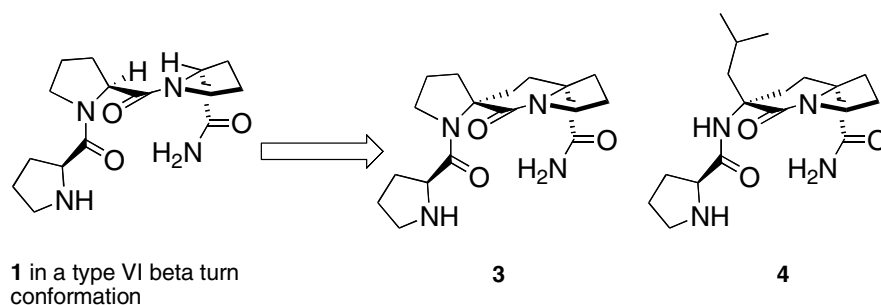


87. SYNTHESIS OF TYPE VI BETA-TURN MIMICS OF L-PROLYL-L-PROLYL-L-PROLINAMIDE

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L-Prolyl L-leucyl glycylamide (PLG) or melanostatin is an endogenous tripeptide known to modulate dopamine receptors. Its bioactive conformation is purported to be a type II beta-turn, a hypothesis that has been supported by the activity profile of a large number of peptidomimetics that restrict PLG in a such a conformation. In one series of PLG analogs, all three residues were replaced by prolyl residues to give L-prolyl-L-prolyl-L-prolinamide (**1**) and L-prolyl-L-prolyl-D-prolinamide (**2**). Compound **1**, which cannot form a beta-turn, was surprisingly more active than **2**; a fact which questions the postulated type II beta-turn bioactive conformation of PLG. Since the prolyl residue supports a cis amide linkage, **1** could assume a type VI beta-turn conformation. To determine if such a conformation may be involved in the activity of **1**, two peptidomimetics **3** and **4** that constrain the “all-L” triproline **1** and L-prolyl-L-leucyl-L-prolinamide, respectively, in a type VI beta-turn have been synthesized.



88. EFFICIENT PREPARATION OF ADRAFINIL ISOMERS

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Attention-deficit/hyperactivity disorder (ADHD) affects approximately 5% of the school age population and is treated with central nervous system stimulants. Stimulants are highly efficacious and safe for treatment of ADHD, however, a subset of patients will either fail to respond to stimulants or have side effects which preclude their use. Furthermore, narcolepsy, another CNS syndrome, is characterized by excessive sleepiness, cataplexy, hypnagogic hallucinations and disturbed night-time sleep. Current pharmacotherapy for narcolepsy which affects approximately 0.06% of the population in North America and Western Europe, involves the use of CNS stimulants to control sleepiness and promote wakefulness. Unfortunately, CNS stimulants are able to produce tolerance and have a strong potential for illicit use. Because of these barriers, other CNS stimulants, such as modafinil, (2-[(diphenyl-methanesulfinyl)]-acetic acid) and adrafinil (2-[(diphenyl-methanesulfinyl)-hydroxy-acetamide] are being developed for ADHD and narcolepsy. Experimental and clinical data suggest that the pharmacological profile of modafinil differs from those of amphetamine and methylphenidate, two classical psychostimulants. The brain targets which modafinil acts on to induce wakefulness, however, remains unknown. Recently, though, it has been shown that the dopamine transporter (DAT) plays a role in promoting wakefulness. This suggests that the mechanism of action of modafinil might involve the DAT. This is interesting because DAT inhibitors have been shown to reduce self-administration of cocaine in rhesus monkeys. As such, modafinil and adrafinil are potential new leads in the development of therapeutics for stimulant abuse. Chemical and biological results to date will be presented.