

## 2-Methyl-AP-237

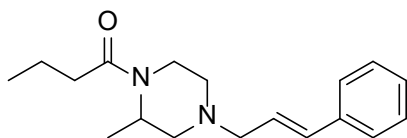
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### Introduction:

2-Methyl-AP-237 is a novel synthetic drug with opioid agonist-like activity. Beginning in 2019, 2-methyl-AP-237 emerged on the illicit synthetic drug market as evidenced by its identification in drug seizures. Abuse of 2-methyl-AP-237, similar to other synthetic opioids, has been associated with adverse health effects, including death. Adverse health effects associated with the abuse of synthetic opioids, their continued evolution, increased popularity, and increased availability of these substances have been a serious concern in recent years and pose an imminent hazard to public safety. As the United States continues to experience an unprecedented epidemic of opioid misuse and abuse, the presence of new synthetic opioids with no approved medical use exacerbates the epidemic.

### Chemistry:

2-Methyl-AP-237 is chemically known as 1-(2-methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl)-1-butanone (CAS 98608-61-8; hydrochloride salt 98608-59-4). 2-Methyl-AP-237 is a methyl analogue of the opioid analgesic bucinnazine, which is also known as AP-237. Chemical syntheses of 2-methyl-AP-237 and other piperizino derivatives, such as AP-237, para-methyl-AP-237, and AP-238, were originally patented in the 1980s. The chemical structure of 2-methyl-AP-237 is shown below:



### Pharmacology:

Data obtained from pre-clinical studies demonstrate that 2-methyl-AP-237 exhibits mu-opioid receptor agonist pharmacological properties. According to the patent, an *in vivo* (in mice) study was conducted with 2-methyl-AP-237 and results indicated that at higher doses it produced analgesic effects in a hot plate assay. Data from *in vitro* studies showed that 2-methyl-AP-237, similar to fentanyl and morphine, binds to the mu-opioid receptors. Additionally, in an *in vitro* functional assay, 2-methyl-AP-237 activated mu-opioid receptors, albeit at a lower percentage of maximum stimulation when compared to fentanyl and morphine. These data demonstrate that 2-methyl-AP-237 has mu-opioid receptor agonist-like activity. It is well established that substances that act as mu-opioid receptor agonists have a high potential for addiction and can cause dose-dependent

respiratory depression. In fact, abuse of 2-methyl-AP-237 has been associated with at least two fatalities and one nonfatal overdose in the United States.

### User Population:

The population likely to abuse 2-methyl-AP-237 appears to be the same as those abusing prescription opioid analgesics, heroin, tramadol, depressants, fentanyl, and other synthetic opioid substances. This is evidenced by the types of drugs co-identified in 2-methyl-AP-237 associated fatal and nonfatal overdose cases. Because abusers of 2-methyl-AP-237 are likely to obtain it through unregulated sources, the identity, purity, and quantity are uncertain and inconsistent, thus posing significant adverse health risks to the end user. 2-methyl-AP-237 may pose potential health and safety risks for users. The positive identification of this substance in overdose and post-mortem cases is of concern to the public safety.

### Illicit Distribution:

Law enforcement data indicate that 2-methyl-AP-237 has appeared in the United States illicit drug market. Law enforcement has encountered 2-methyl-AP-237 as an encapsulated powder. The National Forensic Laboratory Information System (NFLIS-Drug) is a DEA database that collects scientifically verified data on drug items and cases submitted to and analyzed by state, local, and Federal forensic laboratories. According to NFLIS-Drug, there were 21 encounters of 2-methyl-AP-237 in the United States in 2019, 4 encounters in 2020, and 2 encounters in 2021 (as of June 2021). These encounters involved 2-methyl-AP-237 alone or in combination with other substances. The lack of approved medical use and presence of two overdose deaths associated with the abuse of 2-methyl-AP-237 underscores the potential public health threat posed by its presence in the illicit drug market.

### Control Status:

2-Methyl-AP-237 is not approved for medical use in the United States and is not currently controlled under the Controlled Substances Act.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 571-362-4250, Telephone 571-362-3249, or E-mail [DPE@usdoj.gov](mailto:DPE@usdoj.gov).