

# The Structure and Activity of Selegiline, its Functional Groups, and Congeners

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Bioorganic Chemistry

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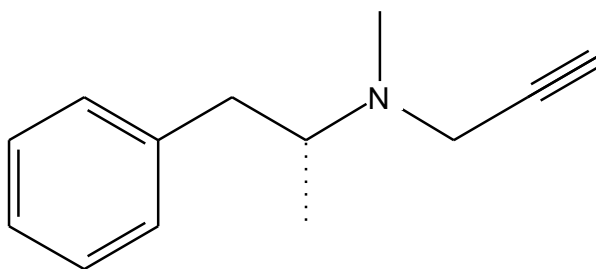


Figure 1: Selegiline (l-deprenyl), N-propargyl levo-methamphetamine

Orbitals are for mathematicians –

Organic chemistry is for people who like to cook!

– Alexander Shulgin

Selegiline, or l-deprenyl, was first synthesized in 1962 by Joseph Knoll. It is a very close derivative of l-methamphetamine 1), identical but for the addition of a propargyl group to its single nitrogen atom. l-Methamphetamine is itself one of the many derivatives of phenethylamine 2, the foundation for a great number of compounds of psychopharmacological interest [19]. While selegiline does inherit some of the pharmacological actions characteristic of phenethylamines, the addition of the rather innocuous-looking propargylamine group compounds and complements those with its own, truly surprising, dimension of activity.

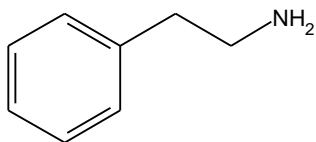


Figure 2: PEA, Phenethylamine

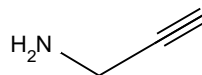


Figure 3: PAA, Propargylamine

## 1 Pharmacological Activity of Propargylamines

The monoamine oxidase enzymes, types A and B, are the body's primary means of deactivating amines, or compounds derived from ammonia by replacing one or more of its hydrogen atoms with hydrocarbon groups. Though both enzymes catalyse the oxidation reaction with amines resulting in the production of ammonia and hydrogen peroxide shown in equation 1, they may be characterized by the compounds (or "substrates") they work on, as well as by the compounds which

inhibit their activity. While MAO-A preferentially deaminates serotonin and norepinephrine and is selectively inhibited by clorgyline, MAO-B tends to catalyse the reduction of dopamine and  $\beta$ -phenethylamine and may be inhibited by aliphatic propargylamines like selegiline [5].



As a selective and irreversible inhibitor of MAO-B, selegiline prevents the deamination of dopamine and  $\beta$ -phenethylamine, thus increasing the concentration of those monoamines while restricting the production of hydrogen peroxide, a pro-oxidant or “reactive oxygen species” (ROS). By increasing dopamine levels, selegiline forestalls and decreases by 30–40% the need for levodopa therapy in cases of Parkinson’s Disease, a condition marked by severe dopamine deficiencies. The increase in phenethylamine caused by selegiline may also contribute to its therapeutic value for Parkinson’s, as it is known to promote the release of dopamine and inhibit its transport. Although most valuable as an adjunct to levodopa therapy, selegiline is somewhat effective as a monotherapy, improving scores on the Unified Parkinson’s Disease Rating Scale by 5–30%.

The “Free Radical Theory of Aging” hypothesizes that the rate at which one ages is proportional to the ratio of pro- to anti-oxidants. When the balance is tipped towards pro-oxidants, ROS are more free to cause oxidative damage, hastening the

aging process. Selegiline is thought to tip the balance in the other direction in part, at least, by inhibiting the metabolism of monoamines by MAO-B and thereby diminishing the production of hydrogen peroxide. This action may seem even more significant in light of reports that MAO-B levels begin increasing with age around 50–60, is more active in Alzheimer’s and Parkinson’s patients, and is found in high concentrations in Alzheimer’s plaques [5].

Selegiline has, additionally, been demonstrated to protect against the oxidative damage to serotonin terminals caused by large doses (40 mg/kg) of MDMA (12). This could be explained by selegiline’s inhibition of MAO-B: by interfering with the deamination of the large amount of dopamine released by MDMA, it would also inhibit the production of the ROS thought to cause the damage [21]. It seems just as likely, however, that this damage could be prevented by the antioxidant enzymes discussed below.

