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Current and Prospective Opioid Analgesics: Assessing Their Value for Ongoing Research and Promise for Therapeutic and Clinical Use

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Abstract

Opioid analgesics, though among the most potent tools for pain relief at our disposal, sit at the epicenter of a growing clinical and societal crisis. Currently, most opioid analgesic drugs like fentanyl function at the μ-opioid receptor (μ-OR), which has notably been linked to respiratory depression, constipation, and high abuse potential. In fact, the abuse of fentanyl has been a primary driver of opioid overdose, leading to over 80,000 deaths in the United States just in the last year. As demand for safer analgesics has surged, the field has responded with a range of innovative approaches, many involving the strategic use of other opioid receptors such as the δ-opioid receptor, κ-opioid receptor, and nociceptin/orphanin FQ receptor (δ-OR, κ-OR, and NOP, respectively). Each of these receptors plays a role in analgesia yet also creates a unique set of complications to accompany it. To combat this issue, dozens of opioid agonists and antagonists are being developed. We have seen new concepts such as biased and bitopic agonism emerge, presenting an updated outlook on how these drugs function. Thus far, no single method has yielded a drug to outcompete the potency of fentanyl and its prevalence in the global market. This review not only brings to light the new classes of opioid drugs but also discusses their relevance to the field. Moreover, many prevalent examples of opioids and their mechanisms are discussed throughout the paper, giving clinically backed insight into the drugs' varying levels of efficacy.

Keywords: opioid analgesics, opioid receptors, biased agonism, bitopic ligands, opioid agonists and antagonists, fentanyl, opioid overdose

1. Introduction

Since first being recorded by the Sumerian Empire for their hypnotic properties in 3400 B.C., opioids have been employed by a myriad of civilizations, including the Egyptians, Indians, Chinese, and Greeks. There is even evidence showing two of the

oldest medical systems using opium derived from poppy seeds to induce analgesia. In Ayurveda (an ancient holistic medical practice from India), Ahiphena—also known as poppy seeds—was used for sedation, pain relief, and gastrointestinal relief. Similarly, in Chinese traditional medicine, the same plant, though here called "Ying Su Ke," was used for pain and cough suppression. Through the years, opioid use has been refined through medical, religious, and recreational contexts, ultimately culminating in the 19th-century isolation of morphine and the 20th-century synthesis of fentanyl (Benet et al., 2017).

Morphine, the first purified opioid analgesic, has been one of the most prominent drugs in medical and pharmaceutical history (Krishnamurti & Rao, 2016). Isolated by Friedrich Sertürner in Germany in 1804, this opium poppy derivative broke ground in the research of analgesics. Morphine functions by binding to the μ-opioid receptors in the brain and spinal cord to block the perception of pain (Zhuang et al., 2022). Its introduction into the clinical and therapeutic settings revolutionized pain management, saving countless lives. During the American Civil War, morphine was widely employed as an analgesic via hypodermic injection or laudanum (Reilly, 2016). Beyond that, however, it helped the scientific community understand addiction, receptor theory, and tolerance. Namely, early patterns of dose-dependent effects and diminishing efficacy with prolonged use provided some of the first evidence for discrete receptor sites and the adaptive changes of tolerance. These ramifications have made morphine both a medical breakthrough and a cautionary tale, sparking the development of newer, safer, and more potent opioid analgesics.

This undertaking eventually gave rise to a new breed of opioid analgesics optimized for the clinical field: synthetic opioids. The most notable of which is fentanyl, an opioid-based drug first synthesized in Belgium by Dr. Paul Janssen in 1959. This drug is widely accepted as the greatest discovery in the field since the introduction of morphine, of which it is 50–100 times more potent (Zhuang et al., 2022). Originally developed for surgical anesthesia and severe pain management, fentanyl's high lipid solubility and rapid onset, coupled with its relatively low cost, have made it one of the most universal analgesics of the modern world. However, its high potency and rapid onset could make even as little as about 2 mg lethal in opioid-naïve individuals, underscoring the need for precaution and safety when in use (Bird et al., 2023). Nevertheless, as of now, fentanyl is still favored in most developed nations for analgesia.

In America, the for-profit healthcare and pharmaceutical system artificially inflates the price of life-saving medicines, making them inaccessible to most Americans living under the poverty line (Blumenthal & Shapiro, 2025). Thus, many Americans are forced to resort to unlicensed distributors to attain their prescriptions at a reasonable price. Unfortunately, however, this results in many preventable deaths every year. The issue is exacerbated by the recreational use of opioids and high mental health crisis rates (usually resulting in substance abuse) among American youths. Moreover, many medical professionals are encouraged to use opioids to treat pain therapeutically, creating high addiction rates in many chronic pain patients. Together, these factors—among many others—have contributed to the ongoing U.S. opioid crisis.

This problem, however, is not uniform throughout the world. Nations like Switzerland, Rwanda, Saudi Arabia, New Zealand, China, Japan, South Korea, and Singapore have been able to keep drug abuse rates low through strict pharmaceutical monitoring and low prescription medication costs (Chan et al., 2021). In stark contrast, regions like Latin America, Eastern Europe, Central and South Asia, and Africa are frequently identified as illicit drug hotspots and trafficking routes. Overall, this disparity can be attributed to an array of factors, from cultural taboos to geopolitical connections to government regulations.

Opioids, unlike other substances like marijuana or nicotine products, can be immediately fatal. While most addictive substances create long-term issues that sometimes lead to cancer, opioid drugs create respiratory depression in overdose,

thus making them fatal in minutes if not counteracted with an antagonist drug. To combat this, many disparate approaches are being taken by researchers and corporations alike. One prevalent avenue involves exploring the different opioid receptors.

