Safinamide
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I. Compound Information

**Common name**: Safinamide

**Structure**:

![Structure of Safinamide](image)

- **PubChem ID**: 131682
- **Mol. Formula**: C_{17}H_{19}FN_{2}O_{2}
- **FW**: 302.34
- **CASRN**: 133865-89-1
- **Polar surface area**: 64.4
- **logP**: 2.2

**IUPAC name**: (2S)-2-(((4-((3-Fluorophenyl)methoxy)phenyl)methyl)amino)propanamide

**Other names**: FCE 26743 [(S)-isomer], FCE 28073 [(R)-isomer]

**Drug class**: monoamine oxidase B inhibitor; dopamine reuptake blocker; and glutamate release inhibitor

**Medicinal chemistry development potential**: High

**Notes**: CINAPS Dossier: Safinamide (3/29/2009)
II. Rationale

IIa. Scientific Rationale / Mechanism

The principle biochemical/neurochemical bases for the therapeutic actions of safinamide (SAF) involve inhibition of monoamine oxidase B (MAO-B), inhibition of dopamine reuptake, and blockade of glutamate release.

**MAO-B inhibition**

SAF is a potent, selective inhibitor of MAO-B in vivo and in vitro that has minimal effect on MAO-A activity. An in vitro IC₅₀ of 100 nm has been determined for SAF (Benedetti, 1994; Caccia, 2006; Chazot, 2001). The inhibition is reversible, but >95% inhibition of MAO-B is observed clinically at dose levels that are efficacious and well-tolerated. The ED₅₀ for MAO-B was ca. 90 μg/kg/day in clinical studies, and no inhibition of MAO-A was observed after 10 mg/kg oral doses (Cattaneo, 2003). The therapeutic benefit MAO-B inhibition in the treatment of Parkinson disease derives from inhibition of the metabolism of dopamine (DA) and dopaminergic agents, as well as diminishing damaging free radical production coincident with DA metabolism (Bonuccelli, 2006).

In the initial stages of PD, L-DOPA is effective in treating motor symptoms, but long-term treatment with L-DOPA has its drawbacks and is accompanied by many side effects, including motor fluctuations and dyskinesias (Bonuccelli, 2006; Chazot, 2007). As such, delaying and minimizing the use of L-DOPA is of benefit, and inhibition of MAO-B by SAF makes it valuable in conjunction with dopamine replacement therapy. Accordingly, it is a successful adjunct to L-DOPA and synergistic with dopamine agonist therapy, and coadministration of SAF improved UPDRS (Unified Parkinson's Disease Rating Scale) motor scores and cognitive function (Chazot, 2007).

It has been noted that, while there was a dose-response in SAF efficacy in combination with dopamine agonists (as measured by UPDRS scores), MAO-B was “fully” inhibited throughout that range, suggesting that SAF exerts its effects through “additional mechanisms of action, such as inhibition of glutamate release, increased dopamine release, or inhibition of dopamine reuptake” (Stocchi, 2006).

**Dopamine reuptake inhibition.**

The literature reviewed noted “dopamine reuptake inhibition,” but did not cite specific measurements of that process. Rather, the assumed consequence of MAO-B inhibition was diminished breakdown of DA and β-phenethylamine, the latter of which inhibits neural dopamine reuptake (Fernandez, 2007; Stocchi, 2004).

**Inhibition of glutamate release**

Voltage-dependent sodium and N-type calcium channel blockade provides the basis for inhibiting glutamate release (Chazot, 2001; Chazot, 2007). The balance of glutamate/GABA achieved by SAF is of therapeutic benefit in the treatment of PD (Fredriksson, 1999; Onofrj, 2008), as is the balance of other pharmacological actions including inhibition of glutamate release, inhibition of MAO-B, and blockade of dopamine.
II. Rationale (cont.)

reuptake (Stocchi, 2004). Although it was noted that inhibition of glutamate release should occur at the doses used (in clinical studies), its exact role is still under investigation (Stocchi, 2006).

Neuroprotection

Prolonged opening of veratridine-sensitive Na$^+$ channels in neuron cultures results in Ca$^{2+}$-dependent cell degeneration. SAF was neuroprotective in vitro in reducing veratridine-induced neuron cell death via blockade of opening voltage-dependent Na$^+$ and Ca$^{2+}$ channels (Caccia, 2006).

