCEP) must be excluded from buffers, vehicles, and laboratory glassware; (b) the molecule exhibits gelling behaviour at high reconstitution concentrations, requiring slow reconstitution with gentle mixing rather than vortexing; and (c) the receptor mechanism is not fully characterised — the β3-adrenergic-receptor finding from Heffernan and colleagues suggests one mediator but does not fully explain all observed preclinical effects.

06 Laboratory Handling, Reconstitution, and Storage

Lyophilised AOD-9604 is supplied under research-use specifications. **Three handling features require attention.** First, the Cys7-Cys14 disulfide is essential for activity — reducing agents must be excluded. Second, gelling behaviour at high reconstitution concentrations requires slow, gentle reconstitution rather than vortexing. Third, the disulfide is susceptible to disulfide-scrambling at extreme pH; neutral aqueous vehicles are preferred. Lyophilised storage at −18 °C, desiccated; reconstituted solutions at refrigerated 2–8 °C for short-term work; aliquoted long-term storage at −18 °C with strict minimisation of freeze–thaw. Working concentrations are determined by the investigator's experimental design.

07 References

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