Table 1: Abbreviations used in lieu of standard terminology throughout the paper

Standard Terminology	Abbreviation Used
G protein-coupled receptor	GPCR
μ-opioid receptor	μ-OR
κ-opioid receptor	κ-OR
δ-opioid receptor	δ-OR
Nociceptin/Orphanin FQ receptor	NOP
U.S. Federal Drug Administration	FDA

Opioid receptors are a specific type of GPCR located throughout the brain, spinal cord, and peripheral nervous system. Currently, we know of four main types of these receptors: μ-OR, κ-OR, δ-OR, and NOP (refer to Table 1; Wang et al., 2023). Each plays a distinct role in analgesia, pain management, and the effects of both endogenous and synthetic opioids. The μ-OR has historically been used for the majority of analgesic drugs, including morphine, heroin, oxycodone, and fentanyl. It governs euphoria and analgesia, but its use also often leads to respiratory depression and addiction (Zhuang et al., 2022). The κ-OR also deals in the domain of analgesia but comes with the complications of dysphoria and hallucinations. While it has historically been overshadowed by the μ-OR and disregarded due to its hallucinogenic properties, it has had renewed interest in recent years for non-addictive therapies (Beck et al., 2019). On the other hand, the δ-OR continues to deter researchers due to its low selectivity and efficacy. While it may be another route to drug discovery, it lacks significant promise, and thus, intrigue in the receptor is scarce. More recently, an opioid-like receptor has taken the international stage. The NOP, being the newest of the four, has been shown to play a part in stress, mood regulation, and pain. As it has shown reduced side effects in comparison to its counterparts, it represents a promising target for next-generation painkillers (Lu et al., 2021; Cipriano et al., 2024).

In addition to exploring the use of different receptors, two major pathways to mitigating side effects have emerged in the field: bitopic and biased ligands. Bitopic ligands interact with both allosteric and orthosteric sites, offering enhanced control over receptor signaling. By engaging the allosteric site in addition to the orthosteric site, they enable finer modulation of receptor activity. This dual binding confers greater differentiation between receptor subtypes and, consequently, more precise control over receptor activation (Gado et al., 2022). Biased ligands present a way to activate only certain signaling pathways preferentially. They aim to retain therapeutic effects while minimizing complications (Stahl et al., 2021). Until now, opioid drug design has focused primarily on orthosteric sites, but recent efforts with biased and bitopic signaling have yielded some positive results, making them a popular topic for continued research.

These discoveries have sparked a surge of interest in the field. Soon after they arose, we saw innumerable researchers begin leveraging these concepts to address the opioid crisis. When hundreds of ligands entered the screening pipeline at once, they quickly overwhelmed existing infrastructure and techniques, underscoring the need for faster, more scalable approaches (Chatterjee et al., 2023). With aid from new technologies like high-throughput screening, scientists are now able to test thousands of compounds simultaneously at a fraction of the cost, significantly accelerating drug discovery.

Alas, with such a vast repertoire of recent innovations in the field, pinpointing promising candidates has become a highly time-intensive task for researchers new to the field. Fortunately, this review aims to sift through the growing body of opioid ligand candidates to identify those demonstrating the most consistent and reproducible therapeutic and clinical promise across clinical studies.

2. Methodology

To report the trends in the field of opioid analgesic drugs, this review utilized primarily qualitative data drawn from open-access sources through PubMed. As the focus of this paper covers next-generation opioid agonists and antagonists, and sources of quantitative data varied greatly between labs for many of these drugs, it would have been counterproductive and scientifically irresponsible to include data collected through such heterogeneous methods. The most accurate method of discussing the various opioid agonists and antagonists was by reviewing clinical studies and reporting trends and inconsistencies in the current data. The inclusion criteria consisted of studies published between 2017 and 2025, with some exceptions made for historical data critical to contextualizing newer developments. Moreover, only peer-reviewed articles were included. Study types were selected with a preference for human clinical trials; however, in cases where such studies were unavailable, particularly for newer opioid drugs, animal studies were included to fill in important knowledge gaps. By using this methodology, bias was mitigated by drawing from a wide range of studies across different labs and experimental designs, accurately displaying the current landscape of the field of opioid agonists and antagonists.

3. Discussion

3.1. Analysis and Overview of μ-OR, κ-OR, δ-OR, and NOP

The main opioid receptors—μ-OR, κ-OR, δ-OR, and NOP—are part of the Class A G protein-coupled receptor (GPCR) family. GPCRs are a large group of cell-surface receptors that transmit signals into the cell via the activation of intracellular G proteins (Wang et al., 2023). When discussing opioid receptors and their agonists/antagonists, a cascade of intricate processes must occur to create the desired—and undesired—effects that we're familiar with.

As per our current understanding of said processes, we focus on three main proteins within the body: Gαi/o, Gβγ, and β-arrestin. While their respective roles in the system are not yet fully understood, recent findings have linked G protein subunits (Gαi/o and Gβγ) to primarily positive effects (i.e., analgesia and sedation) and β-arrestin to mainly negative effects (i.e., respiratory depression, constipation, and tolerance development), though exceptions exist (Bateman & Levitt, 2021; Faouzi et al., 2020; Mores et al., 2019). Opioids usually activate Gαi/o and Gβγ, subsequently phosphorylating the receptor, causing β-arrestin to bind to it. Thus, we receive nearly every effect every time. To that end, many researchers believe that creating ligands biased to G proteins—or even just one subunit of G protein—over β-arrestins could be the foundation for many next-generation opioid drugs, hopefully aiding the opioid addiction crisis by mitigating tolerance issues (Figure 1).