Since MPTP is converted to the proximate neurotoxin, MPP+, by MAO-B, it is not unexpected that pretreatment with SAF protects against MPTP-induced cell body degeneration in the substantia nigra (Chazot, 2001). However, SAF (20 mg/kg) also prevented dopaminergic neuron loss in rats when given 4 h after MPTP, a timepoint at which the transformation to the toxic metabolite MPP+ had already occurred (Caccia, 2006; Chazot, 2001). This indicates protective mechanisms in addition to inhibition of MAO-B. In another model of PD, SAF (10 mg/kg) prolonged the rotational response to L-DOPA in 6-hydroxydopamine-lesioned rats.

Bilateral carotid occlusion (BCO) in animal models is an accepted model of transient ischemia resulting in hippocampal neuron loss. SAF (100 mg/kg ip in gerbil 30 min before and after BCO) almost completely prevented neuron damage (Caccia, 2006).

Kainic acid, a rigid analog of glutamate, also induces hippocampal degeneration. SAF (10 mg/kg), administered 15 min before kainic acid, protects against hippocampal neuron loss (Caccia, 2006).

Other potential biochemical mechanisms explored

SAF is not a dopamine agonist, nor is it an inhibitor of COMT, or of L-DOPA decarboxylase, each of which are mechanisms exploited in therapeutics for treatment of PD (Bonuccelli, 2006; Fariello, 2007; Onofrj, 2008). SAF has low affinity for 5-HT, glutamate, dopamine, nicotinic, muscarininc and GABA receptors (Chazot, 2001).

Ilb. Consistency

n/a
III. Efficacy (Animal Models of Parkinson's Disease)

Ill.a. Animal Models: Rodent

SAF had a neuroprotective effect in animal models of PD, specifically protection against chemically-induced neurotoxicity associated with MPTP or 6-hydroxydopamine (6-OHDA) administration in rodents. Briefly, SAF prevented dopamine depletion and neuronal death in the substantia nigra in mice (Caccia, 2006; Fariello, 2007; Fredriksson, 1999; Onofrj, 2008) and in rats (Chazot, 2001). MPTP was also used in a model of the “wearing off effect” in rats, where L-DOPA tolerance was reversed in rats and mice administered SAF and D-DOPA (Archer, 2002; Caccia, 2006). For additional detail see Section IIa., Scientific Rationale/Mechanism.

SAF also prevented damage caused by free radicals associated with ischemia secondary to bilateral occlusion in gerbils (Caccia, 2006; Fariello, 2007). Diminution of free radical damage secondary to MAO-B inhibition, which has the effect of decreasing radicals produced during the metabolism of dopamine, was also linked to the protective effect of SAF in animal models (Bonuccelli, 2006; Chazot, 2007).

The effect of modulating neurotransmitters, in particular via inhibition of glutamate release, was demonstrated in animal models and cultured cells derived from them. SAF protected against the damage to hippocampal neurons in rats caused by the rigid glutamate analog, kainic acid (Caccia, 2006; Chazot, 2007). Using primary cortical rat neurons, the activity of SAF in blocking \( \text{Na}^+ \) and \( \text{Ca}^{++} \) channels resulted in neuroprotection (Caccia, 2006; Chazot, 2001; Chazot, 2007).

The pharmacokinetics and toxicity of SAF have been investigated in rodent models, as described in Sections VI and VII.

Ill.b. Animal Models: Non-human primates

No studies of safinamide were found in non-human primate models of PD.
IV. Efficacy (Clinical and Epidemiological Evidence)

IVA. Clinical Studies

SAF has demonstrated efficacy in treating Parkinson’s disease (PD) both as a monotherapy and in combination with other dopaminergic drugs, where its action as an MAO-B inhibitor prolongs the activity of both endogenously and exogenously derived dopamine; it also decreases the toxic products of MAO-B-mediated metabolism of dopamine.

In a phase III trial, 270 patients with early Parkinson disease who were receiving a stable dose of a dopamine agonist were randomly assigned to add SAF at 50-100 mg/day, 150-200 mg/day, or placebo to their ongoing therapy (Fernandez, 2007). Addition of SAF at 50-100 mg/day was associated with significantly greater improvement of UPDRS part III motor scores and part II ADL scores vs. placebo. Also improved were cognitive function (including working memory), strategic target detection, and auditory number sequencing. The higher dose range 150-200 mg/day conferred no extra benefit over the lower dose.

In another study SAF (average dose 70 mg/day) improved UPDRS part III scores, with clinically significant improvements when combined with dopamine agonists vs. the agonists alone (Stocchi, 2004). In a follow up study (Stocchi, 2006), higher doses were used (100, 150, and 200 mg/day). Here again SAF improved the efficacy of dopamine agonists, with improvements in UPDRS part III scores and, when combined with L-DOPA induced a significant decrease in motor fluctuations (UPDRS part IV). Cessation of SAF following successful treatment for 12 weeks was attended by worsening of motor function after 15 days (Chazot, 2007).