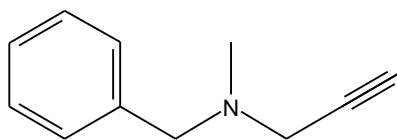


Figure 4: Pargyline

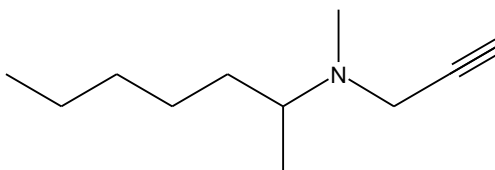


Figure 5: R-2HMP

The propargyl group also appear to protect against neurodegeneration by preventing apoptosis, or programmed cell death. Marumaya *et al* have proposed that selegiline and related compounds bond to a protein with a tertiary structure very

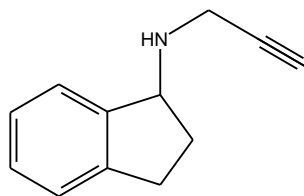


Figure 6: Rasagiline, N-propargyl-1-(R)aminoindan

similar to that of MAO-B, triggering “the cellular process to repress the apoptotic death program,” [15].

Superoxide dismutase (SOD) and catalase are antioxidant enzymes (AOEs) which work to prevent oxidative damage to the body and brain by reactive oxygen species (ROS). Though Knoll initially found that selegiline increased the activity of AOEs, his subsequent research with a different strain of rat failed to corroborate this result. Further work by Kitani *et al* has done much to elucidate the relationship of selegiline to AOEs, concluding that the dose-effect graph follows an inverse U shape, increasing to a certain, optimal dose and declining steadily thereafter [9].

As an aside, the response of AOEs to selegiline is paralleled by that of the lifespan of various animals (mice, rats, hamsters, and beagles) to the same. Both dose-effect graphs follow an inverted U shape, and Kitani *et al* maintain this as the primary support for their working hypothesis that the upregulation of AOEs and extension of lifespan observed with selegiline treatment are causally connected.

This optimal dose is heavily dependent on the activity of the hepatic microsomal cytochrome P-450 enzyme responsible for the metabolism of selegiline, which

itself is dependent not only on the age, sex, and genetic strain of the organism, but also on the length of time over which selegiline is administered. The difficulty of extrapolating these results to humans is illustrated by studies in which Kitani administered various doses of selegiline to our closer relatives, beagles and monkeys: while a dose of 0.17 mg/kg, “roughly” equivalent to that prescribed for Parkinson’s Disease (10 mg/day), was most effective for young male monkeys, a much larger dose of 1.0 mg/kg gave the best results for female beagles.

Other propargylamines share in selegiline’s effect on AOE’s, albeit with varying degrees of potency. Of those listed by Kitani *et al*, selegiline is the most effective, followed by rasagiline (6), R-2HMP (5), and R-2HP. Though the relation of the larger structures of these molecules to their effects on SOD and catalase is largely unknown, Kitani does expect that selegiline should be more potent than desmethylselegiline, given that R-2HMP is more potent than *its* desmethyl derivative [9].

## **2 Catecholamine Activity Enhancement**

Like many derivatives of phenethylamine, selegiline stimulates the activity of the sympathetic system of the brain. As a catecholamine activity enhancer (CAE), selegiline intensifies the response of catecholaminergic neurons by increasing the impulse-mediated release of catecholamines. It is unique, however, in that it does

not *displace* catecholamines from their stores, which property tends to lead to dependence, as exemplified by dextro-methamphetamine [12].

In a fascinating article entitled “Sex, Performance, and Longevity,” Knoll establishes an apparently solid, heretofore unknown, link between sexual activity, learning ability, and lifespan in rats via “a hitherto unknown brain mechanism that controls general activity and thereby, indirectly, the duration of life.”

Knoll first shows that the lifespan of normal, placebo treated rats is proportional to their sexual activity and learning performance: rats predetermined to have “low” sexual and learning performance as measured by standard tests lived about 134 weeks, while those which scored as “high” performers lived about 151 weeks, or about 12% longer.

