Researchers discover new class of safer analgesics

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Researchers at LSU Health New Orleans Neuroscience Center of Excellence and colleagues have discovered a new class of pipeline drugs to relieve pain and reduce fever without the danger of addiction or

damage to the liver or kidneys. The research is published online in the *European Journal of Medicinal Chemistry*. Current drugs have unwanted side effects. Opioids can not only cause addiction; recent studies have shown they can be no more effective at relieving pain than non-narcotic drugs. Non-steroidal anti-inflammatories (NSAIDs) can cause kidney damage. Acetaminophen is an effective drug, but overuse can result in liver damage.

The research team, led by Drs. Hernan A. Bazan, a professor in the Department of Surgery and Program Director of the Vascular Surgery Fellowship at Ochsner Clinic, and Surjyadipta Bhattacharjee, a post-doctoral researcher at the LSU Health New Orleans Neuroscience Center of Excellence, set out to discover what causes the liver damage associated with acetaminophen and then create a drug structurally similar to acetaminophen—as effective, but without liver toxicity. Along with the chemistry team led by Professor Julio Alvarez-Builla, Department of Organic Chemistry at the University of Alcala in Madrid, they tested 21 different compounds as acetaminophen analogs.

Senior author Nicolas Bazan, MD, Ph.D., Boyd Professor and Director of LSU Health New Orleans Neuroscience Center of Excellence says, "The new chemical entities reduced pain in two in models without the liver and kidney toxicity associated with current over-the-counter analgesics that are commonly used to treat pain—acetaminophen and NSAIDs. They also reduced fever in a pyretic model. This is particularly important in the search for an antipyretic with a safer profile in the COVID-19 pandemic and its associated kidney and liver disease in critically ill SARS-CoV-2 patients."

Acute and chronic pain management is one of the most prevalent and costly public health issues worldwide. According to the Centers for Disease Control and Prevention, an estimated 50 million—20.4% of U.S. adults had chronic pain and 8.0% of U.S. adults had high-impact

chronic pain in 2016.

"Given the widespread use of acetaminophen, the risk of hepatotoxicity with overuse, and the ongoing opioid epidemic, these new chemical entities represent novel, non-narcotic analgesics that exclude hepatotoxicity, for which development may lead to safer treatment of acute and chronic pain and fever," adds Dr. Nicolas Bazan.

Other LSU Health New Orleans members of the research team included William C. Gordon, Ph.D., Professor of Neuroscience and Ophthalmology; Dennis Paul, Ph.D., Professor of Pharmacology; Scott Edwards, Ph.D., Associate Professor of Physiology and Neuroscience; Bokkyoo Jun, Ph.D., Research Instructor; and Amanda R. Pahng, Ph.D., a post-doctoral fellow in Dr. Edwards' lab. The research team also included Drs. Carolina Burgos, Javier Recio, and Valentina Abet, at the University of Alcala in Madrid; Jessica Heap, a third-year medical student at the Tulane University School of Medicine and Alexander Ledet, a first-year MD/Ph.D. candidate at the Albert Einstein College of Medicine in New York.

The intellectual property behind these new technologies, which are part of this discovery, have been licensed from LSU Health Sciences Center New Orleans to the life science startup South Rampart Pharma, LLC that is currently developing this new drug in late pre-clinical stages. Drs. Hernan A. Bazan, Carolina Burgos, Dennis Paul, Julio Alvarez-Builla, and Nicolas G. Bazan are named inventors on a patent assigned to LSU Health Sciences Center describing the synthesis and characterization of the novel non-hepatotoxic acetaminophen analogs (PCT/US2018/022029). The company expects to file the first FDA IND (Investigational New Drug) application by early third quarter 2020.

"Our primary goal is to develop and commercialize new alternative pain medications that lack abuse potential and have fewer associated safety

concerns than current treatment options, and this peer-reviewed paper describes the discovery of the initial library of compounds as well as several proof of concept animal and molecular studies," says Dr. Hernan Bazan.

More information: Hernan A. Bazan et al, A novel pipeline of 2-(benzenesulfonamide)-N-(4-hydroxyphenyl) acetamide analgesics that lack hepatotoxicity and retain antipyresis, *European Journal of Medicinal Chemistry* (2020). DOI: 10.1016/j.ejmech.2020.112600

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