A Novel Class of Dual 5-HT Uptake Inhibitors and 5-HT$_{1A}$ Antagonists Combined in One Molecule as a Potential Treatment of Depression

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12:00 noon, Conference Room 323A
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ABSTRACT:
Clinical depression is a disease which can have severe and wide-ranging effects on people’s lives. Depression can be attributed to lower than normal synaptic concentrations of 5-HT (serotonin) in the brain. This concentration can be increased by the administration of a selective serotonin reuptake inhibitor such as Prozac (fluoxetine). While there are a number of SSRIs available, each has a lag time of 2-6 weeks before clinical efficacy is expressed. This is the result of a feedback mechanism involving activation of the 5-HT$_{1A}$ somatodendritic autoreceptor by the SSRI. Some studies have shown that the onset of anti-depressant effects of a SSRI can be accelerated by the co-administration of the partial 5-HT$_{1A}$ antagonist pindolol, and selective antagonist WAY-100635.

Using an overlapping type approach, the combination of an SSRI and a 5-HT$_{1A}$ antagonist into one molecule could serve a dual purpose; The SSRI component would act as the traditional antidepressant, while the 5-HT$_{1A}$ antagonist would serve to reduce the time for the onset of the SSRI. The chemistry and SAR of several series of novel dual 5-HT uptake inhibitors and 5-HT$_{1A}$ antagonists is presented herein. An initial in vivo study resulted in a potential rapid onset antidepressant, validating the hypothesis. Further SAR was carried out on this series and is presented.

References: