

7,8- Dihydroxyflavone

A naturally occurring dihydroxylated flavone identified through cell-based TrkB receptor screening as the first orally bioactive small-molecule brain-derived neurotrophic factor mimetic, distinguished by selective TrkB agonism, blood-brain barrier penetration, and broad preclinical neuroprotective and procognitive efficacy across neurodegenerative, neuropsychiatric, and metabolic disease models.

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ABSTRACT

7,8-Dihydroxyflavone (7,8-DHF), also designated tropoflavin, is a naturally occurring flavone first isolated from the leaves of *Godmania aesculifolia* and subsequently identified in *Tridax procumbens*, *Primula vulgaris*, and other plant species. The compound was characterized in 2010 by Jang et al. at Emory University as the first orally bioactive, blood-brain-barrier-penetrant small-molecule agonist of the tropomyosin receptor kinase B (TrkB), the principal high-affinity signaling receptor for brain-derived neurotrophic factor (BDNF) [1]. 7,8-DHF binds the extracellular domain of TrkB with a dissociation constant of approximately 320 nM by filter binding assay and approximately 15.4 nM by surface plasmon resonance, triggering receptor dimerization, autophosphorylation at tyrosine residues 706/707, and activation of the downstream PI3K/Akt and MAPK/ERK signaling cascades that mediate neuronal survival, synaptic plasticity, and long-term potentiation [1, 2]. The compound displays selectivity for TrkB over the related neurotrophin receptors TrkA and TrkC and does not activate TrkB kinase-dead mutants, confirming that the phosphorylation signal arises from the receptor itself rather than from off-target tyrosine kinases [2].

Pharmacokinetic characterization in rodents reveals oral bioavailability of approximately 4.6 percent, a plasma half-life of approximately 134 minutes, rapid brain penetration with peak brain concentrations at 10 minutes after oral dosing, and primary hepatic metabolism through glucuronidation, sulfation, and catechol-O-methyltransferase-mediated methylation [3, 4]. The O-methylated metabolites (7-methoxy-8-hydroxyflavone and 7-

hydroxy-8-methoxyflavone) retain TrkB agonist activity in vitro and in vivo, extending the effective pharmacodynamic window beyond the parent compound [5]. The modest oral bioavailability prompted the development of the prodrug R13 (a carbamate ester derivative) by the Ye laboratory, which increases oral bioavailability to approximately 10.5 percent and extends the plasma half-life to approximately 220 minutes [6]. R13 has entered Phase 1 clinical evaluation for Alzheimer's disease, representing the most advanced clinical translation of TrkB agonist pharmacology from this scaffold.

Preclinical pharmacology is extensive. In Alzheimer's disease models, 7,8-DHF reduces BACE1 elevation, decreases amyloid-beta deposition, restores hippocampal synaptic density, and rescues spatial and working memory deficits in 5XFAD, APP/PS1, and Tg2576 transgenic mice at oral doses of 5 mg/kg/day [7, 8, 9]. In Parkinson's disease models, the compound protects dopaminergic neurons from MPTP- and rotenone-induced degeneration and improves motor function [10]. In depression models, 7,8-DHF reverses learned helplessness, chronic mild stress, and social defeat stress phenotypes through restoration of hippocampal and prefrontal cortical TrkB-BDNF signaling [11, 12]. Additional preclinical efficacy has been demonstrated in models of Huntington's disease, amyotrophic lateral sclerosis, traumatic brain injury, post-traumatic stress disorder, Rett syndrome, fragile X syndrome, retinal ganglion cell degeneration, and diet-induced obesity [13, 14, 15, 16, 17, 18, 19].

Safety characterization in chronic rodent studies at 5 mg/kg/day for periods up to 6 months has revealed no pathological changes in major organs, no hematological abnormalities, and no observable toxicity at doses producing robust TrkB activation [2].

A 7-month oral dosing study in a non-human primate model of Parkinson's disease similarly reported no toxic reactions [20]. No human clinical trial data for the parent compound 7,8-DHF have been published; clinical development has proceeded through the prodrug R13. This monograph reviews the chemistry, natural sources, and structure-activity relationships of 7,8-DHF; the TrkB receptor pharmacology in molecular and cellular detail; the pharmacokinetic profile including metabolism and prodrug development; the preclinical evidence base across neurodegenerative, neuropsychiatric, and metabolic indications; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event and safety characterization; and a comparative assessment of five TrkB-targeted candidates against 7,8-DHF on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: 7,8-Dihydroxyflavone.

Synonyms: 7,8-DHF, tropoflavin, 7,8-dihydroxy-2-phenyl-4H-chromen-4-one.

Chemical Abstracts Service registry number: 38183-03-8.

PubChem compound identifier: CID 1880.

International Union of Pure and Applied Chemistry name: 7,8-dihydroxy-2-phenyl-4H-chromen-4-one.

Development codes for prodrug: R13 (also designated BrAD-R13, Braegen-01).

1.2 Structural class and chemistry

7,8-Dihydroxyflavone belongs to the flavone subclass of flavonoids, a large family of polyphenolic natural products characterized by a 2-phenylchromen-4-one backbone. The compound is distinguished from other flavones by the catechol motif (vicinal dihydroxyl substitution) at the 7- and 8-positions of the A ring, which is essential for TrkB agonist activity. Structure-activity relationship studies have established that the 7,8-dihydroxy substitution pattern is critical: 5,7-dihydroxyflavone (chrysin), 5,6-dihydroxyflavone, and 5,6,7-trihydroxyflavone (baicalein) do not activate TrkB [2]. The oxygen atom in the C ring is essential for activity; replacement with a nitrogen atom abolishes TrkB binding. Substitution at the 4-prime position of the B ring with an amino group enhances potency, while a 3-prime hydroxyl group increases agonistic activity [2].

Molecular formula: C₁₅H₁₀O₄.

Exact mass: 254.0579 g/mol (monoisotopic).

Molecular weight: 254.24 g/mol.

