WEP Warwick Evans Publishing

International Journal of Public Health and Medical Research

ISSN: 3006-7707 (Print), ISSN: 3006-3752 (Online) | Volume 5, Number 3, Year 2025
DOI: https://doi.org/10.62051/ijphmr.v5n3.02
Journal homepage: https://wepub.org/index.php/IJPHMR/index

Advances in Biased Opioid Agonists for Analgesia: Side Effects Minimisation and Addiction Prevention

Kaiyun Zhang *

International Department, Shenzhen Middle School, Shenzhen, Guangdong, 518000, China
*Corresponding Author: (e-mail: kaiyun.zhang.zzz@gmail.com)

ABSTRACT

Opioids, as frontline analgesics, are associated with substantial adverse effects. For example, μ-opioid receptor agonists commonly cause respiratory depression and carry high addictive potential, while κ-opioid receptor agonists can produce depression-like reactions and aversion. The introduction of biased agonism has offered a strategy to dissociate opioid-induced adverse effects from analgesic efficacy. In recent years, biased agonists developed for different opioid receptor types have shown promise in reducing side effects, lowering addictive liability, and achieving analgesia with improved therapeutic windows, suggesting the possibility of a safer next generation of analgesics. However, important obstacles and challenges remain.

KEYWORDS

Biased agonist; Opioid receptor; Analgesia; Novel analgesic; Opioid-induced adverse effect; Opioid use disorder

1. INTRODUCTION

Opioid receptors (ORs) are G protein-coupled receptors (GPCRs) broadly expressed across the central and peripheral nervous systems. They mediate endogenous analgesia and play key roles in pain-modulatory and reward circuits. Beyond analgesia, however, opioid drugs commonly produce adverse effects such as respiratory depression, nausea, and constipation and are associated with severe withdrawal syndromes as well. Repeated or excessive opioid use can lead to addiction and even death [1-2]. The opioid crisis has long been a pressing global public-health problem, and the quest for a resolution remains imperative and ongoing.

Since the late twentieth century, researchers have shifted attention from classical non-selective full opioid agonists (e.g., morphine) to the concept of biased agonism. Biased agonists selectively activate certain GPCR downstream signalling pathways while antagonising or not engaging in others [3], offering a potential avenue to avoid or reduce opioid-induced adverse effects and addiction while preserving analgesic efficacy. A variety of biased ligands targeting different opioid receptor types have been developed: several have achieved positive results in animal models, and a small fraction have reached clinical use or regulatory approval. This review summarises reported biased agonists for different opioid receptor types and their progress towards analgesia with minimised side effects and lower abuse liability.

2. OPIOID RECEPTORS AND THE OVERVIEW OF BIASED AGONISM THEORY

Human opioid receptors are members of the GPCR superfamily [4]. In the central nervous system (CNS), they are concentrated on pre- and postsynaptic membranes of neurones involved in nociceptive transmission and pain-modulatory regions such as the dorsal horn of the spinal cord and the periaqueductal grey (PAG). They are also expressed in structures of the limbic system and cortex, involved in processes like reward, motivation, learning, and modulating synaptic plasticity, and to varying degrees in the peripheral nervous system [5].

As GPCRs, opioid receptors mainly signal through two typical downstream routes, one mediated by G proteins and the other by β-arrestins.

All types of opioid receptors couple to heterotrimeric Gi/o family proteins, whose principal downstream effects include the inhibition of intracellular cyclic AMP synthesis, reduction of calcium influx, and promotion of potassium efflux. When acting at presynaptic sites, these effects reduce neurotransmitter release from vesicles, thereby inhibiting nociceptive transmission from primary afferents to second-order ascending neurones; at postsynaptic sites, they cause membrane hyperpolarisation and block the propagation of action potential, ultimately attenuating ascending nociceptive signalling to the cortex [5-7]. Thus, the classic inhibitory (analgesic) function of opioid receptors is largely mediated by Gi/o protein signalling.

β-arrestin-mediated signalling subserves other physiological processes, most notably receptor internalisation and trafficking. Active-state GPCRs are phosphorylated by G protein-coupled receptor kinases (GRKs), which promote β-arrestin recruitment [8]. Activated β-arrestin can sterically hinder G protein coupling, triggering receptor desensitisation, and then initiate receptor endocytosis through interactions with clathrin, the AP-2 (adaptor protein 2) complex, and other trafficking proteins [9]. Internalised receptors may be dephosphorylated and recycled back to the cell surface membrane or ubiquitinated, sorted, and targeted to the lysosome for degradation [10].