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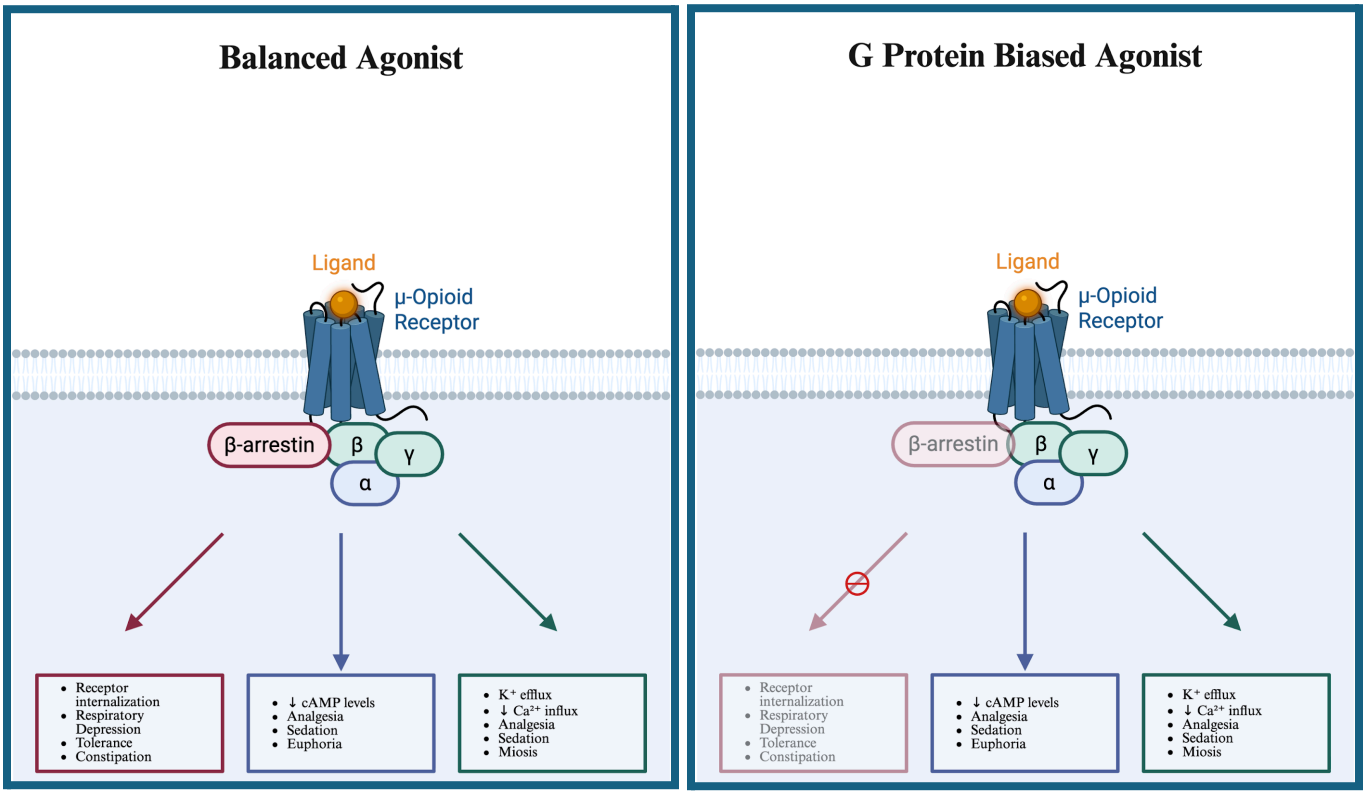

Figure 1: Both panels show the proteins activated by agonists at the μ-OR. These are the Gαi/o, Gβγ, and β-arrestin. Additionally, a set of common effects associated with each protein type is shown in the boxes below. The balanced agonists (shown left) activate both G protein signaling and β-arrestin pathways to a similar extent. In contrast, G protein-biased agonists (shown right) preferentially activate G protein signaling while minimizing β-arrestin recruitment. This figure was created using BioRender (Roy, A., 2025).

Biased agonists have become increasingly prominent in our ongoing pharmacological search for a drug with the aforementioned qualities. They function primarily through the controlled phosphorylation of the opioid receptor. By preventing phosphorylation, they reduce the recruitment of β-arrestins, producing a G protein-biased agonist (Figure 1, shown right). Inversely, by increasing the recruitment of β-arrestins, they become β-arrestin-biased agonists. Each is hypothesized to take on solely the properties of its protein, thus giving researchers greater governance over the opioid functions (Jayakody et al., 2025). Generally, scientists favor the G protein activity due to its more desirable analgesic effect; however, both routes have some exploration, as the concept is a very recent development.

While the information and processes mentioned can be generalized to all the opioid receptors, there also lie distinct pharmacological profiles, therapeutic and clinical potentials, and sets of complications among the μ-OR, κ-OR, δ-OR, and NOP. Understanding and exploiting these factors is vital for the development of more effective opioid agonists and antagonists. For any researcher looking to do so, it is crucial to acknowledge these disparities.

The μ-OR, encoded by the OPRM1 gene, is primarily involved in the analgesic and euphoric effects of opioids. It is predominantly expressed in the periaqueductal gray, thalamus, dorsal horn of the spinal cord, nucleus accumbens, and brainstem respiratory centers, allowing it a great degree of control over pain management. This receptor has strong supraspinal and spinal analgesia, making it effective for acute pain. Thus far, it has long been considered the clinical standard for analgesia due to our longstanding knowledge of its nature and its effectiveness. However, especially in recent years, it has become infamous due to its high risk of respiratory depression, constipation, tolerance, dependence, and euphoria-driven abuse (Pellissier et al., 2018; Madariaga-Mazón et al., 2017; Ehrlich et al., 2019; Mann et al., 2015).

The κ-OR is encoded by the OPRK1 gene, and while perhaps overshadowed by the μ-OR, has consistently shown promise in analgesia. It produces potent spinal analgesia, antipruritic effects, and minimal respiratory depression. Dense in the hypothalamus, amygdala, periaqueductal gray, spinal cord dorsal horn, and pituitary, this receptor has become increasingly valuable as we search for a replacement to traditional μ-OR drugs like fentanyl. Alas, it is also known to cause dysphoria, hallucinations, sedation, and aversion in many patients. For this reason, it has historically been avoided for opioid use. Recently, however, significant promise with the receptor has been shown. In Japan, a κ-OR drug, nalfurafine, has even been conditionally approved for certain therapeutic prescriptions like pruritus in dialysis patients (Table 3), showing net positive effects in many patients thus far (Liu-Chen & Huang, 2022; Hampsey et al., 2024; Escudero-Lara et al., 2021; Han et al., 2023).

On the other hand, the δ-OR, encoded by the OPRD1 gene, is predominantly expressed in the cortex, olfactory bulb, dorsal root ganglia, hippocampus, and limbic regions. In general consensus, it has shown little promise compared to its counterparts. While it does show some mild analgesic, antidepressant, and anxiolytic effects, its risk of seizure is high and its potency for pain relief is low. Generally, the risk of seizures alongside analgesia is not a tradeoff viewed favorably in drug development. To that end, δ-OR selective agonists have been largely passed over by researchers in the field (Gavériaux-Ruff & Kieffer, 2011; Saigusa et al., 2017).