Physical properties: Yellow crystalline powder. Soluble in dimethyl sulfoxide, ethanol, and methanol; sparingly soluble in water. Melting point approximately 230 to 234 degrees Celsius. The compound is supplied commercially as the hydrate form (CAS 38183-03-8 encompasses both anhydrous and hydrate presentations).

Stability: Stable under dry storage at room temperature. The catechol group is susceptible to oxidation in alkaline aqueous solution and in the presence of transition metal ions; stock solutions should be prepared in organic solvent or in mildly acidic aqueous buffer and stored under inert atmosphere when feasible.

1.3 Natural sources

7,8-Dihydroxyflavone has been isolated from the leaves and bark of *Godmania aesculifolia* (Bignoniaceae), a neotropical tree distributed across Central and South America [21]. The compound has also been identified in *Tridax procumbens* (Asteraceae), a pantropical herb used in traditional medicine; in *Primula vulgaris* (Primulaceae), the common European primrose; in *Lepisorus ussuriensis*, a fern used in traditional Chinese medicine for heat-clearing preparations; and in *Malus hupehensis*, the Chinese crabapple [22, 23]. The concentrations in natural sources are low, and commercial supply is predominantly through chemical synthesis rather than botanical extraction.

1.4 Synthesis

The synthesis of 7,8-dihydroxyflavone proceeds through standard flavone synthetic methodologies. The most common route involves the Allan-Robinson reaction or Baker-Venkataraman rearrangement starting from 2,3-dihydroxyacetophenone and benzoyl chloride. The 2,3-dihydroxyacetophenone is acylated with benzoyl chloride under basic conditions to form the benzoyloxy intermediate, which undergoes base-catalyzed intramolecular cyclization and dehydration to yield the flavone skeleton. The catechol hydroxyl groups may be protected as methyl ethers during the synthesis and deprotected in a final step using boron tribromide or hydrobromic acid. Alternative synthetic approaches include the Algar-Flynn-Oyamada oxidation of 2-prime-hydroxychalcone precursors. Industrial and research-grade synthesis typically achieves purity greater than 98 percent by HPLC, with the product isolated as a yellow crystalline solid by recrystallization from ethanol or ethyl acetate [24].

2. Abstract

7,8-Dihydroxyflavone (tropoflavin) is a naturally occurring flavone and the first orally bioactive small-molecule agonist of the TrkB receptor, the principal high-affinity signaling receptor for brain-derived neurotrophic factor (BDNF). The compound was identified in 2010 by Jang et al. through a cell-based screening assay that selected for compounds capable of promoting TrkB-dependent neuronal survival [1]. The discovery addressed a longstanding translational limitation of BDNF itself: despite the central role of BDNF-TrkB signaling in neuronal survival, synaptic plasticity, long-term potentiation, and neurogenesis, the BDNF protein is not orally bioavailable, does not cross the blood-brain barrier in pharmacologically relevant quantities, and has a short plasma half-life, rendering it unsuitable for systemic therapeutic administration.

7,8-DHF overcomes these limitations by binding the TrkB extracellular domain at a site distinct from the BDNF binding pocket, triggering receptor dimerization and activation of the same downstream intracellular signaling cascades (PI3K/Akt, MAPK/ERK, PLCgamma1) that mediate the neurotrophic, neuroprotective, and neuroplastic effects of BDNF [1, 2]. The compound is orally bioavailable (approximately 4.6 percent in mice), penetrates the blood-brain barrier within minutes of systemic administration, and produces sustained TrkB phosphorylation for more than 3 hours without inducing receptor ubiquitination or degradation, a favorable pharmacodynamic distinction from BDNF itself [2].

The preclinical evidence base is among the most extensive for any small-molecule neurotrophic agent. Positive pharmacological effects have been documented in validated animal models of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, depression, post-traumatic stress disorder, anxiety, schizophrenia, traumatic brain injury, stroke, Rett syndrome, fragile X syndrome, retinal degeneration, hearing loss, obesity, and metabolic syndrome [2, 7, 8, 10, 11, 13, 14, 15, 16, 17, 18, 19]. Effect sizes in these models are generally moderate to large, with the cognitive and motor endpoints showing the most consistent dose-dependent responses.

No human clinical trials of the parent compound 7,8-DHF have been published. Clinical translation has proceeded through the prodrug R13, which was developed to address the modest oral bioavailability of the parent compound. R13 has entered Phase 1 clinical evaluation for Alzheimer's disease [6]. The compound is not approved as a medicine in any jurisdiction. It is available as a research-grade preparation from multiple commercial suppliers and as a dietary supplement in some markets, though the latter application has no regulatory endorsement for therapeutic claims.

3. Discovery and Development History

3.1 Origin

The identification of 7,8-dihydroxyflavone as a TrkB agonist was reported by Jang et al. in 2010 in the Proceedings of the National Academy of Sciences [1]. The research group, led by Keqiang Ye at the Department of Pathology and Laboratory Medicine, Emory University School of Medicine, developed a cell-based screening strategy using T48 cells (which express TrkB and depend on TrkB signaling for survival) and SN56 cells (which do not express TrkB) as a counter-screen. The library was screened for compounds that selectively protected T48 cells but not SN56 cells from staurosporine-induced apoptosis. Of approximately 2000 compounds screened, 66 selectively protected T48 cells; among these, 5 were flavone derivatives. 7,8-Dihydroxyflavone emerged as the most potent and selective TrkB agonist in subsequent binding and phosphorylation validation assays.

3.2 Validation of TrkB agonism

The initial Jang et al. report demonstrated that 7,8-DHF (a) activated TrkB phosphorylation in primary cortical neurons; (b) activated TrkB in mouse brain after intraperitoneal administration at 5 mg/kg; (c) inhibited kainic acid-induced seizure neurotoxicity in a TrkB-dependent manner; (d) reduced cerebral infarct volumes in middle cerebral artery occlusion models of stroke; and (e) produced neuroprotective effects in a 6-hydroxydopamine model of Parkinson's disease [1]. These initial demonstrations established the compound as a broad-spectrum neurotrophic agent and catalyzed a rapidly expanding literature.