Finally, he reports that maintaining rats with a daily, 0.25 mg/kg dose of selegiline until death lengthened lifespan and increased scores in tests of sexual and learning performance: selegiline-treated, low-performing rats lived about 152 weeks, or 13% longer than their untreated peers, and selegiline-treated, high-performing rats lived about 185 weeks, or 22% longer.

At each step, increases in lifespan are linked with increases in sexual performance, and each of these is tied to learning ability. Moreover, life-long maintenance of rats on selegiline is shown to increase all three as compared to placebo-treated peers; initially low-performing rats treated with selegiline outlive their un-

treated, high-performing peers by roughly a month, improve in measures of sexual and learning performance, and maintain their ability to perform beyond that of their untreated peers [11].

### 3 Pharmacokinetics

Selegiline is administered therapeutically at a dose of 5-10 mg. It is taken up by the body quickly, and reaches its peak concentration in the plasma within 30–120 minutes. MAO-B is irreversibly inhibited by 90% within 30–90 minutes, and remains so until it can be re-synthesized by the body – a period of up to 40 days.

Selegiline is primarily metabolized in the liver by the cytochrome P450 enzyme into desmethylselegiline (7), l-methamphetamine (9), and l-amphetamine (8). These compounds are further metabolized by ring hydroxylation into *p*-hydroxyamphetamine (11), *p*-hydroxymethamphetamine, and *p*-hydroxy-N-propargylamphetamine, or by  $\beta$ -carbon hydroxylation into ephedrine (10), norephedrine, pseudoephedrine, and norpseudoephedrine.

Though selegiline is typically taken orally, transdermal administration may, in some ways, be favorable. When first-pass metabolism in the liver is circumvented, the maximum plasma concentration of selegiline is increased 60-fold, and the balance of metabolites is altered significantly, halving the production of (levo) amphetamines while increasing levels of desmethylselegiline, which is itself a propar-



gylamine [5].

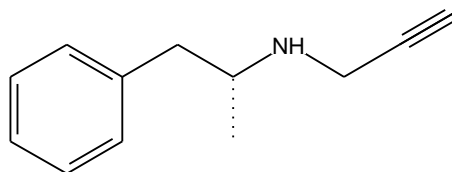


Figure 7: Nordeprenyl, Desmethylselegiline

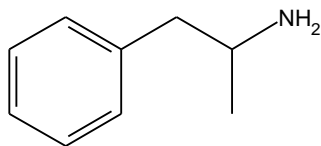


Figure 8: Amphetamine

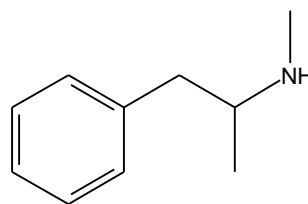


Figure 9: Methamphetamine

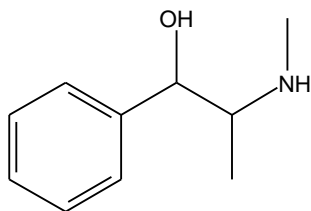


Figure 10: Ephedrine

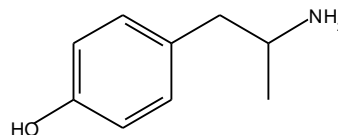


Figure 11: PHA, p-hydroxyamphetamine

Composed primarily of a phenethylamine base and a propargylamine group, selegiline inherits characteristics of both. From phenethylamine, selegiline derives its ability to enhance catecholamine activity, multiplying the response of catecholaminergic nerves. From propargylamine, selegiline inherits its ability to inhibit monoamine oxidase B, prevent apoptosis, protect against oxidative damage caused by the deamination of monoamines, and increase the activity of antioxidant