More recently, the atypical NOP has come into play. Encoded by the OPRL1 gene, this receptor is widespread in the cerebral cortex, amygdala, spinal cord, locus coeruleus, and dorsal root ganglia. It has shown great promise in the production of spinal and peripheral analgesia without the creation of respiratory depression, euphoria, or extreme tolerance issues. However, due to its often dual analgesic/anti-analgesic behavior, many feel it to be counterintuitive. Regardless, it has shown significant promise in the field, especially in combination with other receptors. Notably, NOP's synergy with μ-OR signaling has spurred interest in dual agonists, which will be discussed in a later section (examples can be seen in Table 3; Post et al., 2016; Raffaeli et al., 2006; Göhler et al., 2019; Scholz et al., 2018; Koch et al., 2019; Christoph et al., 2017).

3.2. The Rise of New Classes of Opioid Agonists: Biased and Dual Agonism

Until the late 1990s, medical professionals and researchers alike were wary of opioid drugs, using them only when absolutely necessary (i.e., late-stage cancer) and in small quantities, but in 1996, the company Purdue Pharma produced OxyContin, a drug that would change the opioid landscape for decades to come. OxyContin, a brand name for an extended-release formulation of oxycodone, was introduced by Purdue Pharma to treat moderate–severe pain over long periods of time. As opioids had long since been considered addictive and having many complications, most care providers were averse to their use. Nevertheless, Purdue Pharma confidently cited a one-paragraph letter from the renowned New England Journal of Medicine (Porter & Jick, 1980). This report—using a small test group of hospitalized patients—was taken out of context by

Purdue Pharma, cited as definite proof that opioids were safe and non-addicting for long-term outpatient use. When coupled with more influential clinical papers; aggressive, misleading, and FDA-backed promotional marketing (Table 1; Van Zee, 2009); and pressure from the "Pain as the 5th Vital Sign" marketing, doctors' fears were assuaged, and the mass prescription of opioids began (Rosenman et al., 2025). In 2020, Purdue Pharma pleaded guilty to their false advertising, taking OxyContin's extended-release form off the market. Unfortunately, by then, the damage was done, leaving us with an opioid crisis we don't have a solution to. Even today, while under closer security and restriction, opioids are being prescribed to those with chronic pain-causing afflictions, as they are currently thought to be the best method of pain mitigation. However, even when medical professionals stop the opioid prescription, there is a high likelihood of addiction, tempting patients to continue their use through non-controlled substances like diacetylmorphine (heroin), illicit morphine, or illicitly manufactured fentanyl (refer to Figure 2 for structures).

Table 2: Common characteristics of therapeutic and clinical opioid usage

	Duration	**Risk of Addiction**	**Level of Supervision**
Therapeutic (Outpatient) Use	~2 Months – Indefinite	Usually **higher risk** than clinical	Initially prescribed by a medical professional, generally with occasional updates
Clinical (Inpatient) Use	~2 Hours – 24 Hours	Usually **lower risk** than therapeutic	Near-constant monitoring and adjusting by a medical professional

Currently, for outpatient therapeutic use (Table 2), we have a variety of opioids at our disposal. For this purpose, we tend to use longer-acting drugs such as morphine (Zhuang et al., 2022; Krishnamurti & Rao, 2016; Reilly, 2016), oxycodone, hydromorphone, methadone, and fentanyl transdermal patches (Figure 2 and Table 3; Nihadha et al., 2022; Lorch et al., 2021; Yamaguchi et al., 2021; Bird et al., 2023; Cipriano et al., 2024; Göhler et al., 2019). We do this for several reasons, including duration of action, potency, overdose risk, abuse risk, cost, and government regulation. Conversely, for inpatient clinical care (Table 2), shorter-acting drugs with faster onset and offset, like fentanyl and remifentanil, are often utilized (Figure 2 and Table 3; Brown et al., 2020; Sutcliffe et al., 2022). This can also be attributed to the aforementioned reasons, but their inverse.

Perhaps some of the most acute examples of this idea are the uses of morphine and fentanyl. Morphine (a large, hydrophilic substance) has a much longer onset and offset when compared to fentanyl (a smaller, lipophilic substance; refer to Figure 2 for structures; Brown et al., 2020; Sutcliffe et al., 2022). Thus, morphine is mostly used for chronic and cancerous conditions, while fentanyl is reserved for general surgery under the watch of an anesthesiologist. Each has its benefits and drawbacks, making them ideal for different scenarios. Morphine lasts longer than fentanyl, increasing the risk of complications like nausea and constipation but decreasing the risk of overdose in long-term situations, as it will be administered less often (Table 2). Fentanyl is ~50–100 times more potent than morphine, making it cheaper when diluted and given properly, but deadly if overdosed. Fentanyl may have greater reinforcement potential due to rapid onset and high potency, but if taken for prolonged periods of time, as morphine usually is, both can become extremely addictive due to euphoric effects and unregulated dopamine levels. To synthesize, morphine and fentanyl are two very different drugs, targeting the same issue but in unique ways, making them best suited for different tasks. While often discussed, these are not the only two opioid drugs that follow these principles. As mentioned earlier, medical professionals have dozens of drugs—approved, obsolete, and in

development—to treat patients with (Table 3). However, especially with more recently developed opioids, most of the medical community is wary of change, with good reason, considering the recent history with OxyContin. Thus, it is important to recognize the disparate effects (both short and long term) and tailor opioid use to the task it is performing. We can do this through clinical trials, where a near-definite assessment is reached, but even before that, we are able to form a rough hypothesis based on the structure (Figure 2) and intended route of function (Table 3). Here, we will be comparing the structure, receptor, and other known factors of next-generation agonists to their clinically and therapeutically established counterparts, reporting trends and inconsistencies between these factors and the drugs' effects.