3.3 Subsequent characterization

Liu et al. (2014) provided the detailed molecular characterization of 7,8-DHF binding to TrkB using surface plasmon resonance, filter binding assays, and site-directed mutagenesis [2]. This report established the 320 nM K_d by filter binding and 15.4 nM by SPR, confirmed selectivity for TrkB over TrkA and TrkC, demonstrated

that kinase-dead TrkB mutants were not activated (confirming intrinsic receptor kinase dependency), and characterized the sustained TrkB phosphorylation without receptor degradation that distinguishes 7,8-DHF from BDNF.

3.4 Prodrug development

The Ye laboratory recognized that the 4.6 percent oral bioavailability of 7,8-DHF, while sufficient for proof-of-concept preclinical studies, was a translational limitation. Chen et al. (2018) reported the systematic development of ester and carbamate prodrug derivatives, screening through in vitro ADME assays combined with in vivo pharmacokinetic studies in mice [6]. The prodrug R13 emerged as the lead candidate, increasing oral bioavailability to 10.5 percent, extending the plasma half-life from 134 to 220 minutes, and maintaining dose-dependent TrkB activation and amyloid-beta reduction in 5XFAD transgenic mice on chronic oral administration. R13 entered clinical development under the designation BrAD-R13 (Braegen-01) for Alzheimer's disease, amyotrophic lateral sclerosis, depressive disorders, Parkinson's disease, and schizophrenia [25].

3.5 Controversy regarding TrkB agonist authenticity

A 2017 report by Boltaev et al. in *Science Signaling* raised methodological concerns about several reported small-molecule TrkB agonists, including 7,8-DHF [26]. Using multiplex quantitative phosphoprotein assays, the authors reported that 7,8-DHF, LM22A-4, deoxygedunin, amitriptyline, and other putative TrkB agonists failed to demonstrate direct TrkB activation under their assay conditions. The Ye laboratory and other groups subsequently addressed these findings, noting that assay conditions, cell types, receptor expression levels, and ligand concentrations can substantially affect the detection of partial agonist activity at receptor tyrosine kinases. Multiple independent laboratories have continued to report 7,8-DHF-dependent TrkB phosphorylation in primary neurons and in vivo, and the compound remains the most widely used small-molecule TrkB agonist in the research literature, with over 500 publications as of 2025 [27]. The controversy has not been definitively resolved and represents an important methodological consideration for investigators.

4. Mechanism of Action

7,8-Dihydroxyflavone is a small-molecule agonist of the TrkB receptor tyrosine kinase. The principal molecular activities, characterized in heterologous expression systems, primary neuronal cultures, and in vivo rodent and primate models, are direct TrkB activation, downstream neurotrophic signaling cascade engagement, and secondary antioxidant and anti-inflammatory effects.

4.1 TrkB receptor agonism

The TrkB receptor (NTRK2 gene product) is a single-pass transmembrane receptor tyrosine kinase belonging to the tropomyosin receptor kinase family. It is expressed at high density in the hippocampus, cerebral cortex, cerebellum, basal forebrain cholinergic neurons, striatal medium spiny neurons, substantia nigra dopaminergic neurons, retinal ganglion cells, and dorsal root ganglion sensory neurons. The canonical ligand is BDNF; neurotrophin-4/5 (NT-4/5) is a secondary ligand. Ligand binding to the extracellular immunoglobulin-like domains (particularly the d5 domain) triggers receptor dimerization, trans-autophosphorylation at intracellular tyrosine residues (Y706/Y707 in the activation loop, Y515 in the Shc binding site, Y816 in the PLCgamma1 docking site), and activation of three principal intracellular signaling cascades: the PI3K/Akt survival pathway, the Ras/MAPK/ERK proliferation and differentiation pathway, and the PLCgamma1/IP3/DAG/PKC calcium signaling pathway [28].

7,8-DHF binds the TrkB extracellular domain at a site that overlaps with but is not identical to the BDNF binding site. Binding triggers receptor dimerization and autophosphorylation. In contrast to BDNF, 7,8-DHF produces sustained TrkB phosphorylation (more than 3 hours in primary neurons) without inducing receptor ubiquitination or lysosomal degradation, resulting in a longer effective signaling window per binding event [2]. The compound does not activate the low-affinity p75NTR neurotrophin receptor, which mediates proapoptotic signaling, and therefore does not engage the proapoptotic arm of neurotrophin signaling.

4.2 Downstream signaling

Activation of the PI3K/Akt pathway by 7,8-DHF promotes neuronal survival through phosphorylation and inactivation of proapoptotic mediators (BAD, caspase-9, FOXO transcription factors) and through activation of mTOR-dependent protein synthesis [2]. The MAPK/ERK pathway activation supports synaptic plasticity, long-term potentiation, and neurogenesis. The PLCgamma1 pathway contributes to intracellular calcium mobilization and PKC-dependent modulation of synaptic transmission. In Huntington's disease models, the PLCgamma1 pathway has been identified as particularly critical for the therapeutic effect of 7,8-DHF [13].

4.3 Secondary mechanisms

Beyond direct TrkB agonism, 7,8-DHF exhibits secondary pharmacological activities consistent with its flavonoid chemical class. The catechol group confers antioxidant capacity through radical scavenging (demonstrated in DPPH and ABTS assays) [29]. The compound activates the AMPK/PGC-1alpha/NRF1 mitochondrial biogenesis pathway in skeletal muscle, contributing to the anti-obesity phenotype observed in chronic dosing studies [19]. Anti-inflammatory activity through reduction of NF-kappaB, iNOS, and caspase-3 expression has been reported in neuroinflammatory models [30]. A 2024 report by Trieu et al. in *eLife* identified 7,8-DHF as a direct inhibitor of pyridoxal phosphatase, the enzyme responsible for dephosphorylation of pyridoxal 5-prime-phosphate (the active form of vitamin B6), suggesting a novel mechanism by which the compound may increase brain bioactive B6 levels [31]. The relative contributions of TrkB agonism, antioxidant activity, mitochondrial biogenesis, anti-inflammatory effects, and pyridoxal phosphatase inhibition to the *in vivo* pharmacological profile have not been fully dissected and likely vary by tissue and disease context.

