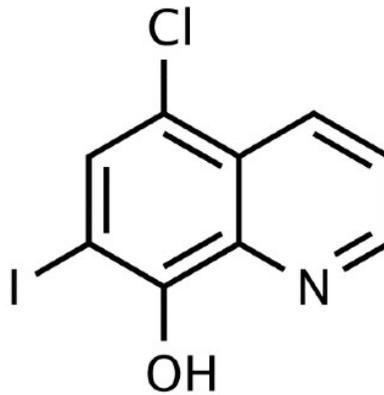


# CINAPS Compound Dossier

## Clioquinol



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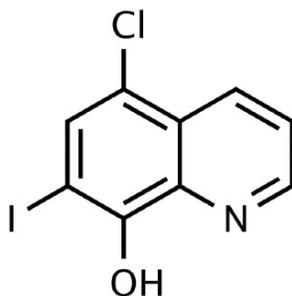


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## I. Compound Information

**Common name:** Clioquinol



**Structure:**

**PubChem ID:** 2788 **Mol. formula:** C<sub>9</sub>H<sub>5</sub>ClINO **FW:** 305.5

**CASRN:** 22112-03-4; 130-26-7 **Polar surface area:** 33.12 **logP:** 3.36

**IUPAC name:** 5-Chloro-7-iodoquinolin-8-ol

**Other names:** Vioform; iodochlorhydroxyquin

**Drug class:** Metal chelator; antifungal (topical); antiviral; anti-protozoal

**Medicinal chemistry development potential:** Moderate

## II. Rationale

### Ila. Scientific Rationale / Mechanism

Clioquinol was originally approved as an oral antibiotic, antifungal and amoebicidal with particular activity against *Trichomona* sp. Over 500 million patients worldwide had received clioquinol as an oral agent<sup>1</sup> prior to its withdrawal by Japan in 1970, and by other regulatory agencies, as a result of 10,000 cases of subacute myelo-optico-neuropathy (SMON) during the 1960's.<sup>2</sup> While the incidence of SMON, at the time was attributed to clioquinol exposure and toxicity, current thinking indicates that the post-war diet in Japan may have lacked sufficient vitamin B12 and this may have been a significant contributing factor in of the SMON incidence. Indeed, 25% of the total number of SMON cases reported in Japan at the time were not taking clioquinol in any form and there were, over the same time period, only 220 cases reported in the rest of the world.<sup>1</sup>

The more recently proposed use of clioquinol in patients suffering from neurodegenerative disorders (Parkinson's disease and Alzheimer's disease in particular) is targeted at a fraction of the dose level used in the 1960's and includes co-administered with vitamin B12 supplementation.<sup>1</sup>

The neuroprotective actions of clioquinol are thought to relate directly to its metal ion chelating activity, particularly that of iron, zinc and copper. These metal ions catalyze the production of reactive oxygen species and are thought to play a major role in the oxidative stress related to most neurodegenerative disorders.<sup>3-8</sup> Dexter *et al.* (1989) demonstrated a significant elevation in iron and zinc levels in the substantia nigra (total or zona compacta alone) of post-mortem human brains from Parkinson's patients, as compared to control samples from patients who presented no neurological impairment at the time of death.<sup>3</sup> Copper levels in the substantia nigra were lower in Parkinson's patients than controls, and manganese levels were lower in Parkinsonian putamen than controls. Sđic *et al.* (1991) reported similar differences for iron levels of in the substantia nigra zona compacta of Parkinson's patients relative to controls. was reported by Sđic *et al.* (1991). Interestingly, Sđic *et al.* (1991) clarified the ionic state of the iron and demonstrated that the increase was predominantly in iron (III) and that the normal balance of 2:1 iron (II) to iron (III) was inverted to 1:2.<sup>7</sup>

An complication arose during development of clioquinol as a potential neuroprotective agent. Prana Biotechnology (Melbourne, Australia) was developing clioquinol (PBT1) when it came into dispute with P.N. Gerolymatos, S.A. (PNG) over the right to exploit several clioquinol patent claims. In 2004 the two companies settled out of court with Prana retaining the rights to

clioquinol in their primary markets (i.e., the U.S. and Japan) and PNG retaining the rights in Europe and other territories (see [www.pranabio.com](http://www.pranabio.com)). Prana had achieved Clinical Trials Authorization to advance PBT1 (clioquinol) into a pivotal Phase 2/3 trial in Alzheimer's patients during 2004 when the program was cancelled. Prana Biotech reported ([www.pranabio.com](http://www.pranabio.com)) that they had encountered impurities related to the synthesis of clioquinol. These *di*-iodo forms of PBT1 could not be readily removed or avoided with a refined synthetic path and they carried a significantly greater toxicity. Prana reported, "...increased risks of side-effects and mutagenicity" and that these impurities could not be reduced to adequately safe levels to permit continued development. They have switched their product development focus to PBT2 – another metal chelating agent with neuroprotective potential.

Given the particular demographics and socio-economic factors impacting the SMON findings in Japan during the 1960's, and the significantly lower dose range thought to be neuroprotective (i.e., extrapolating from animal efficacy models) it seems that continued development of clioquinol as a potential neuroprotective agent is feasible. However, elimination of the toxic impurities discussed by Prana Biotech in 2004 could be a significant hurdle for production of GMP test material for large-scale clinical efficacy trials in Phase 2/3.

## **IIb. Consistency**

n/a

## **III. Efficacy (Animal Models of Parkinson's Disease)**

### **IIIa. Animal Models: Rodent**

Kaur *et al.* (2003) have demonstrated that iron chelation, either through transgenic over-expression of the iron sequestering protein ferritin, or through the administration of clioquinol to mice protected against MPTP-induced loss of substantia nigral cells. Interestingly, over-expression of ferritin also decreased measures of oxidative stress in substantia nigra neurons<sup>5</sup> but this effect was not observed with clioquinol. Kalivendi *et al.* (2003) demonstrated that MPP<sup>+</sup>-induced apoptosis and mitochondrial oxidant generation in cerebellar granule cells and SH-SY5Y cells could be inhibited or completely blocked by various iron chelating approaches (e.g., a metalloporphyrin antioxidant enzyme mimic [FeTBAP], over-expression of glutathione peroxidase, or pretreatment with the lipophilic, cell permeable iron chelator HBED).<sup>9</sup>

### **IIIb. Animal Models: Non-human primates**

n/a

## **IV. Efficacy (Clinical and Epidemiological Evidence)**

### **IVa. Clinical Studies**

No clinical efficacy studies have been performed with clioquinol in Parkinson's disease.

### **IVb. Epidemiological Evidence**

n/a

## **V. Relevance to Other Neurodegenerative Diseases**

Early (phase 1) studies have been conducted with the intention of pursuing clioquinol for Alzheimer's disease but, as noted above, the development of this compound was dropped owing to problems in synthesizing clioquinol without the more toxic di-iodo impurities (see Section IIa).

Ritchie *et al.* (2003) published findings from a pilot phase 2 study in Alzheimer's patients, targeting the dissolution of deposited  $\beta$ -amyloid by the removal or chelation of the zinc and copper ions thought to be responsible for precipitation of soluble  $\beta$ -amyloid plaques.<sup>6</sup> Clioquinol was dosed at 3.3 mg/kg/day [as compared to FDA's listed Maximum Reasonable Tolerated Dose in man of 25 mg/kg/day ([www.fda.gov](http://www.fda.gov))] along with a vitamin B12 supplement and there was no significant increase in reported adverse events as compared to controls.

In a transgenic mouse model of Alzheimer's disease (TgCRND8), clioquinol was reported to alter brain concentrations of biometals (i.e., copper, zinc, and iron), to reduce the amyloid-beta plaque burden in cortex and hippocampus (i.e., the same brain regions where the drug was found to be localized), to attenuate astrogliosis, and to reverse working memory impairments.<sup>10</sup>

## **VI. Pharmacokinetics**

### **VIa. General ADME**

With the use of clioquinol as a clinical anti-infective, the pharmacokinetics has clearly been defined in very early studies. More recent publications, including the 2008 review by Mao and Schimmer, provide some insight into absorption and metabolism of clioquinol.<sup>11</sup> Kotaki *et al.* (1983) reported a  $T_{max}$  of 30 min to 1 h following ip dosing to rats of 100 and 200 mg/kg.<sup>12</sup> In humans  $T_{max}$  was typically closer to 4 h after ingestion (oral dosing) and the clinical half-life was between 11 h and 14 h. Using <sup>14</sup>C-labeled clioquinol, approximately 25% of a 750 mg oral dose is excreted in the urine over 72 hours. After daily dosing for a week, plasma levels of clioquinol fell to undetectable levels within 3 days after cessation of dosing.<sup>13</sup> Once absorbed clioquinol is metabolized to sulfate and glucuronide derivatives, and it is excreted as both free clioquinol and

as the metabolites.<sup>14</sup> In a more recent study of clioquinol in Alzheimer's disease, Ritchie *et al.* (2003) found through serum levels in a the range of 13  $\mu$ M to 25  $\mu$ M, concentrations adequate to produce substantial chelation of zinc and iron in test patients.