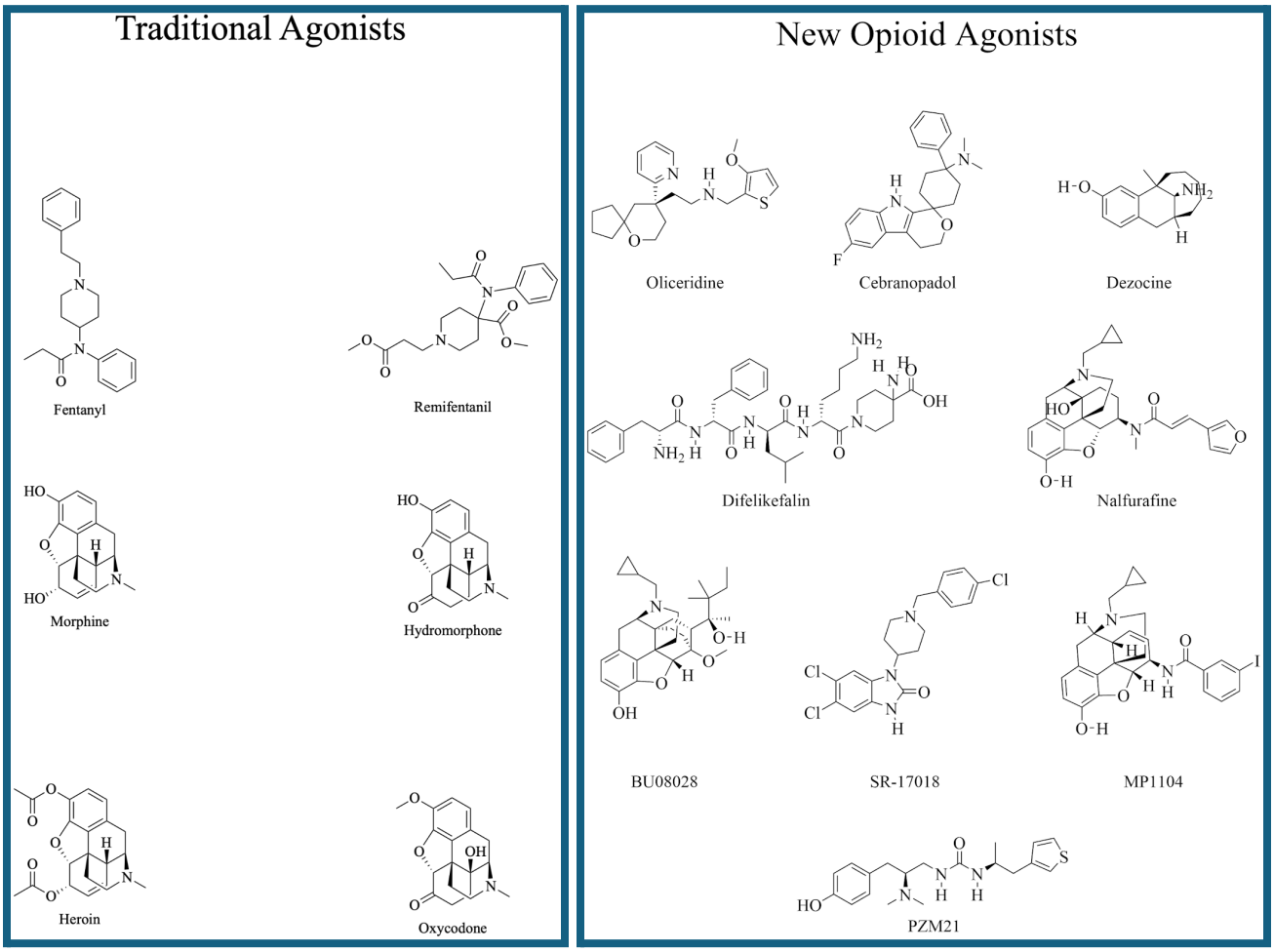

Figure 2: Panels show structures of traditional agonists (left) and new opioid agonists (right).

Table 3: Name, common brand name, target, effects (both positive and negative), and stage of development (indicating how far a drug has advanced through testing and approval) of different established and upcoming agonists

Name	Common Brand Name(s)	Target	Positive Effects	Negative Effects	Stage of Development / Use
Oliceridine	Olinvyk	μ-OR – G protein–partial bias	Strong IV analgesia, slightly reduced GI and respiratory issues compared to morphine	Nausea, dizziness, respiratory depression still possible, limited duration	Approved (US) for acute pain (IV)
PZM21	–	μ-OR – low β-arrestin recruitment	Analgesia in preclinical and early human studies	Respiratory depression in later animal studies, low analgesic effects	Preclinical/ early clinical
SR-17018	–	μ-OR – G protein biased	Potent, long-acting analgesia in animals, reduced tolerance issues in mice	No human data; bias claims debated, possible side effects typical of μ-OR agonists	Preclinical
Dezocine	Dalgan	μ-OR partial agonist + κ-OR partial antagonist + SERT/NET inhibitor	Analgesia, possible mood elevation, lower abuse liability reports	Typical opioid adverse events, mild sedation	Approved (China); formerly marketed in US
Nalfurafine	Remitch	κ-OR full agonist + μ-OR partial agonist	Antipruritic with reduced dysphoria compared to classical κ-OR agonists	Low analgesia, Sedation, possible mild dysphoria	Approved (Japan) for uremic pruritus
Difelikefalin	Korsuva	κ-OR peripheral agonist	Pruritus relief, minimal CNS sedation/respiratory depression	Low analgesia, mild nausea, diarrhea	Approved (US) for CKD-associated pruritus; IV in dialysis
MP1104	–	κ-OR full agonist + δ-OR full agonist	Analgesia in rodents, reduced classic κ-OR aversion	Unknown human safety; possible κ-OR side effects	Preclinical

BU08028	–	μ-OR partial agonist + NOP partial agonist	Strong analgesia in NHPs, minimal respiratory depression or abuse liability	Unclear long-term safety, typical opioid effects possible	Preclinical
Cebranopadol	–	μ-OR full agonist + NOP agonist	Very long-lasting analgesia, fewer classic μ-OR adverse events	Some sedation, opioid-like side effects	FDA Fast Track Designation for chronic low back pain
Morphine	Zomorph, Sevredol, MS Contin, and Oramorph	μ-OR full agonist (balanced signaling)	Strong analgesia, sedation	Respiratory depression, constipation, histamine release, tolerance	Approved, widely used
Hydromorphone	Dilaudid	μ-OR full agonist (balanced signaling)	Potent analgesia, less histamine release than morphine	Respiratory depression, constipation, sedation	Approved, widely used
Diacetylmorphine	Heroin	μ-OR full agonist	Very rapid and strong analgesia/euphoria	High abuse liability, respiratory depression, rapid dependence, low regulation	Approved in some countries for opioid dependence; illicit in most
Oxycodone	OxyContin	μ-OR full agonist + minor κ-OR agonist	Effective oral analgesic	Abuse liability, respiratory depression, constipation	Approved, widely used
Fentanyl	Sublimaze (Intravenous), Duragesic (Transdermal patches), Actiq (Oral transmucosal lozenges), Fentora (Effervescent	μ-OR full agonist	Very rapid, potent analgesia and sedation	Respiratory depression, tolerance issues, addiction potential	Approved, widely used (anesthesia, severe pain)

	buccal tablets), Abstral (Sublingual tablets), Subsys (Sublingual sprays), and Lazanda (Nasal sprays)				
Remifentanil	Ultiva	μ-OR full agonist	Rapid onset, rapid offset, precise titration	Respiratory depression during infusion, little residual analgesia after stop	Approved, widely used in anesthesia

