28AB-ISMS27 **Medicinal Chemistry in the Discovery of Perampanel (Fycompa®), as a First-in-Class Orally Active Noncompetitive AMPA Receptor Antagonist**

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Here we describe the discovery of a series of 1,3,5-triaryl-1*H*-pyridin-2-one derivatives as non-competitive antagonists of AMPA-type ionotropic glutamate receptors. The structure-activity relationships for this series of compounds were investigated by manipulating individual aromatic rings located at position 1,3, and 5 of the pyridone ring which was discovered as an appropriate core structure. This culminated in the discovery of 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile (perampanel) a novel, orally active non-competitive AMPA receptor antagonist that showed potent activity in an *in vitro* AMPA-induced Ca^{2+} influx assay (IC_{50} = 60 nM) and in an *in vivo* AMPA-induced seizure model (minimum effective dose = 2 mg/kg *po*). Perampanel (Fycompa®) has been approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) as an adjunctive treatment for partial-onset seizures with or without secondary generalized seizures in patients with epilepsy age 12 years and older since 2012 and also as an adjunctive treatment for Primary Generalized Tonic-Clonic Seizures in Patients with Epilepsy Age 12 and Older since June 2015.