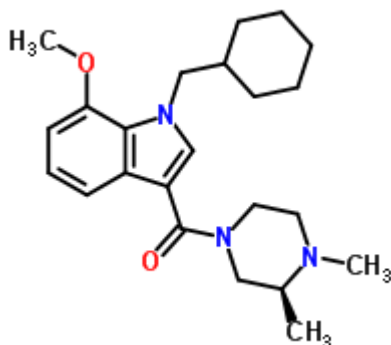


Org 28611 (SCH 900111)

Org 28611, a potent cannabinoid receptor full agonist at both the CB₁ and CB₂ receptors, was developed by Organon International with the aim of finding a water soluble cannabinoid agonist suitable for intravenous use as an analgesic, and while it achieved this aim and has progressed as far as Phase II clinical trials in humans as both a sedative and an analgesic, results against the comparison drugs (midazolam and morphine respectively) were not particularly favourable in initial testing.



C₂₃H₃₃N₃O₂

[1-(Cyclohexylmethyl)-7-methoxy-1H-indol-3-yl][(3S)-3,4-dimethyl-1-piperazinyl]methanone

Solubility, Binding, and Pharmacokinetic Profile

In general, the cannabinoid receptor agonists known in the literature are characterized by high lipophilicity, poor water solubility and suboptimal pharmacokinetic profiles, which have hampered their evaluation as therapeutic agents. A new series of intrinsically water soluble, drug-like indole-3-carboxamide CB₁ receptor agonists that has been designed and synthesized in the laboratory was reported.

Compounds **33** (Org 28611, pEC₅₀ 7.6; solubility 2809 mg/L at pH 4.9 and 129 mg/L at pH 6.9) and **34** (Org 28312, pEC₅₀ 7.6; solubility >4000 mg/L at pH 5.0 and 12 mg/L at pH 7.0) were selected for further profiling based on their overall solubility, potency and efficacy profiles.

Org 28611 exhibited high affinity for both CB₁ (pK_i 8.9) and CB₂ (pK_i 8.8) cannabinoid receptors, as determined by radioligand competition binding assays using [³H]CP 55,940 binding to either hCB₁ or hCB₂ receptors expressed in insect Sf9 membranes. Also, the compound exhibited good general selectivity, with greater than 100-fold selectivity against a panel of 42 unrelated molecular targets, including the hERG channel (data not shown).

The *in vitro* and *in vivo* drug metabolism (DMPK) profiles of Org 28611 revealed that it was rapidly metabolized (>270 CL_{int}/μl/min/mg) by mouse and human hepatic microsomes. Mouse brain and plasma levels were determined following intravenous administration of a 3 μmol/kg dose (terminal sampling using CO₂). Org 28611 was rapidly cleared *in vivo*, as predicted from the rapid microsomal metabolism. Org 28611 also showed higher total levels in brain compared to plasma (B:P C_{max} ratio of 4.0). Brain concentration vs. time profiles for this compound mirrored the profiles seen in plasma indicating rapid equilibration across the blood–brain barrier.

Antinociceptive Activity

Org 28611 demonstrated potent antinociceptive activity in the mouse tail flick test, a preclinical threshold model of nociception. Intravenous administration of Org 28611 (0.2 – 1.0 μmol/kg) increased tail flick latency in a dose-dependent manner with a rapid onset and a longer duration of

action as compared to Org 28312 (return to the baseline value following a twice ED₅₀ dose being 90 min for Org 28611 and 50 min for Org 28312).

Org 28611 also demonstrated potent antinociceptive activity in the mouse formalin paw test, a model that assesses behavioral responses to continuous, noxious stimulation generated by injection of a dilute solution of formalin into one hindpaw. The injection of formalin induces an inflammatory response in the paw that elicits licking behavior in two distinct phases, an early phase of 4-5 min immediately after injection and a second phase of nociceptive behavior (20–30 min) after a quiescent phase of 5–10 min. Both Org 28611 and Org 28312, administered intravenously (0.01–0.3 µmol/kg), dose-dependently reduced the amount of time spent licking the injected paw during both phases of licking.

Antinociception produced by either compound in this test was antagonized by the selective CB1 receptor antagonist SR141716A (rimonabant), indicating that their activity in this model was mediated by activation of CB1 receptors (data not shown). Following further preclinical evaluation, Org 28611 was selected as a development candidate for clinical evaluation as a potential intravenous peri-operative analgesic agent.

Reference :

Julia M. Adam, Jim Cairns, Wilson Caulfield, Phillip Cowley, Iain Cumming, Morag Easson, Darren Edwards, Morag Ferguson, Richard Goodwin, Fiona Jeremiah, Takao Kiyoi, Ashvin Mistry, Elizabeth Moir, Richard Morphy, Jason Tierney, Mark York, James Baker, Jean E. Cottney, Andrea K. Houghton, Paul J. Westwood and Glenn Walker. Design, synthesis, and structure–activity relationships of indole-3-carboxamides as novel water soluble cannabinoid CB1 receptor agonists, Med. Chem. Commun., 2010, 1, 54.

Pharmacokinetic/Pharmacodynamic Analyses (PK/PD)

In human subjects, Org 28611 did not have a rapid onset of action like midazolam. Maximum Org 28611 concentrations were reached at the end of the infusion indicating that steady state was not reached. This is confirmed by the mean concentration versus time profiles during and after infusion. The maximum concentration of Org 28611 that was found in a 24 h blood sample was 0.4 ng/mL in a single subject.

In addition, Org 28611 had a much longer half-life than midazolam. For the 25 min infusion, the PK parameters were elimination half-life 3.5–5.5 h, clearance 13.7 L/h, whereas, for the bolus dose administration, elimination half-life 6–10 h and clearance 11.4 L/h. These characteristics make Org 28611 less suitable for short-outpatient treatments.

Cardiovascular Effect

In general, cardiovascular effects of Org 28611 in rodents were comparable with the effects of the reference compound, THC. Org 28611 causes dose-dependent bradycardia and hypotension but does not induce respiratory depression (Organon, data on file).

After infusion of Org 28611 (>6 µg/kg) in humans, an increase in heart rate by 16-17% was observed. However, no changes in heart rate were observed after bolus administration of Org 28611 (≤3 µg/kg). In this study, blood pressure was not changed by Org 28611.

Sedation

Rodent models showed that Org 28611 has sedative properties in addition to analgesic effects. In human study, Org 28611 did not cause the same type of conscious sedation as midazolam and, in contrast, it showed a discrepancy between subjective and objective sedation. The scores for VAS alertness, an indication for subjective sedation, were significantly lower scores after infusion of Org

28611 (at doses above 1 µg/kg) compared with placebo. However, subjects were awake and reacted quickly to verbal stimuli as observed on the Observer's Assessment of Alertness/Sedation.

In addition, Org 28611 did not change saccadic peak velocity movements, an objective measure of sedation for benzodiazepines. There is a possibility that higher doses of Org 28611 would have induced conscious sedation, but this was precluded by pronounced subjective effects, including reduced calmness and psychomimetic effects.

Subjective Effect

Org 28611 (either administered as a slow 25 min infusion or a bolus dose in healthy human subjects) caused pronounced subjective and psychomimetic effects that did not seem to agree with the usual pleasant effects of relaxation and mild euphoria seen after recreational cannabis use.

Doses higher than the maximum tolerated dose (3 µg/kg) of Org 28611 caused untoward psychiatric (anxiety, derealisation, hallucinations, altered body perception), and psychotropic (feeling high) effects and diminished mood and calmness. The composite score of internal and external perception on the Bowdle visual analogue scales (VAS) was higher after slow 25 min infusion of Org 28611 (6 µg/kg and higher).

Anterograde Amnesia

Although the highest two doses of Org 28611 caused an impairment of active immediate and delayed recall (retrieval difficulties of newly stored information), unlike, midazolam, there was a remarkable preservation of the number of recognized (and hence stored) words during the delayed recognition phase of the memory test.

Although impaired retrieval may reduce the capacity of the patient to recall the details of a surgical or diagnostic procedure, it is unclear how retained storage with diminished retrieval would affect the subconscious impact of a traumatic experience. Moreover, this only seems to be relevant for higher doses of Org 28611, because no memory effects were observed with doses up to 3 µg/kg.

Reference:

Zuurman L, Passier PC, de Kam M, Kleijn HJ, Cohen AF, van Gerven JM. Pharmacodynamic and pharmacokinetic effects of the intravenously administered CB1 receptor agonist Org 28611 in healthy male volunteers. *J Psychopharmacol.* 2009 Aug;23(6):633-44.

Clinical Trial

A Comparison of Analgesic Efficacy Between a Single Dose of ORG 28611, Morphine, and Placebo After Dental Impaction Surgery (Organon International Study P05800)

Enrollment: 11; Study Start Date: July 2007

Patients will receive a single intravenous (IV) infusion administered over 3 minutes of either ORG 28611 (SCH 900111), 0.12 mg/kg morphine sulphate, or placebo, within 6 hours after dental surgery, when they experience moderate to severe dental pain. Patient will then be evaluated with pain assessments (total pain relief score, pain intensity on a visual analog scale, pain relief on a categorical scale with intensity difference, and other parameters) at Baseline, 5, 10, 15, 30, 45, 60, and 90 minutes; and 2 through 8 hours or before rescue medication is needed.

Dec 08: Study terminated due to lack of efficacy compared to other pain killers at a safe dose (no publication).

Source: <http://clinicaltrials.gov/ct2/show/NCT00782951>