Current research suggests that Gi/o proteins and β-arrestins engage opioid receptors in a manner that they compete for overlapping sites [8], and 'biased agonism' arises from subtle differences in how distinct ligands bind and induce receptor conformational changes [11]. Meanwhile, different phosphorylation patterns may also affect the selectivity of downstream pathways [12]. Accordingly, it is possible, in principle, to design specific ligands that selectively stimulate specific downstream signalling cascades and thereby elicit desired physiological effects while minimising undesired ones.

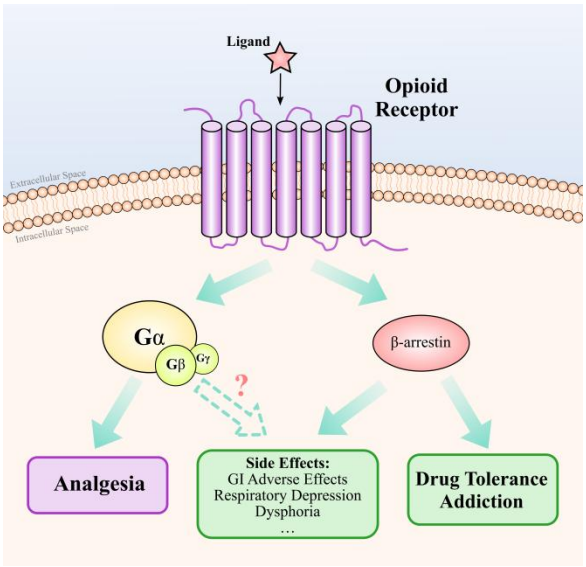

Figure 1. Mapping ORs' downstream pathways to physiological outcomes

3. BIASED AGONIST RESEARCH BY OPIOID RECEPTOR TYPES

3.1. μ-Opioid Receptor (MOR)

The μ-opioid receptor (MOR) is the most classic and the most extensively studied member of the opioid receptor family, a principal CNS target for analgesia. Its main endogenous ligands are β-endorphin and enkephalins. MOR distribution substantially overlaps with pain-regulatory and reward circuits – indeed, the main site of action of opioid drugs is the MORs in the CNS, and all morphine, heroin, fentanyl and its derivatives are potent MOR agonists [13].

In the design of biased MOR agonists, researchers aim to minimise adverse outcomes associated with MOR activation, particularly respiratory depression, tolerance, and addiction. Respiratory depression is considered to be the chief cause of opioid-related overdose deaths, which is linked to the suppression of brainstem respiratory centres by MOR activation. Both respiratory and gastrointestinal adverse effects of opioids have been at least partly attributed to β-arrestin signaling [14]. On the other hand, tolerance and addiction are associated with a decline in baseline analgesia and with positive reinforcement mechanisms; both processes involve down-regulation of MOR. Importantly, β-arrestin-mediated receptor internalisation is a key mechanism that drives this receptor down-regulation.

In response to the various side effects associated with β-arrestin signalling, Trevena, Inc., from Pennsylvania, USA, has developed a 'G protein-biased' selective MOR agonist, oliceridine (TRV130), which received FDA approval for medical use in 2020. Compared with conventional opioids such as morphine, TRV130 demonstrated an improved therapeutic index, more effective analgesia, attenuated respiratory depression, and fewer severe nausea events [15]. A phase II clinical trial by Viscusi et al. reported superior pain relief with TRV130 versus morphine in postoperative volunteers (96.8% achieved meaningful pain relief, while the morphine group was 56.4%), with tolerability within acceptable limits [16]. However, later-phase clinical studies after the approval indicated that the overall benefit-risk profile of TRV130 resembled that of conventional opioids, with only modest improvements in respiratory safety relative to theoretical expectations [17-18]; other animal studies have also reported tolerance and abuse potential comparable to morphine and oxycodone [17-19].

In 2016, Manglik et al. used computational docking and structure-based optimisation to obtain PZM21, described as a 'potent, selective, Gi-biased' MOR agonist. In mice, PZM21 produced a longer analgesic duration than maximal doses of morphine or TRV130 in the same experiments (at 120 minutes, PZM21 retained more than 40% analgesic effect, while the latter two had fallen below 20%) and exhibited side effects like constipation and respiratory depression, but to a lesser degree than morphine [20]. Later, Kudla et al. further confirmed its dose-dependent analgesia without reward or reinforcement-related effects and reported that PZM21 induced moderate striatal dopamine release and strong serotonin release, with the result that pretreatment with PZM21 enhanced morphine analgesia, suggesting potential clinical value. Nevertheless, repeated dosing led to tolerance and naloxone-like withdrawal symptoms [21]. Overall, PZM21 remains experimental under continued investigation and has not yet entered clinical trials.