Note: Data for Oliceridine are from Wolf et al. (2024). Data for PZM21 are from Manglik et al. (2016). Data for SR-17018 are from Pradhan et al. (2021). Data for Dezocine are from Zhou et al. (2023). Data for Nalfurafine are from Kozono et al. (2018). Data for Difelikefalin are from Fishbane et al. (2022). Data for MP1104 are from Zádor et al. (2019). Data for BU08028 are from Ding et al. (2016). Data for Cebranopadol are from Schroeder et al. (2021). Data for Morphine are from Gutstein and Akil (2025). Data for Hydromorphone are from Kharasch (2020). Data for Diacetylmorphine are from Darke et al. (2019). Data for Oxycodone are from Gudin and Fudin (2021). Data for Fentanyl are from Volpe (2023). Data for Remifentanil are from Egan (2019).

Based on the factors analyzed, several predictions can be drawn. It is important to note, however, that these are solely predictions, and the true effects of drugs are shown through human clinical studies and continued therapeutic use. With that said, this preemptive style of analysis can be extremely useful for researchers looking to explore very recently developed avenues of creating opioid drugs and assess which growing ideas have had the most success thus far.

Firstly, it is crucial to understand which areas of research have had the least success and least exploration with regard to opioid analgesics. To this end, we can cite the limited results of full and partial δ-OR agonists. Most drugs developed for the δ-OR either show low efficacy with analgesia, inordinate complications, or a combination of both issues (for specific examples, refer to Table 3). Thus, the data for the receptor is limited, and the results are not quite promising. Moreover, certain agonists, namely PZM21, were initially thought to be biased agonists due to their lessened side effects (Figure 1), but it was later discovered that the effects could be attributed to low intrinsic efficacies (Hillhouse & Negus, 2016). Furthermore, the κ-OR, once considered among the most promising candidates for analgesic drug development, has shown mixed results. In many κ-OR agonists in use, low analgesic effects in relation to dysphoric issues have been noted (Table 3). However, the antipruritic (anti-itch) benefits of κ-OR agonists such as nalfurafine and difelikefalin have not gone unnoticed (Table 3). This receptor—while perhaps not as indicative of heralding the future of less issue-prone analgesic drugs—presents a unique pathway for antipruritic drugs, with a plethora of reassuring, trial-based evidence to support it (Beck et al., 2019; Liu-Chen & Huang, 2022).

More optimistically, we have a number of agonists employing a variety of strategic approaches to drug design. Not only is it important to understand which drugs are successful and unsuccessful, but the underlying mechanisms of said drugs are just as important to the field. To that end, we have seen many drugs with success, but it is still important to define and categorize

that success, as different issues necessitate different criteria. The main uses for analgesic drugs are therapeutic and clinical. In outpatient therapy, the patient will be exposed to the drug for longer durations and generally at lower doses. Conversely, in clinical procedures, higher doses are given but far less frequently and in tightly controlled settings. Some drugs, like fentanyl (see Table 3), are even used for both cases via different routes like the fast-acting intravenous formula for surgical procedures and the slower-release transdermal patches for chronic pain (Nihadha et al., 2022; Lorch et al., 2021; Yamaguchi et al., 2021; Bird et al., 2023; Cipriano et al., 2024; Göhler et al., 2019).

For acute clinical use, we have seen agonists at the μ-OR work the quickest and safest, but still retain some drawbacks of constipation, nausea, respiratory depression, and continually increasing tolerance. However, when biased to the G proteins Gαi/o and Gβγ, several agonists showed reduced complications, especially with tolerance, as the β-arrestin was no longer causing the internalization and degradation of the receptor. For example, oliceridine—an agonist that preferentially activates G protein signaling over β-arrestin recruitment—has already been shown to have a lower risk of several side effects in humans. Oliceridine has rapid analgesia like fentanyl and morphine but lower respiratory depression and gastrointestinal complications at equianalgesic doses of those same traditional opioids (Table 3). This drug has shown us that G protein bias can be successful, but it is still not perfect: side effects can still occur, especially at higher doses (Faouzi et al., 2020; Stahl et al., 2021; Bateman & Levitt, 2021). Oliceridine has not been widely tested for human surgical use, mostly used to counteract moderate to severe acute pain in-clinic. Moreover, it is important to note that not all studies consistently replicate the same balance of β-arrestin versus G protein outcomes, so results should be interpreted with caution and may depend on the specific ligand and experimental system. Due to this, the community is still searching for an even better opioid analgesic to compete with fentanyl, and many feel G protein bias is the way to get there.

In chronic therapeutic development, on the other hand, many of the most promising agonists also utilize the concept of dual agonism/antagonism, where agonists target multiple receptors. For example, BU08028 and cebranopadol are both mixed agonist drugs (Table 3). BU08028 primarily targets the μ-OR and NOP, reaping analgesia via a classical opioid pathway, and also modulating pain while reducing side effects like addiction risk through the NOP. If hypotheses are confirmed by human trials, this drug could provide potent, long-lasting analgesia without as many complications for chronic and acute pain. Cebranopadol is a first-in-class mixed opioid receptor. The drug targets the μ-OR and NOP as a full agonist and δ-OR and κ-OR as a partial agonist. By providing strong analgesia through the μ-OR, modulating pain through the NOP, and utilizing δ-OR and κ-OR for some neuropathic pain, this drug shows use for both acute and long-term pain management (Göhler et al., 2019; Scholz et al., 2018; Koch et al., 2019; Christoph et al., 2017). Taking a different approach, dezocine, a drug widely used in China for chronic pain in humans but taken off the American market (for economic, not safety concerns), is a μ-OR agonist, κ-OR antagonist, and a serotonin-norepinephrine reuptake inhibitor. By partially agonizing the μ-OR, the drug creates potent analgesia but with a ceiling effect, lowering the risk of respiratory depression. Being a κ-OR antagonist, this opioid analgesic also reduces dysphoria and sedation risk.