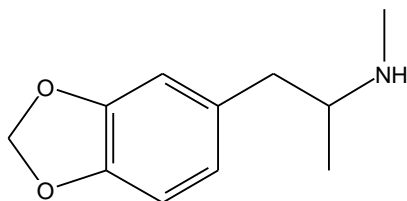


Figure 12: MDMA (Ecstasy), 3,4-methylenedioxyamphetamine

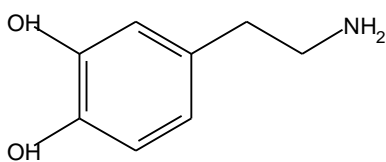


Figure 13: Dopamine, 3,4-dihydroxyphenylethylamine

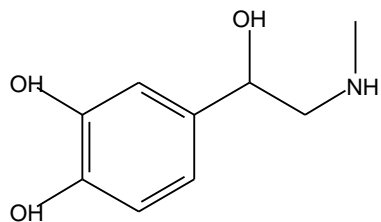


Figure 14: Epinephrine (Adrenaline)

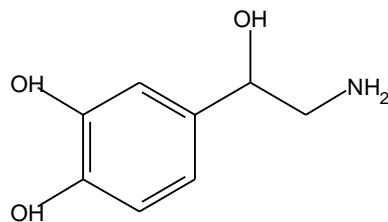


Figure 15: Norepinephrine

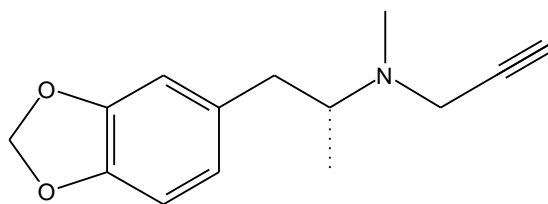


Figure 16: MDPL, 3,4-methylenedioxy-N-propargylamphetamine [19]

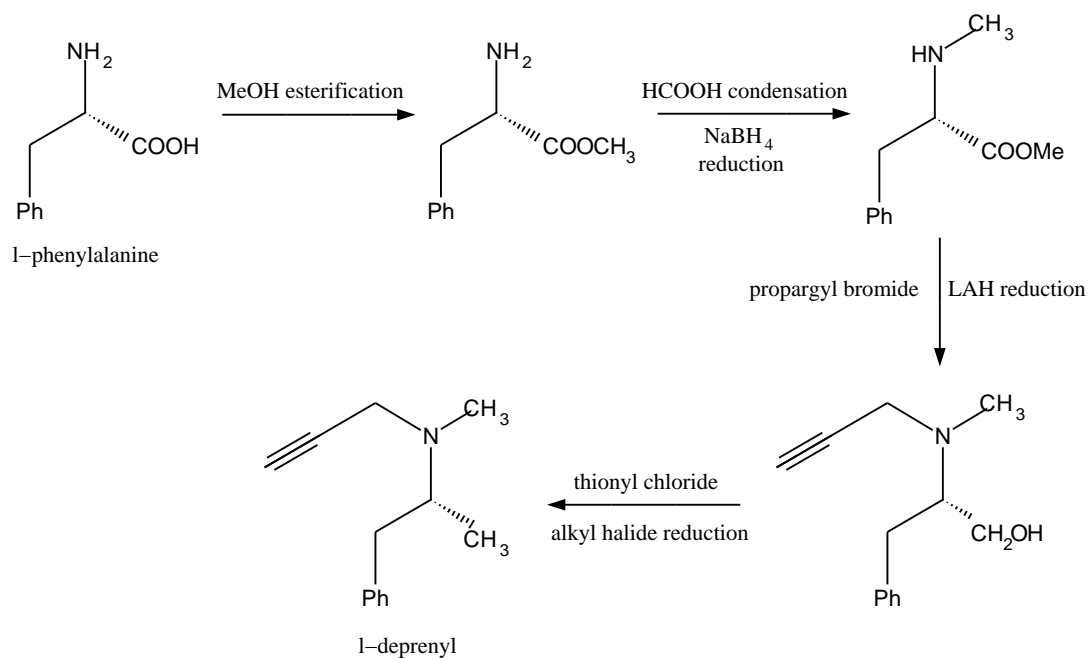


Figure 17: Synthesis of l-deprenyl from phenylalanine [17]

enzymes. With the combination of these groups, selegiline exhibits more novel properties, including CAE without catecholamine release, and offers a unique and unlikely combination of mechanisms which work to make it a valuable treatment for Parkinson's Disease. Last, but not least, is evidence that it can actually extend lifespan and preserve sexual and learning performance.

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