4.4 Interaction with estrogen receptor signaling

Several studies have reported sex-dependent effects of 7,8-DHF, particularly in metabolic endpoints. The anti-obesity effects in chronic high-fat diet feeding paradigms are more pronounced in female mice, potentially reflecting synergistic interaction between estrogen receptor alpha (ERalpha) and TrkB signaling pathways [19, 32]. The molecular basis of this interaction is incompletely characterized but may involve ERalpha-dependent transcriptional regulation of TrkB expression or direct ERalpha-TrkB receptor crosstalk.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

7,8-Dihydroxyflavone is absorbed from the gastrointestinal tract after oral administration. Oral bioavailability in mice is approximately 4.6 percent, reflecting extensive first-pass hepatic metabolism of the catechol group [3]. Despite this modest systemic bioavailability, the compound achieves pharmacologically relevant brain concentrations: peak plasma concentration of approximately 70 ng/mL and peak brain concentration of approximately 50 ng/g are achieved within 10 minutes of oral administration in mice [3]. The rapid absorption and brain penetration are consistent with the compound's moderate lipophilicity and confirmed blood-brain barrier permeability in PAMPA-BBB assays.

5.2 Distribution

The compound distributes to the central nervous system within minutes of systemic administration. Brain penetration has been confirmed by direct tissue measurement following oral and intraperitoneal dosing [1, 3]. The compound is a weak substrate of P-glycoprotein, which does not substantially limit central nervous system exposure at pharmacologically relevant doses. Plasma protein binding data are limited in the published literature.

5.3 Metabolism

7,8-DHF is metabolized primarily in the liver. The catechol group undergoes three principal conjugation reactions: glucuronidation by UDP-glucuronosyltransferases, sulfation by sulfotransferases, and methylation by catechol-O-methyltransferase (COMT) [3, 4]. The compound is stable in liver microsomes but labile in hepatocytes, consistent with phase II conjugation as the primary metabolic pathway rather than cytochrome P450-mediated oxidation [3].

The O-methylated metabolites are of particular pharmacological significance. Liu et al. (2013) demonstrated that both mono-methylated metabolites (7-methoxy-8-hydroxyflavone and 7-hydroxy-8-methoxyflavone) activate TrkB in vitro and in vivo, and that these metabolites distribute to mouse brain after oral administration of the parent compound [5]. The active metabolites extend the effective pharmacodynamic window beyond what the parent compound's plasma half-life would predict, potentially accounting for the sustained in vivo efficacy observed with once-daily dosing in chronic preclinical studies.

The compound does not inhibit or induce major cytochrome P450 enzymes in vitro. The hERG IC₅₀ is greater than 25 micromolar, indicating low cardiac ion channel liability [3].

5.4 Elimination

Plasma concentrations decline to approximately 5 ng/mL by 8 hours after oral dosing in mice. Brain concentrations fall below quantifiable limits by 6 hours [3]. The primary elimination pathway is hepatic conjugation followed by renal and biliary excretion of glucuronidated and sulfated metabolites. Less than 5 percent of an administered dose is excreted as unchanged parent compound.

5.5 Prodrug pharmacokinetics

The prodrug R13 was developed to improve the pharmacokinetic limitations of the parent compound. R13 is a carbamate ester derivative that is cleaved in vivo to release 7,8-DHF. Oral bioavailability of 7,8-DHF from R13 administration is approximately 10.5 percent (a 2.3-fold improvement over the parent compound). The C_{max} of 7,8-DHF after oral R13 administration is approximately 1555 ng/mL (a 22-fold increase), with T_{max} of approximately 17 minutes and a terminal half-life of approximately 220 minutes [6]. These improved pharmacokinetic parameters are the basis for the clinical advancement of R13 rather than the parent compound.

A separate prodrug optimization identified compound R7, an ester derivative that achieved 84.2 percent oral bioavailability in early reports, though this compound was not advanced as the clinical lead [2].

5.6 Routes of administration in preclinical research

Three routes are used in published preclinical studies: oral gavage (the most common, typically at 5 mg/kg in mice), intraperitoneal injection (used in acute neurotoxicity and behavioral paradigms), and dissolution in drinking water (used in chronic metabolic studies spanning several months). Intracerebral microinjection has been used in mechanistic studies targeting specific brain regions (medial prefrontal cortex, hippocampal dentate gyrus, CA3, amygdala).

6. Preclinical Pharmacology

6.1 Alzheimer's disease

The preclinical evidence for 7,8-DHF in Alzheimer's disease models is extensive and spans multiple transgenic mouse lines and multiple endpoints.

Devi and Ohno (2012) reported that oral administration of 7,8-DHF at 5 mg/kg/day to 5XFAD transgenic mice (which express five familial Alzheimer's disease mutations in APP and PS1 and develop aggressive amyloid pathology) rescued memory deficits in the Y-maze alternation task, reduced BACE1 protein elevation, and decreased cortical and hippocampal amyloid-beta 40 and amyloid-beta 42 levels [7]. The mechanism involved TrkB-dependent suppression of BACE1 expression, reducing the amyloidogenic processing of APP.

Zhang et al. (2014) extended these findings with chronic oral 7,8-DHF (5 mg/kg starting at 2 months of age and continuing through 5 months) in APP/PS1 transgenic mice. The treatment activated TrkB signaling, prevented amyloid-beta deposition, and preserved hippocampal synaptic markers [8].

Gao et al. (2016) studied aged Tg2576 mice (which carry the Swedish APP mutation) and reported that 7,8-DHF increased dendritic spine density, restored synaptic plasticity as measured by long-term potentiation, and elevated GluA1 and GluA2 AMPA receptor subunit expression and phosphorylation [9].

The prodrug R13 recapitulated these findings in 5XFAD mice with improved dose-response relationships, activating TrkB signaling, inhibiting the pathological cleavage of APP and tau by asparagine endopeptidase (AEP), and inhibiting hippocampal synapse loss [6].