3.2. κ-Opioid Receptor (KOR)

The endogenous ligand for the κ-opioid receptor (KOR) is dynorphin. KORs are distributed centrally and peripherally and are particularly dense in structures such as the claustrum, which is implicated in consciousness; their activation can thus produce hallucinations and dissociative effects [22]. They are also abundant in limbic structures and the prefrontal cortex, where they robustly suppress dopamine release [23], thereby causing strong anhedonia, depression-like dysphoria, and nausea, as well as sedation and behavioural disruption. These adverse effects have limited the clinical use of KOR agonists despite their analgesic properties. However, they present advantages including low addiction

risk (even with potential anti-addiction and MOR-antagonising effects [24]), minimal adverse effects on gastrointestinal and respiratory tracts, and additional antipruritic activity. As such, KORs show certain prospects for new analgesic approaches [25].

KOR-mediated adverse effects have been linked to β-arrestin signalling. Ehrich et al. demonstrated that in ventral tegmental area (VTA) dopaminergic neurones, KOR activates p38 MAPK via GRK3 and the β-arrestin pathway [26], and that p38 activation can suppress neuronal excitability by modulating GIRK channel function, causing depressive and aversive reactions [27]. Thus, similar to MOR, design strategies for biased KOR agonists typically aim to selectively activate Gi/o protein signalling for analgesia while avoiding β-arrestin recruitment.

Nalfurafine (TRK-820), approved in Japan for uremic pruritus, is the only clinically approved KOR agonist with biased signalling properties so far [28]. Although not originally developed as a biased ligand, later studies by Schattauer et al. showed that nalfurafine is G protein-biased, exhibiting potency for the G protein pathway roughly 250-fold greater than for the β-arrestin pathway of human KOR in vitro [29]; other clinical data suggest it lacks the typical anxiety- and depression-like adverse effects of conventional KOR agonists [30]. However, analgesic potential assessments carried out by Lazenka et al. indicated that the apparent effects of nalfurafine administration seemed to be derived from a broad motor suppression or central sedation, rather than a specific anti-nociception [31]. Therefore, despite extensive clinical experience, oral efficacy, and a favourable safety profile, nalfurafine has not demonstrated ideal analgesic characteristics to date, and further research would be required to develop it into a standalone analgesic.

Triazole 1.1 is a class of small non-peptide molecules reported by Brust et al. in 2016 to be substantially G protein-biased at KOR, with a calculated biased factor (G protein/β-arrestin-2) of 28. The compound retained antipruritic and antinociceptive effects while markedly reducing depressive and motor-suppressive central side effects. Brust et al. also detected that Triazole 1.1 does not reduce the concentration of dopamine in the nucleus accumbens of mice, which supports a lack of central sedation-driven reductions in spontaneous behaviour; in rat intracranial self-stimulation (ICSS) models, it provided effective antinociception without depression-like side effects [32-33]. Additional studies showed Triazole 1.1 can alleviate oxycodone-induced scratching and potentiate its thermal antinociceptive effect, inducing no behavioural disruption or sedation at the same time [34-35]. Nevertheless, its duration of action is relatively short (≈56 min), and its efficacy is lower than that of nalfurafine and U50,488H (a conventional non-biased KOR agonist) [36-37]. Triazole 1.1 overall shows good application prospects, while systematic studies regarding risks of tolerance and dependence associated with long-term administration are currently lacking.

3.3. δ-Opioid receptor (DOR)

The δ-opioid receptor (DOR), like MOR, mediates analgesia via Gi/o protein signalling, with the β-arrestin pathway implicated in the development of tolerance. Their endogenous ligands are primarily enkephalins, and DORs are distributed centrally and peripherally, with notable expression in the basal ganglia and the neocortex [38]. DOR-mediated analgesia is generally less potent than MOR and is often more relevant to the modulation of chronic pain. Relevant abuse liability is moderate and develops more slowly than at MOR; mild respiratory depression may be induced, yet, similar to KOR agonists, DOR demonstrates certain antipruritic activities.