IVB. Epidemiological Evidence

n/a
V. Relevance to Other Neurodegenerative Diseases

Although SAF has proceeded to Phase III clinical trials for the treatment of PD, it was initially developed for the treatment of epilepsy (Chazot, 2001; Chazot, 2007; Fariello, 2007; Marzo, 2004). In epilepsy there is an imbalance of inhibitory and excitatory mechanisms within the CNS. The efficacy of SAF in treating epilepsy has been attributed to its action in decreasing excitatory transmission via reduction of glutamate release and control of voltage regulated channels (Chazot, 2007).

The neuroprotective action of SAF was also demonstrated in stroke/reperfusion models in which the damage associated with ischemia and attendant free radical mechanisms was demonstrated in bilateral occlusion experiments in gerbils (Caccia, 2006; Fariello, 2007).
VI. Pharmacokinetics

VIa. General ADME

The pharmacokinetics of SAF has been determined in mice, rats, and monkeys, as well as in clinical trials.

Oral doses ranging from 1.25 to 5.0 mg/kg were given to healthy volunteers in a steady state kinetic evaluation of SAF. Plasma pharmacokinetics (measured for dose day 7) were linear throughout that range; the half-life was found to be 24 h, allowing a once-a-day dosing, and Tmax of was about 2 h (Fariello, 2007). SAF was found to be highly protein bound in plasma (92%). A high fat diet delayed the rate but not extent of absorption. The pharmacokinetics of a broader range of repeat daily oral doses, 25 μg/kg to 10 mg/kg, was reported by Marzo et al. (Marzo, 2004) and Bo et al. (Dal Bo, 2006), inclusive of the data reported by Fariello (Fariello, 2007); a Tmax of 2-4 h and a half-life of 22 h were measured, and steady state was reached after 5 days with an accumulation factor of 1.5 - 1.7.

Oral doses of SAF (10 mg/kg) in rats were well absorbed, with a Tmax of about 20 min, and an elimination half life of about 2 h. Levels in plasma and brain were parallel, but concentrations in brain were about ten-fold higher (Fariello, 2007).

Studies were performed in mice rats, and monkeys after administration of SAF given as a single iv or oral dose or as daily multiple oral doses (Caccia, 2006). SAF is rapidly absorbed, with a Tmax of 0.5-2 h and a terminal half-life of about 3, 7, and 13 h in mice, rats, and monkeys, respectively. Bioavailability was high, ranging from 80-92%. Brain/plasma ratios of SAF were 16, 16, and 9 in mice, rats, and monkeys, respectively. Unfortunately, dose levels were not specified, nor were primary pharmacokinetic parameters tabulated.

Even though SAF has advanced to Phase III clinical trials for PD, there was little information on its metabolism in the literature. A recent account (Onofrj, 2008), with no accompanying data, indicated that, in man, SAF is extensively biotransformed, with only 7-10% and 1.5% excreted unchanged in urine and feces, respectively. After single oral administration, the main SAF-derived components in plasma and two metabolites, ‘safinamide acid’ and the ‘N-dealkylated acid’. In urine, the main metabolites were the ‘safinamide acid’ and the ‘glucuronide of the N-dealkylated acid’. This metabolism was attributed to MAO-A (presumably an N-debenzylation reaction), amidases (cleaving the NH2 to yield safinamide acid), and glucuronyltransferase (presumably forming an acyl glucuronide from the acid formed subsequent to N-benzylation). Ready conversion of the amide to the acid may explain the absence of ‘alaninamide’ in the urine of mice administered SAF (Benedetti, 1994), as ready hydrolysis of the amide would yield alanine as a metabolite, and would be further processed.

Induction and inhibition potential for SAF in modulating P450 enzymes from human and animal sources was markedly low (detailed in section VIIb. Drug Interaction Potential); SAF is a powerful inhibitor of MAO-B, but not MAO-A. This was consistent with the fact that no adjustment of the dose of the anti-epileptic drugs phenobarbital and...
carbamazepine were needed in combination with SAF. However, blood levels of SAF were about 30% lower in repeat dose clinical studies, suggesting that SAF is metabolized by enzymes that are induced by these drugs (Fariello, 2007).