6.2 Parkinson's disease

Jang et al. (2010) included a 6-hydroxydopamine mouse model of Parkinson's disease in the initial discovery report, demonstrating that 7,8-DHF protected nigrostriatal dopaminergic neurons [1]. Subsequent studies extended these findings to MPTP and rotenone models, demonstrating that 7,8-DHF alleviated motor dysfunction and blocked striatal dopaminergic neuron degeneration through TrkB-depen-

dent mechanisms [10]. He et al. reported a 7-month oral dosing study in an MPP-plus-induced Parkinson's disease model in non-human primates, with 7,8-DHF reducing dopaminergic neuron loss in the midbrain without observable toxicity [20].

6.3 Huntington's disease

Jiang et al. (2013) demonstrated that 7,8-DHF ameliorated cognitive and motor deficits in R6/1 Huntington's disease transgenic mice through specific activation of the PLCgamma1 pathway downstream of TrkB [13]. The selective engagement of PLCgamma1 (rather than the Akt or ERK pathways, which were also activated) was identified as the critical pathway for the therapeutic effect. Striatal neuronal survival was improved and motor coordination on the rotarod was preserved.

6.4 Depression

7,8-DHF has been evaluated in multiple depression-relevant behavioral paradigms. A synthetic derivative (4-prime-dimethylamino-7,8-dihydroxyflavone) was reported by Liu et al. (2010) to promote hippocampal neurogenesis and exhibit potent antidepressant activity in the forced swim test and tail suspension test [11]. The parent compound 7,8-DHF produces antidepressant-like effects in learned helplessness, chronic mild stress, chronic unpredictable mild stress, lipopolysaccharide-induced depression, and social defeat stress models [12]. Microinjection into the medial prefrontal cortex, dentate gyrus, and CA3 hippocampal subfields was sufficient to reverse depression-like behaviors, implicating local TrkB-BDNF signaling deficits as the target [12]. Combination with fluoxetine enhanced antidepressant efficacy in perimenopausal depression models, with synergistic effects on sucrose preference and forced swimming immobility [33].

6.5 Post-traumatic stress disorder and fear memory

Andero et al. (2011) reported that 7,8-DHF facilitated fear extinction learning when administered systemically prior to extinction training in mice, an effect dependent on TrkB signaling in the amygdala [34]. Subsequent work demonstrated that the compound prevented fear generalization and anxiety-like behavior in PTSD models, potentially through preservation of hippocampal astrocytic and synaptic integrity [16].

6.6 Traumatic brain injury

Wu et al. (2014) demonstrated that administration of 7,8-DHF at 3 hours post-injury reduced brain tissue damage in a controlled cortical impact model of traumatic brain injury, with the neuroprotective effect mediated through PI3K/Akt pathway activation [17]. The compound promoted neuronal survival and reduced apoptosis in cortical neurons surrounding the injury site.

6.7 Stroke

The initial Jang et al. (2010) report demonstrated that 7,8-DHF reduced cerebral infarct volumes in a middle cerebral artery occlusion model of ischemic stroke [1]. The neuroprotective effect was TrkB-dependent, as demonstrated by loss of protection in TrkB heterozygous knockout mice.

6.8 Retinal neurodegeneration

Gupta et al. (2013) reported that 7,8-DHF protected retinal ganglion cells from excitotoxic and oxidative stress-induced apoptosis through TrkB-dependent mechanisms [18]. The compound has been evaluated in glaucoma models and in models of retinal ischemia-reperfusion injury.

6.9 Obesity and metabolic syndrome

Chan et al. (2015) reported that chronic oral administration of 7,8-DHF (dissolved in drinking water) for 6 months to mice on a high-fat diet decreased body weight gain by approximately 20 to 30 percent, reduced white adipose tissue mass, improved insulin sensitivity, and decreased blood glucose and insulin levels [19]. The mechanism involved activation of muscular TrkB receptors, induction of uncoupling protein 1 (UCP1) expression, AMPK activation, and a shift in respiratory exchange ratio favoring lipid oxidation. The metabolic effects were more pronounced in female mice, suggesting an estrogen-dependent component. Subsequent work identified the gut microbiome as a required mediator of the metabolic protection, as germ-free mice did not respond to 7,8-DHF treatment [35].

6.10 Other preclinical indications

Additional preclinical efficacy has been reported in Rett syndrome (rescue of respiratory dysfunction and synaptic deficits in MeCP2-deficient mice) [14], fragile X syndrome (restoration of synaptic plasticity) [15], amyotrophic lateral sclerosis (motor neuron protection) [36], hearing loss and spiral ganglion neuron degeneration [37], axonal regeneration in peripheral nerve injury [38], and schizophrenia (early intervention reducing cognitive and synaptic plasticity deficits in maternal immune activation offspring) [39].

7. Clinical Evidence Base

7.1 Parent compound

No human clinical trials of 7,8-dihydroxyflavone itself have been published in the peer-reviewed literature as of the most recent monograph revision. The compound is available as a dietary supplement in some markets, but no controlled human studies have evaluated its safety, pharmacokinetics, or efficacy in any indication. Anecdotal reports from the nootropics and biohacking communities describe subjective cognitive and mood effects at oral doses of 10 to 50 mg daily, but these reports lack controlled comparisons, objective endpoints, and pharmacokinetic characterization.

7.2 Prodrug R13

R13 (BrAD-R13, Braegen-01) has entered Phase 1 clinical evaluation for Alzheimer's disease [25]. The prodrug was designed to overcome the pharmacokinetic limitations of the parent compound while maintaining the same TrkB-mediated mechanism of action. Preclinical efficacy data supporting the clinical program include dose-dependent cognitive improvement, amyloid-beta reduction, and tau phosphorylation attenuation in 5XFAD transgenic mice. The clinical program also encompasses potential indications in amyotrophic lateral sclerosis, Parkinson's disease, depressive disorders, and schizophrenia. No Phase 1 results have been published as of the current revision.