3.3. Opioid Antagonists: Uses, Drawbacks, and New Technologies

As the opioid drug crisis remains unsolved, more and more people are overdosing on opioid drugs and experiencing respiratory depression, and thus, opioid antagonists are needed increasingly more. In the United States, many school districts located in high-drug-trafficking areas keep a narcotic reversal agent on hand, usually naloxone (Narcan). However, just as fentanyl has drawbacks and welcomes alternative agonists, naloxone has sparked a new wave of innovation for better opioid antagonists.

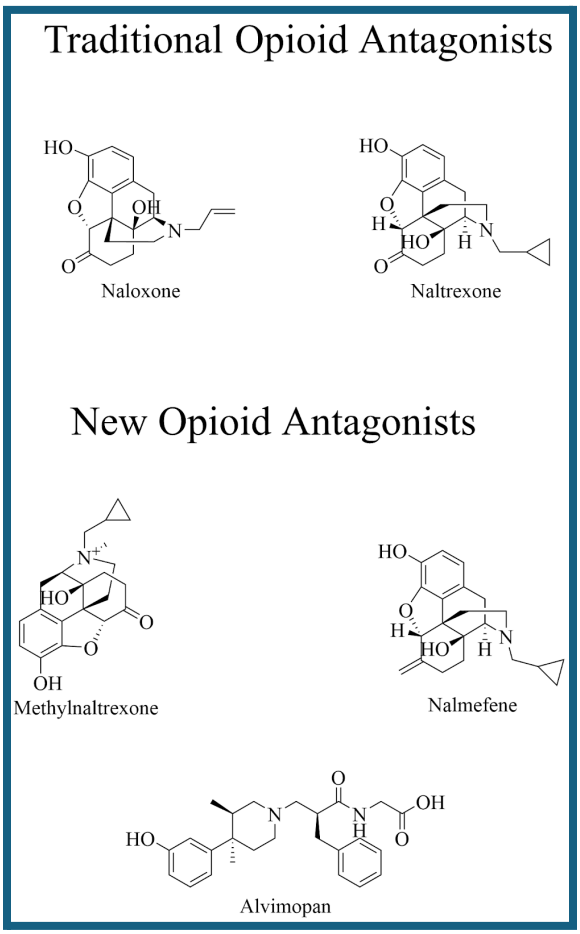

Figure 3: Chemical structures of traditional and in-development (new) antagonists. Each structure is labeled with its name underneath.

Table 4: Name, common brand name, target, effects (both positive and negative), and stage of development of different established and upcoming antagonists.

Name/Brand(s)	Delivery Methods	Target	Positive Effects	Negative Effects	Stage of Development/ Use
Naloxone (Narcan, Kloxxado, Evzio)	Intravenous (IV), Intramuscular (IM), Subcutaneous	Full antagonist at μ-OR; Partial antagonist at κ-OR and δ-OR	Rapid reversal of opioid overdose, restores respiration	Short half-life (risk of re-narcotization), may cause severe	Approved; gold standard emergency

	(SC), Intranasal spray			withdrawal symptoms in opioid-dependent patients	overdose treatment
Naltrexone (ReVia, Vivitrol, Depade)	Oral tablet, Extended-release intramuscular injection	Full antagonist at μ-OR, weak κ-OR antagonism	Prevents relapse in opioid/alcohol use disorder, longer duration than naloxone	Hepatotoxicity risk at high doses, poor adherence in oral form, precipitates withdrawal	Approved for opioid and alcohol dependence treatment
Methylnaltrexone (Relistor)	Subcutaneous injection, Oral tablet	Peripherally acting μ-opioid receptor antagonist (PAMORA); does not cross BBB	Reverses opioid-induced constipation without affecting analgesia	Abdominal pain, won't reverse overdose	Approved for opioid-induced constipation in palliative care or chronic pain
Alvimopan (Entereg)	Oral capsule	PAMORA; selective peripheral μ-opioid receptor antagonist	Reverses opioid-induced constipation without affecting analgesia	Cardiovascular risk with long-term use (restricted to short-term access)	Approved for short-term hospital use post-surgery (REMS program)
Nalmefene (Selincro, Revex)	Intravenous, Intramuscular, Subcutaneous, Oral tablet (Europe)	Full antagonist at μ-OR, partial agonist at κ-OR and δ-OR	Reversal of opioid overdose (longer duration than naloxone), reduces alcohol consumption	Nausea, dysphoria, precipitates withdrawal	Approved in some regions for alcohol dependence; approved in U.S. (IV) for overdose reversal

Note: Naloxone data are from Bailey and Wermeling (2014) and Barton et al. (2005). Naltrexone data are from Comer et al. (2018) and Mark and Jones (2022). Methylnaltrexone data are from Webster et al. (2023) and Deibert (2011). Alvimopan data are from Viscusi and Singla (2019) and Tan et al. (2008). Nalmefene data are from LiverTox (2015) and Smith et al. (2025).

Just as with agonists, antagonist drugs are present in a variety of structures, delivery routes, and mechanisms of action (Figure 3 and Table 4). Naloxone is still the gold standard emergency overdose treatment: it works with few complications and is usually life-saving. The largest issue is its short half-life, as it only works for ~30–90 minutes, whereas some opioid agonists function for hours (Table 3). This can cause re-narcotization, where overdose symptoms return after naloxone wears off, requiring repeat dosing or IV infusion. Some other issues involve rapid withdrawal symptoms in opioid-dependent individuals (due to naloxone's rapid onset) and limited efficacy with ultra-potent opioids like carfentanil. Additionally, the intravenous

version of naloxone requires training to administer, but trained staff may not be available at the time of overdose (Bird et al., 2023; Beck et al., 2019; Lu et al., 2021; Cipriano et al., 2024).