Research on biased DOR agonists began later than for MOR and KOR, but still, relatively lower dependence risk makes DOR an equally appealing target. In 2020, Conibear et al. reported PN6047, a biased DOR ligand derived structurally from a selective μ-δ OR heterodimer agonist, SCN80. PN6047 fully activates G protein signalling and partially engages β-arrestin recruitment, with $\Delta\Delta\log(\tau/KA)$ values (G protein/β-arrestin-2) between ~1.0 and 1.5. In mouse pain models, 3 mg PN6047 markedly reduced mechanical hyperalgesia with analgesic duration over two hours; no tolerance developed during a 16-day dosing period, no conditioned place preference (CPP) was

observed (indicating lack of abuse liability), and no respiratory depression was recorded for 70 min post-administration. Additionally, in forced-swim tests, 10 mg PN6047 significantly reduced immobility time one hour after dosing, suggesting antidepressant-like activities. Unlike SNC80 and some conventional DOR agonists, PN6047 did not elicit convulsions or seizure-like symptoms. However, according to tail-flick and related assays, PN6047's efficacy against acute thermal nociception is limited, and its therapeutic potential for acute pain states is significantly lower than that of MOR agonists like methadone. This suggests that PN6047's analgesic utility may be more selective for chronic pain indications than acute ones [39].

In 2024, Cheng et al. used the cryo-EM structure of the DOR-Gi complex to design ADL06, a Gi-biased DOR agonist. Across acute and chronic pain models in mice, ADL06 outperformed ADL5859 (a conventional DOR agonist and the predecessor of ADL06) in antinociception, though it remained less effective than MOR agonists like morphine. It exhibited low convulsion activity and no analgesic tolerance, avoiding the gastrointestinal inhibition observed with ADL5859 and SNC80 as well. Pharmacokinetic analysis indicated that ADL06 had a longer half-life, greater systemic exposure, and faster absorption compared to ADL5859, conferring a superior duration of therapeutic effects. These findings further help researchers understand and elucidate the connections between β-arrestin signalling and DOR-associated adverse effects [40].

4. CONCLUSION AND OUTLOOK

The crisis associated with conventional opioids such as morphine has underscored the importance of maximising analgesic benefit while minimising harm. Researchers thus aim to reduce drug side effects and tolerance, achieving safer analgesia and addiction prevention. The theory of biased agonism has provided a promising framework for developing novel opioids, and over the past two decades, biased ligands for each receptor type have been investigated. Among them, oliceridine has reached clinical approval, triazole 1.1 shows encouraging preclinical properties, and ADL06 and others are emerging. However, most candidates remain at the discovery or preclinical stage, and translating experimental findings into clinical trials and listed drugs faces significant challenges. At present, they are either limited by incomplete safety evaluation, pharmacokinetic drawbacks, or marginal improvement in efficacy that confines further investment. Thus, the field of biased opioid drugs is still unsettled, and multiple critical issues remain to be resolved.

REFERENCES

[1] Kosten, T. R., & George, T. P. (2002) The neurobiology of opioid dependence: implications for treatment. Science & practice perspectives, 1(1): 13.

[2] Ramirez, J. M., Burgraff, N. J., & Wei, A. D. et al. (2021) Neuronal mechanisms underlying opioid-induced respiratory depression: our current understanding. Journal of Neurophysiology.

[3] Rankovic, Z., Brust, T. F., & Bohn, L. M. (2016) Biased agonism: An emerging paradigm in GPCR drug discovery. Bioorganic & medicinal chemistry letters, 26(2): 241-250.

[4] Zhang, P., Johnson, P. S., & Zöllner, C. et al. (1999) Mutation of human μ opioid receptor extracellular "disulfide cysteine" residues alters ligand binding but does not prevent receptor targeting to the cell plasma membrane. Molecular brain research, 72(2): 195-204.

[5] Sobczak, M., Sałaga, M., & Storr, M. A. et al. (2014) Physiology, signaling, and pharmacology of opioid receptors and their ligands in the gastrointestinal tract: current concepts and future perspectives. Journal of gastroenterology, 49(1): 24-45.

[6] Lambert, D. G. (2023) Opioids and opioid receptors; understanding pharmacological mechanisms as a key to therapeutic advances and mitigation of the misuse crisis. BJA open, 6: 100141.

[7] Al-Hasani, R., & Bruchas, M. R. (2011) Molecular mechanisms of opioid receptor-dependent signaling and behavior. Anesthesiology, 115(6): 1363.

[8] Mafi, A., Kim, S. K., & Goddard III, W. A. (2020) Mechanism of β-arrestin recruitment by the μ-opioid G protein-coupled receptor. Proceedings of the National Academy of Sciences, 117(28): 16346-16355.

[9] Tian, X., Kang, D. S., & Benovic, J. L. (2013) β-arrestins and G protein-coupled receptor trafficking. Arrestins-Pharmacology and therapeutic potential, 173-186.

[10] Marchese, A., Paing, M. M., & Temple, B. R. et al. (2008) G protein–coupled receptor sorting to endosomes and lysosomes. Annu. Rev. Pharmacol. Toxicol., 48(1): 601-629.