7.3 Clinical translation considerations

The absence of human data for the parent compound and the early-phase status of R13 represent the principal limitation of the 7,8-DHF research program. The extensive preclinical literature (over 500 publications across more than 15 disease models) provides a strong rationale for clinical investigation, but the history of neurotrophic factor therapeutics cautions against extrapolation from animal models. The BDNF Val66Met polymorphism, which affects BDNF secretion and is present in approximately 25 to 35 percent of human populations, may influence the response to TrkB agonism in ways not captured by standard inbred mouse models. The con-

troversy regarding the directness of TrkB activation by 7,8-DHF (Section 3.5) further complicates clinical translation, as the mechanism-of-action certainty required for regulatory submissions may necessitate additional molecular pharmacology validation.

8. Sourcing and Quality Verification

Research-grade 7,8-dihydroxyflavone is supplied by multiple chemical and pharmaceutical research suppliers, including Sigma-Aldrich (catalog D5446), Tocris Bioscience (catalog 3826), Cayman Chemical (catalog 16946), MedChemExpress, Santa Cruz Biotechnology, Abcam, and others, at greater than 98 percent purity by HPLC. The compound is typically supplied as the hydrate form, as a yellow crystalline powder, in milligram to gram quantities. Pricing is moderate, in the range of \$30 to \$150 per gram of research-grade material.

The compound is also available as a dietary supplement from consumer-oriented vendors, though these preparations are not subject to pharmaceutical-grade quality assurance, and purity, identity, and potency verification are inconsistent.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ of 255.07)
- Proton nuclear magnetic resonance spectroscopy for structural confirmation
- Karl Fischer or thermogravimetric analysis for water content (relevant for the hydrate form)
- Certificate of analysis review for heavy metal content and residual solvent analysis

Third-party analytical laboratories provide independent confirmation of vendor certificates. The 7,8-DHF research market is well established and counterfeit material is uncommon, but the catechol group is susceptible to oxidation during storage, and degraded material may show reduced TrkB agonist activity. On-receipt analytical confirmation is appropriate for investigations where dose-response precision is important.

9. Reconstitution and Handling

7,8-Dihydroxyflavone has limited aqueous solubility. For in vitro research applications, the compound is typically dissolved in dimethyl sulfoxide (DMSO) to prepare concentrated stock solutions (typically 10 to 100 mM). These DMSO stocks are then diluted into aqueous cell culture media or buffer immediately before use, with the final DMSO concentration maintained below 0.1 percent to avoid solvent-related cytotoxicity. Ethanol and methanol are alternative stock solvents for applications where DMSO is contraindicated.

For in vivo oral administration, the compound is dissolved in DMSO at a concentrated stock and then diluted into a vehicle consisting of polyethylene glycol 400, Tween-80, or cyclodextrin in saline. Dissolution in drinking water (with or without a small quantity of DMSO or ethanol as cosolvent) has been used for chronic metabolic studies spanning months [19]. For intraperitoneal injection, the compound is typically dissolved in DMSO and diluted with saline or phosphate-buffered saline to the desired concentration.

Storage recommendations: the solid compound should be stored at minus 20 degrees Celsius under desiccant and protected from light for long-term stability. DMSO stock solutions should be aliquoted into single-use volumes and stored at minus 20 degrees Celsius; repeated freeze-thaw cycles should be minimized. Aqueous solutions should be prepared fresh before each experiment, as the catechol group is susceptible to oxidation in aqueous conditions, particularly at alkaline pH.

10. Stack Interaction Considerations

Investigators conducting research with 7,8-dihydroxyflavone in combination with other compounds should consider the following interactions:

COMT inhibitors: Catechol-O-methyltransferase inhibitors (entacapone, tolcapone, opicapone) inhibit the primary metabolic pathway of 7,8-DHF and may increase systemic exposure to the parent compound while reducing formation of the active O-methylated metabolites. The net pharmacological consequence (increased parent compound exposure versus decreased active metabolite formation) is unpredictable without empirical characterization.

Other TrkB ligands and modulators: BDNF, NT-4/5, and other TrkB agonists (LM22A-4, deoxygedunin) produce additive or potentially competitive effects at the TrkB receptor. The combination has not been systematically studied in vivo. Concurrent administration of BDNF and 7,8-DHF may produce receptor desensitization at high combined occupancy.

Antidepressants affecting BDNF-TrkB signaling: Selective serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine), tricyclic antidepressants (amitriptyline, imipramine), and ketamine all increase BDNF expression or TrkB signaling through indirect mechanisms. Concurrent 7,8-DHF administration may produce additive neurotrophic effects; this has been formally demonstrated for fluoxetine in a perimenopausal depression model [33]. The combination may also produce excessive TrkB-driven excitability in susceptible circuits.

Polyphenol metabolism interactions: Other dietary flavonoids and polyphenols (quercetin, luteolin, fisetin, resveratrol) share glucuronidation and sulfation metabolic pathways and may compete for conjugation enzymes, potentially altering 7,8-DHF clearance. The clinical significance of these interactions at typical dietary or supplemental doses is uncertain.

Acetylcholinesterase inhibitors: Donepezil, rivastigmine, and galantamine increase cholinergic tone and may produce additive or synergistic neurotrophic effects with 7,8-DHF through convergent signaling at the level of CREB phosphorylation and BDNF transcription. The combination is mechanistically rational for Alzheimer's disease research but has not been formally evaluated for safety.

Metabolic agents: Metformin and other AMPK activators share a downstream pathway with the metabolic effects of 7,8-DHF. Concurrent use may produce additive effects on lipid oxidation and insulin sensitivity.

11. Adverse Events and Safety

11.1 Preclinical safety

The safety profile of 7,8-DHF in preclinical studies is favorable. Chronic administration at 5 mg/kg/day in C57BL/6 mice for 3 weeks produced no pathological changes in kidney, liver, lung, muscle, spleen, cortex, hippocampus, heart, intestine, or testis on histological examination [2]. Complete blood count analyses showed no significant differences from vehicle-treated controls. Female mice receiving 7,8-DHF dissolved in drinking water for 20 weeks (approximately 2.4 micrograms per day) displayed normal complete blood count values [2]. The compound did not inhibit HEK293 cell proliferation at concentrations up to 50 micromolar.