To that end, researchers and scientists are working to develop and test several new reversal agents to hopefully solve some of naloxone's issues without sacrificing its efficacy. So far, drugs like naltrexone and nalmefene have been created and FDA-approved for certain cases (Table 4 and Figure 3). They tend to last much longer than naloxone but have been associated with immediate acute withdrawal symptoms, so newer opioid antagonist drugs are still in development (Martinez et al., 2023; Baehr et al., 2020; Smith et al., 2019). Moreover, we now have several oral sprays, nasal sprays, and oral capsules to make untrained administration easier (Table 4). While some critics have argued that the widespread availability of reversal agents could embolden opioid users and agitate the issue, widespread consensus agrees that the lives saved overshadow this issue. Additionally, a new class of antagonist drugs known as PAMORAs (peripherally acting μ-opioid receptor antagonists) has emerged (Table 4). These drugs, like alvimopan and methylnaltrexone, are actually not used to treat opioid overdose. Rather, they are utilized mainly for opioid-induced constipation. PAMORAs, unlike most antagonists, do not reduce analgesic effects, making them a great resource for patients in chronic pain or for post-operative care (Pellissier et al., 2018; Madariaga-Mazón et al., 2017).

Another issue is that while traditional antagonist drugs create a rapid reversal effect, they cannot be given preemptively, as they have a short half-life. However, a unique class of drugs known as monoclonal antibody–based opioid binders presents a new way to combat the issue: the idea of opioid "vaccines." Unlike traditional antagonists, monoclonal antibodies could prevent opioid agonists from crossing the blood-brain barrier (BBB). This would effectively reduce the effects of opioids over a long period, thus "vaccinating" patients against them. Nevertheless, many concerns and debates exist over this topic. For instance, the design of these drugs is very specific, usually only targeting one or a few agonists. So, if a person suffering from opioid addiction were to get treated against heroin, thus nulling its effects, they may resort to other drugs such as fentanyl for the same euphoria. Moreover, if a patient is vaccinated against too many opioids and needs a surgical procedure, the anesthesiologist may have a difficult time finding an opioid drug to administer analgesia. This applies even more so for an emergency room (ER) case in which the patient's medical record may not be on hand. So, even though traditional antagonists and monoclonal antibody–based drugs strive to aid the same issue—the ongoing opioid crisis—both take very different routes and expect very different outcomes (Martinez et al., 2023; Baehr et al., 2020; Smith et al., 2019). Thus, they are not in competition with each other, as neither can replace the other, but expanding our research in both areas would benefit the same problem.

4. Conclusion

In synthesis, opioid pharmacology represents a path to improving both therapeutic tools and clinical medicine. Our growing understanding of opioid receptor function has revealed opportunities to separate beneficial analgesic effects from unwanted side effects, but the path toward safer and more effective drugs remains largely open. Nevertheless, historical missteps remind us that scientific innovation must not come at the cost of foregoing rigorous testing, regulation, and responsible clinical use. This evolving landscape can be summarized in three key areas. First, progress in biased and bitopic agonism has highlighted promising strategies, such as the development of biased agonists that preferentially activate pathways linked to analgesia and the exploration of dual-acting compounds that target multiple receptors simultaneously. Second, persistent limitations remain in translating encouraging preclinical findings into reliable clinical outcomes, underscoring the need for cautious interpretation and stringent validation. Third, the outlook for rational design—integrating receptor structure and

pharmacological innovation—offers a forward-looking path toward safer and more effective opioid drugs. It is important to note, however, that in the global market thus far, no opioid agonist has yet surpassed fentanyl, and similarly, no opioid antagonist has yet usurped naloxone; both are remarkable innovations that have saved countless lives, regardless of their shortcomings. Ultimately, addressing the opioid crisis will not come from a single breakthrough but rather an integrated approach. Continued research in all of these areas offers the best chance of balancing the essential role of opioids in pain relief with the urgent need to minimize their risks.

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Author Biography

Aman Roy is an 11th-grade student at the Texas Academy of Math & Science with a strong interest in chemical sciences, biomedical research, and medicine. As a motivated student researcher and aspiring anesthesiologist, he is particularly interested in the intersection of chemistry, biology, and clinical applications, and he is driven by a desire to help others through both academic and community-based efforts.

In addition to his research pursuits, Aman is an advocate for teen mental health—an area he believes remains significantly underrepresented and underserved. He founded a mental health-focused student group in the Dallas-Fort Worth Area to promote awareness, dialogue, and peer support, reflecting his commitment to improving student well-being beyond the classroom.

In his free time, Aman enjoys reading fantasy novels, playing tennis with friends, and exploring new places. He has a strong appreciation for travel, diverse cuisines, and learning about different cultures, which he believes broadens his perspective both personally and professionally.

Mentor Contribution Statement

Dr. Hamidreza Shaye served as an academic mentor by providing conceptual guidance and educational support relevant to the broader scientific context of this work. His primary contribution consisted of delivering instructional lectures and discussions on genetics, molecular biology, and emerging research technologies, which helped build the foundational knowledge necessary to understand modern approaches to opioid receptor research. These lectures enhanced the author's ability to interpret primary literature and evaluate current analgesic drug development efforts within a larger biological and technological framework.

Dr. Shaye also offered occasional feedback on the manuscript, primarily focused on scientific clarity, accuracy of terminology, and text organization. He did not participate in the generation of the manuscript's research questions, hypotheses, analyses, interpretations, or conclusions. He did not write, edit, or directly contribute text to the manuscript.

All ideas, literature synthesis, data interpretation, trend analysis, and writing were conducted independently by the author. Dr. Shaye's role was strictly advisory and educational, providing the background tools necessary to engage with the field at an advanced level rather than shaping the content itself. His mentorship enabled the author to better understand new technologies and concepts, but did not influence the originality or authorship of the work. Responsibility for the content, conclusions, and any errors in the manuscript rests entirely with the author.

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Dr. Tetz did not generate research ideas, propose hypotheses, perform analyses, interpret results, or write any portion of the manuscript. She did not influence the conclusions drawn or the perspectives presented. All literature review, synthesis of information, evaluation of drug candidates, and overall manuscript writing were performed independently by the author.

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