#### **VIb. CNS Penetration**

No direct assessment of CNS penetration has been performed but the neurotoxicity at high doses and the efficacy in several CNS models strongly implies good CNS penetration.

#### **VIc. Calculated log([brain]/[blood]) (Clark Model)**

0.16

### **VII. Safety, Tolerability, and Drug Interaction Potential**

#### **VIIa. Safety and Tolerability**

Since clioquinol has been used clinically for many years there is considerable historical data on the toxicity of the compound. Aside from the clinical indications of SMON that have been attributed to a concomitant dietary deficiency of B12, there are many published reports of toxicology studies in laboratory animals.<sup>11</sup>

**Rodents:** In rodents, i.p. clioquinol i.p. was not well tolerated by male Wistar rats, with animals dying in every dose level tested (200, 300, and 400 mg/kg/day for 7 days). In the surviving animals, optic nerve and dorsal root ganglion changes were observed at all three dose levels.<sup>15</sup> Ataxia was observed in the same rat strain after 1 week of treatment at 400 mg/kg/day i.p..<sup>16</sup> Similarly, Kotaki *et al.* (1983) demonstrated a NOAEL of 100 mg/kg/day and neurological symptoms at 200 and 300 mg/kg/day i.p. in male Wistar rats.<sup>12</sup>

In mice (strains not specified), LD50 values have been reported between 100 mg/kg and 1300 mg/kg depending on the strain.<sup>17</sup>

**Dogs:** Over 20 studies have been performed in dogs with clioquinol. Typical signs of toxicity were related to unsteady gait and convulsions, hyperreflexia, anemia, weight loss and emaciation.<sup>18-20</sup> Further to these effects, neurological deficits have been reported in many studies dosing orally or intraperitoneally at doses of 200 mg/kg/day and higher. Table 1 below (from Mao and Schimmer, 2008<sup>11</sup>) provides a summary of those studies reporting neurotoxicity. Neurological deficits presented primarily in issues of gait, ataxia and some reports of paralysis. Pathology changes were observed at the level of the posterior spinal cord and optic nerves. Typically, the duration of clioquinol exposure was greater than 7 days, and in some cases up to 70+ days for presentation of neurotoxicity. The general dose range and exposure level related to neurotoxicity was 100+ fold that of the anti-tumor concentrations.<sup>11</sup>

Similar to rodents, the NOAEL for clioquinol across studies in dogs would be estimated at around 100 mg/kg/day for 7 days or longer.<sup>11</sup>

Species	Dose (mg/kg/day)	References
Rat	400	15
“	400	16
“	200, 400	12
Cat	240	21
Dog	400	19
“	250	20
“	300	23, 24
“	200	25, 26
“	400	18
Baboon	600	22

**Table 1:** Animal studies reporting neurotoxicity with clioquinol. Selected animal studies reporting neurotoxicity after systemic administration of clioquinol are summarized. Studies with ambiguous dosing schedules have not been included in the table.<sup>11</sup>

**Other Species:** Some additional toxicology data is available from cats and baboons.<sup>21, 22</sup> In the cat, clioquinol dose escalation from 45 mg/kg/day to 240 mg/kg/day over the course of 200 days lead to decreased conduction in the peripheral nerves as compared to control cats.<sup>21</sup> In the baboon, no neurotoxicity was observed following 28 weeks of 200 mg/kg/day orally administered clioquinol administered orally. However, during dose escalation from 600 mg/kg/day to 1,500 mg/kg/day, 8 of 10 baboons lost weight and one of ten developed neurotoxicity at 600 mg/kg/day and an additional five developed neurotoxicity at 1,500 mg/kg/day.<sup>22</sup>

#### VIIb. Drug Interaction Potential

n/a

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