He et al. reported a 7-month oral dosing study of 7,8-DHF in a non-human primate model of Parkinson's disease with no toxic reactions [20]. This is the longest-duration safety study in a higher species reported for the compound.

11.2 Theoretical safety concerns

BDNF-TrkB signaling is implicated in multiple physiological processes, and excessive activation carries theoretical risks. Studies in BDNF-overexpressing transgenic mice have demonstrated seizure susceptibility and neuronal hyperexcitability, suggesting that chronic high-dose TrkB agonism could lower the seizure threshold [40]. BDNF-TrkB signaling has also been implicated in cancer biology, with TrkB activation promoting survival of tumor cells in some contexts (particularly neuroblastoma, lung cancer, and pancreatic cancer), raising a theoretical concern about chronic TrkB agonist administration in individuals with occult malignancy [41]. These theoretical risks have not been observed in the published chronic 7,8-DHF dosing studies at 5 mg/kg/day but have not been specifically evaluated at higher doses or over periods longer than 7 months.

11.3 Human safety data

No controlled human safety data for the parent compound 7,8-DHF have been published. The compound is marketed as a dietary supplement in some jurisdictions at doses of 10 to 50 mg daily; adverse-event reports in the supplement literature are sparse and unverified. Common self-reported effects in online forums include mild headache, gastrointestinal discomfort, and transient fatigue, none of which can be attributed to the compound with confidence in the absence of controlled data.

11.4 Pregnancy and lactation

No pregnancy or lactation safety data are available for 7,8-DHF in any species. Given the central role of BDNF-TrkB signaling in embryonic neural development, the use of TrkB agonists during pregnancy should be approached with extreme caution.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five TrkB-targeted or neurotrophic candidates against 7,8-dihydroxyflavone, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal TrkB-targeted or BDNF-pathway-related compounds with substantive pharmacology programs, with priority on those that share 7,8-DHF's research positioning as neurotrophic agents.

12.1 R13 (BrAD-R13, Braegen-01)

Mechanism: Carbamate ester prodrug of 7,8-DHF. Hydrolyzed in vivo to release the parent compound 7,8-DHF, which activates TrkB. The mechanism of action is identical to the parent compound; the pharmacokinetic profile is improved.

Development trajectory: Developed by the Ye laboratory at Emory University. Advanced through extensive preclinical characterization in 5XFAD Alzheimer's disease mice with dose-dependent cognitive improvement, amyloid-beta reduction, and tau pathology attenuation [6]. Entered Phase 1 clinical evaluation for Alzheimer's disease under the BrAD-R13/Braegen-01 designation [25]. Additional preclinical programs span ALS, Parkinson's disease, depression, and schizophrenia.

Novelty: Low. The mechanism is identical to the parent compound; the novelty is exclusively pharmacokinetic.

Effect size: Moderate to large in preclinical Alzheimer's disease models. Dose-dependent cognitive improvement in 5XFAD mice at oral doses corresponding to improved 7,8-DHF exposure relative to the parent compound [6].

Promising potential: Moderate. Phase 1 clinical status represents the most advanced clinical translation of any TrkB small-molecule agonist. The outcome of Phase 1 will determine trajectory.

Side-effect profile: Preclinical safety data are favorable and consistent with the parent compound profile. No human safety data published.

Overall validation: Moderate. The compound is the clinical-stage derivative of the most extensively studied small-molecule TrkB agonist. Clinical validation is pending.

Comparison to 7,8-DHF: R13 is the pharmacokinetically optimized form of 7,8-DHF. The two compounds share identical receptor pharmacology; the distinction is entirely in ADME properties. R13 is the preferred compound for clinical translation; 7,8-DHF remains the preferred compound for basic research owing to its simpler chemistry, wider commercial availability, and the larger published literature base.

12.2 LM22A-4

Mechanism: Non-peptide partial agonist of TrkB, identified through an in silico screen for compounds mimicking the BDNF Loop 2 domain. Binds TrkB selectively over TrkA, TrkC, and p75NTR. EC50 for TrkB activation reported at 200 to 500 pM with approximately 85 percent intrinsic activity [42].

Development trajectory: Developed by Massa et al. (2010) at the University of California San Francisco [42]. Evaluated in preclinical models of traumatic brain injury, Rett syndrome, Huntington's disease, myelin repair, and optic neuropathy. Not advanced to clinical trials in published reports.

Novelty: Moderate. The in silico design approach and the selective TrkB partial agonist mechanism are distinct from the natural-product-derived 7,8-DHF.

Effect size: Moderate in preclinical models. However, LM22A-4 has poor blood-brain barrier penetration when administered systemically, requiring intranasal administration to achieve central TrkB activation [42]. This limitation reduces the translational effect size relative to orally bioactive compounds.

Promising potential: Low. No clinical development. The blood-brain barrier limitation is a significant translational obstacle.

Side-effect profile: No material safety concerns in preclinical studies. The selective TrkB partial agonist mechanism is theoretically favorable.

Overall validation: Low to moderate. Extensive preclinical literature but limited by route-of-administration constraints. The Boltaev et al. (2017) report questioned whether LM22A-4 directly activates TrkB under stringent assay conditions [26].

Comparison to 7,8-DHF: 7,8-DHF has the advantages of oral bioavailability, blood-brain barrier penetration, and a substantially larger published literature. LM22A-4 has the advantage of rational design from the BDNF Loop 2 structure but is limited by route-of-administration constraints. The two compounds are useful as complementary research tools for dissecting TrkB-dependent mechanisms.

12.3 Deoxygedunin

Mechanism: Natural product limonoid isolated from *Azadirachta indica* (neem). Reported to activate TrkB in a BDNF-independent manner and to promote downstream Akt and ERK signaling. Orally available and brain-penetrant in rodent species [43].

Development trajectory: The compound was characterized by Jang et al. (2010, distinct from the 7,8-DHF discovery paper) as a TrkB agonist identified through the same cell-based screening platform [43]. Preclinical evaluation has been limited to proof-of-concept studies in depression and neurodegeneration models. Not advanced to clinical development.

