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Küleon Bioscience Announces Scientific Breakthrough with First Known "Trifunctional" 5-HT2C Receptor Agonist that is also a Full Antagonist of the 5-HT2A and 5-HT2B Receptors, Creating an Exciting Drug Lead for Multiple Neuropsychiatric Disorders

Seattle, WA. and Irvine, CA., October 5, 2023 – Küleon LLC, a private biotechnology company that has built the industry's largest library of serotonergic drugs exhibiting G protein-biased signaling (*i.e.*, "functionally selective" ligands), today announced the development of what is believed to be the world's first "trifunctional" serotonergic small molecule that is a full 5-HT2C receptor agonist and *full antagonist* of the 5-HT2A and 5-HT2B receptors.

The development of the compound, known as KB-128, is a monumental achievement for the company and the industry. KB-128 is creating great excitement among experts seeking to develop novel therapeutics for treating disorders that can be modulated though 5-HT2C receptors, including schizophrenia, Alzheimer's psychosis, depression, obesity, and addiction. Full 5-HT2B *antagonism* is an attractive – yet elusive – property in a drug candidate because it is often associated with the prevention of primary pulmonary hypertension and heart hypertrophy, which are side effects of most serotonergic drugs that activate 5-HT2B. Further, full antagonism at the 5-HT2A receptor is a unique characteristic seldom seen in serotonergic drugs. Specifically, 5-HT2A agonism can create inherent hallucinogenic liability, which disqualifies such compounds from being used as antipsychotics. Conversely, 5-HT2A antagonism has been shown to reduce compulsive and impulsive-type behaviors in rodents, which are cardinal features in substance use disorders.

In addition, and perhaps more importantly, KB-128 exhibits a strong G protein signaling bias with little-to-no β-arrestin recruitment at the 5-HT2C receptors. G protein-coupled signaling bias is an attribute that has been found to be critical for long term therapeutic efficacy of many serotonergic drugs. Indeed, several recent studies have shown that β-arrestin recruitment attenuates G protein-mediated signaling, which can result in drug tolerance due to signaling interference and receptor desensitization.

"Over the last several months we've achieved several unprecedented technological advancements," said Küleon's CEO, Allen Barbieri. "Our R&D team continues to develop novel small molecule assets that exhibit unique and desirable biological characteristics the industry has never seen before. There is a significant unmet need to develop new therapeutic options for patients suffering from devastating and often debilitating psychotic and addictive disorders. KB-128 is a drug that could potentially treat psychotic disorders like schizophrenia and their associated comorbidities, such as obesity and substance abuse. No such treatments exist in the market today. This is the unique opportunity that functionally selective modulation of 5-HT2C provides."

David Gilles, Küleon's CTO, also noted that "KB-128 has successfully passed its initial ADMEPK studies with flying colors. KB-128 exhibits high free drug in plasma, high $T_{1/2}$, and excellent brain Kp. Additionally, results from our initial toxicology studies demonstrate that KB-128 has limited off-target activity, including minimal hERG liability, which is atypical for most serotonergic drugs. We are excited to move KB-128 further through IND-enabling studies that will support its advancement into Phase I clinical trials."

Küleon is in discussions with several companies and academic groups interested in advancing KB-128 into clinical trials for treating diseases and disorder such as schizophrenia, Alzheimer's psychosis, psychostimulant drug use, obesity and alcohol use disorder (AUD). KB-128 is one of several highly selective drug compounds the company is advancing through preclinical testing.

Küleon has filed 40+ original patent applications and is currently pursuing broad international patent protection on its vast library of compounds. Küleon's extensive patent filings cover KB-128 and its associated analogs, the company's other drugs in preclinical programs, and tens of thousands of other novel compounds.

About Küleon. Küleon is a private biotechnology company based in Seattle, WA. Küleon, which is primarily self-funded by its founders, has remained largely in "stealth" mode prior to this initial press release. Through the use of AI/ML tools and *in silico* modeling, the company has identified and screened thousands of novel compounds, which are all covered by its extensive patent portfolio. Küleon is now advancing several of their most promising compounds through IND-enabling studies. In addition to its large portfolio of novel and selective non-hallucinogenic serotonin receptor modulators for treating various psychotic and addictive disorders, Küleon is also advancing a variety of proprietary neuroplastogenic and psychoplastogenic analogs, their prodrugs, and various solid forms.

Learn more at www.kuleonbio.com.

Notes:

- Küleon exclusively owns all of its patents and pending applications
- Küleon (f/k/a PsiloSterics) is based in Seattle's Ballard district.

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