VIb. CNS Penetration

SAF penetrates very well into the brain, as demonstrated by its CNS activity, as well as by direct measurements of brain levels of SAF and brain/plasma ratios in animal studies. As described in the Scientific Rationale/Mechanisms section (IIa.), the pharmacological activity of SAF in improving UPDRS motor scores, cognitive function, inhibition of CNS MAO-B activity, activity at Na⁺ and Ca²⁺ channels, and neuroprotection against agents that target specific areas of the brain all demonstrate delivery of SAF to the CNS. Additionally, the anti-convulsant activity of SAF in rats correlated well with brain levels of the drug throughout the time course of the 8 h experiment; brain levels were ten times those measured in plasma (Fariello, 2007). Similarly, brain/plasma ratios of SAF were 16, 16, and 9 in mice, rats, and monkeys, respectively after oral dosing (Caccia, 2006). The authors calculated that, given this ratio, steady state brain levels of SAF in clinical trials would reach 40-50 μM, well above the measured EC₅₀ for several therapeutic actions of SAF.

Vlc. Calculated log([brain]/[blood]) (Clark Model): -0.48
VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

SAF was characterized as well-tolerated in clinical studies in the literature reviewed, with minor symptoms including headache and dizziness (Chazot, 2001; Fariello, 2007; Fernandez, 2007; Marzo, 2004; Stocchi, 2004; Stocchi, 2006), and other side effects common with many anti-epileptic drugs (Chazot, 2001). In a study of 97 volunteers receiving 10 mg/kg single or 5 mg/kg/day repeat doses, there were only minor side effects, all of which subsided before the end of the study (Fariello, 2007). Clinical chemistries monitored in another study were normal, with the exception of one individual dosed at 5 mg/kg (Marzo, 2004). ALT values were three times higher than normal values, but reverted to the normal range.

Most MAO-B inhibitors lack the specificity of SAF, and inhibit MAO-A as well. Adverse reaction to tyramine (present in foodstuffs such as cheeses and wine) is a well-established consequence of MAO-A inhibition. Consistent with the demonstrated specificity of SAF towards inhibition of MAO-B, but not MAO-A, the pressor effect of tyramine was not exacerbated when coadministered with SAF in clinical studies (Cattaneo, 2003).

In subchronic (13 weeks) and chronic (26 week) toxicity studies in rats and chronic (39 week) studies in monkeys, the no observable adverse effect level (NOAEL) was selected based on reversible clinical chemistry changes and was not associated with target organ toxicity; those toxicities have not been observed in clinical studies (Fariello, 2007). Unfortunately, details such as dose levels and route of administration were not reported for these studies which were conducted by Newron Pharmaceuticals.

SAF did not impair passive avoidance responses in rats, suggesting a low potential for cognitive side effects (Chazot, 2001). SAF is neither mutagenic or genotoxic in vivo and in vitro (Fariello, 2007). As noted in the Drug Interaction Potential section (VIIb), there were no significant drug interactions mediated through human CYP enzymes in vitro, and animal studies indicated that repeat administration of SAF would not result in induction of metabolic enzymes.

VIIb. Drug Interaction Potential

Adverse drug interactions commonly associated with pharmaceuticals in general often involve inhibition of cytochrome P450 (CYP) enzymes, and those specific to MAO-inhibition in particular, were investigated in the literature reports. Using methodology appropriate to the determination of human CYP activity in vitro, there was no relevant inhibition of CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, and minimal effects on CYP1A2 at physiologically relevant concentrations; these CYP enzymes are involved in the metabolism of >90% of pharmaceuticals (Marzo, 2004). Potential induction of CYP enzymes (de novo synthesis of metabolic enzymes following repeat administration) was assessed in rats (Benedetti, 1994). At a dose of 91 mg/kg/day for 4 days, there were no increases in the activity of hepatic CYPs of the 2B, 2C, or 3A
families. While increases in these enzymes are associated with the pregnane X receptor (PXR), and there is some difference in PXR between rat and human, these data would suggest that chronic administration of SAF to humans would not cause alterations in pharmacokinetics linked to induction of metabolic enzymes and transporters upregulated by PXR (which include CYPs and glucuronyltransferases).

No adjustment of dose of carbamazepine or phenobarbital was required in epilepsy patients taking SAF with those anti-epilepsy drugs (Fariello, 2007).
VIII. Bibliography

Archer, 2002


Benedetti, 1994


Bonuccelli, 2006


Caccia, 2006


Cattaneo, 2003


Chazot, 2001


Chazot, 2007


Dal Bo, 2006


Fariello, 2007


Fernandez, 2007

Fredriksson, 1999

Marzo, 2004

Onofrj, 2008

Stocchi, 2004

Stocchi, 2006