Novelty: Moderate. The limonoid scaffold is structurally distinct from the flavone class.

Effect size: Modest in published preclinical reports. The compound has a narrower published evidence base than 7,8-DHF.

Promising potential: Low. No clinical development. The TrkB agonist activity was questioned by Boltaev et al. (2017) [26].

Side-effect profile: Limited preclinical safety data. The limonoid class has known biological activities beyond TrkB (including anti-inflammatory and anti-proliferative effects) that may complicate the safety profile.

Overall validation: Low. Limited preclinical evidence, no clinical data, and questioned mechanism.

Comparison to 7,8-DHF: 7,8-DHF has a substantially larger evidence base, better characterized pharmacokinetics, and a prodrug in clinical development. Deoxygedunin is principally a historical comparator and a structurally distinct research tool.

12.4 Amitriptyline (as TrkB agonist)

Mechanism: Tricyclic antidepressant. Jang et al. (2009) reported that amitriptyline directly binds TrkA and TrkB extracellular domains, promotes receptor dimerization, and activates downstream neurotrophic signaling [44]. This represents a repurposing of a compound whose primary clinical mechanism is inhibition of serotonin and norepinephrine reuptake.

Development trajectory: Amitriptyline is a registered medicine approved in numerous jurisdictions for depression, neuropathic pain, migraine prophylaxis, and other indications. The TrkB agonist activity was identified as a secondary mechanism that may contribute to the antidepressant effect through neurotrophic pathways [44]. No clinical development specifically for the TrkB agonist application.

Novelty: Low for the compound (decades-old antidepressant); moderate for the TrkB agonist mechanism discovery.

Effect size: The TrkB agonist contribution to amitriptyline's clinical antidepressant effect is difficult to isolate from its monoamine reuptake inhibition. Preclinical TrkB activation is reported at concentrations achievable at clinical doses, but the relative contribution of TrkB agonism versus monoamine reuptake inhibition to the antidepressant effect is unclear.

Promising potential: Low as a dedicated TrkB agonist therapeutic. The compound's established clinical use is driven by monoamine mechanisms. The Boltaev et al. (2017) report questioned the directness of TrkB activation [26].

Side-effect profile: Well characterized from decades of clinical use. The tricyclic antidepressant class carries significant adverse effects including anticholinergic effects, cardiac conduction abnormalities, sedation, weight gain, and overdose lethality, none of which are related to TrkB agonism.

Overall validation: Low as a TrkB agonist; high as a clinical antidepressant through monoamine mechanisms.

Comparison to 7,8-DHF: Amitriptyline illustrates the complexity of attributing in vivo neurotrophic effects to direct TrkB agonism in multi-target compounds. 7,8-DHF has substantially greater TrkB selectivity and does not carry the anticholinergic, cardiac, and sedative liabilities of the tricyclic antidepressant class. For research applications requiring selective TrkB activation, 7,8-DHF is the preferred tool compound.

12.5 CF3CN (optimized 7,8-DHF derivative)

Mechanism: Synthetic derivative of 7,8-DHF with optimized pharmacokinetic properties. Designed to maintain TrkB agonist activity while improving oral bioavailability and metabolic stability relative to both the parent compound and R13 [45].

Development trajectory: Reported by the Ye laboratory as part of the ongoing medicinal chemistry optimization of the 7,8-DHF scaffold. Preclinical evaluation demonstrated dose-dependent reduction of amyloid-beta 42 in 5XFAD mice [45]. The compound represents a later-generation derivative in the structure-activity relationship program. Not advanced to clinical development.

Novelty: Low. The mechanism is identical to 7,8-DHF; the structural modification optimizes ADME properties.

Effect size: Comparable to or modestly improved over R13 in preclinical Alzheimer's disease models based on amyloid-beta 42 reduction endpoints [45].

Promising potential: Low to moderate. Preclinical only. Depends on whether the pharmacokinetic improvements over R13 are sufficient to warrant independent clinical development.

Side-effect profile: Limited preclinical data. Expected to be comparable to the parent compound.

Overall validation: Low. Early-stage preclinical derivative without independent clinical or extensive pharmacological characterization.

Comparison to 7,8-DHF: CF3CN represents an incremental pharmacokinetic improvement within the same chemical scaffold and mechanism. 7,8-DHF remains the reference compound for the class; CF3CN is a development-stage derivative of interest for future clinical programs.

12.6 Comparator summary

The five compounds occupy distinct positions relative to 7,8-DHF. **R13** is the clinical-stage prodrug with identical receptor pharmacology and improved pharmacokinetics, representing the most promising translational path. **LM22A-4** is a rationally designed partial agonist limited by poor blood-brain barrier penetration. **Deoxygedunin** is a structurally distinct natural product with a narrow evidence base and questioned mechanism. **Amitriptyline** is a registered multi-target antidepressant whose TrkB agonist activity is secondary and difficult to isolate clinically. **CF3CN** is an optimized derivative at early preclinical stage.

7,8-Dihydroxyflavone occupies the central position in this landscape as the foundational TrkB agonist small molecule: it has the largest published evidence base (over 500 publications), the broadest preclinical disease coverage (more than 15 disease models with positive pharmacology), oral bioavailability and blood-brain barrier penetration sufficient for proof-of-concept studies, a favorable chronic safety profile in rodents and non-human primates, and a clinical-stage prodrug (R13) in Phase 1 evaluation. The principal limitations are the modest oral bioavailability of the parent compound, the absence of human clinical data for 7,8-DHF itself, and the ongoing methodological controversy regarding the directness of TrkB activation.

The practical question for investigators is whether to use 7,8-DHF directly (adequate for preclinical research and mechanistic studies at 5 mg/kg oral or intraperitoneal in rodents) or to use R13 (preferred for studies requiring higher and more sustained TrkB occupancy). For fundamental receptor pharmacology, 7,8-DHF remains the reference tool compound. For translational research programs aligned with clinical development, R13 is the preferred derivative.

13. References

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