[11] T Andresen, B. (2011) A pharmacological primer of biased agonism. Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders), 11(2): 92-98.

[12] Doll, C., Konietzko, J., & Pöll, F. et al. (2011) Agonist-selective patterns of μ-opioid receptor phosphorylation revealed by phosphosite-specific antibodies. British journal of pharmacology, 164(2): 298-307.

[13] Edinoff, A. N., Kaplan, L. A., & Khan, S. et al. (2021) Full opioid agonists and tramadol: pharmacological and clinical considerations. Anesthesiology and Pain Medicine, 11(4): e119156.

[14] Imam, M. Z., Kuo, A., & Ghassabian, S. et al. (2018) Progress in understanding mechanisms of opioid-induced gastrointestinal adverse effects and respiratory depression. Neuropharmacology, 131: 238-255.

[15] Soergel, D. G., Subach, R. A., & Burnham, N. et al. (2014) Biased agonism of the μ-opioid receptor by TRV130 increases analgesia and reduces on-target adverse effects versus morphine: a randomized, double-blind, placebo-controlled, crossover study in healthy volunteers. Pain, 155(9): 1829-1835.

[16] Viscusi, E. R., Webster, L., & Kuss, M. et al. (2016) A randomized, phase 2 study investigating TRV130, a biased ligand of the μ-opioid receptor, for the intravenous treatment of acute pain. Pain, 157(1): 264-272.

[17] Viscusi, E. R., Skobieranda, F., & Soergel, D. G. et al. (2019) APOLLO-1: a randomized placebo and active-controlled phase III study investigating oliceridine (TRV130), a G protein-biased ligand at the μ-opioid receptor, for management of moderate-to-severe acute pain following bunionectomy. Journal of pain research, 927-943.

[18] Singla, N. K., Skobieranda, F., & Soergel, D. G. et al. (2019) APOLLO-2: a randomized, placebo and active-controlled phase III study investigating oliceridine (TRV 130), a G protein–biased ligand at the μ-opioid receptor, for management of moderate to severe acute pain following abdominoplasty. Pain Practice, 19(7): 715-731.

[19] Negus, S. S., & Freeman, K. B. (2018) Abuse potential of biased mu opioid receptor agonists. Trends in pharmacological sciences, 39(11): 916-919.

[20] Manglik, A., Lin, H., & Aryal, D. K. et al. (2016) Structure-based discovery of opioid analgesics with reduced side effects. Nature, 537(7619): 185-190.

[21] Kudla, L., Bugno, R., & Skupio, U. et al. (2019) Functional characterization of a novel opioid, PZM21, and its effects on the behavioural responses to morphine. British Journal of Pharmacology, 176(23): 4434-4445.

[22] Stiefel, K. M., Merrifield, A., & Holcombe, A. O. (2014) The claustrum's proposed role in consciousness is supported by the effect and target localization of Salvia divinorum. Frontiers in integrative neuroscience, 8: 20.

[23] Tejeda, H. A., Wang, H., & Flores, R. J. et al. (2021) Dynorphin/kappa-opioid receptor system modulation of cortical circuitry. The Kappa Opioid Receptor, 223-253.

[24] Pan, Z. Z. (1998) μ-Opposing actions of the κ-opioid receptor. Trends in pharmacological sciences, 19(3): 94-98.

[25] El Daibani, A., Paggi, J. M., & Kim, K. et al. (2023) Molecular mechanism of biased signaling at the kappa opioid receptor. Nature communications, 14(1): 1338.

[26] Bruchas, M. R., Macey, T. A., & Lowe, J. D. et al. (2006) Kappa opioid receptor activation of p38 MAPK is GRK3-and arrestin-dependent in neurons and astrocytes. Journal of Biological Chemistry, 281(26): 18081-18089.

[27] Ehrich, J. M., Messinger, D. I., & Knakal, C. R. et al. (2015) Kappa opioid receptor-induced aversion requires p38 MAPK activation in VTA dopamine neurons. Journal of Neuroscience, 35(37): 12917-12931.

[28] Inui, S. (2015) Nalfurafine hydrochloride to treat pruritus: a review. Clinical, cosmetic and investigational dermatology, 249-255.

[29] Schattauer, S. S., Kuhar, J. R., & Song, A. et al. (2017) Nalfurafine is a G-protein biased agonist having significantly greater bias at the human than rodent form of the kappa opioid receptor. Cellular signalling, 32: 59-65.

[30] Kozono, H., Yoshitani, H., & Nakano, R. (2018) Post-marketing surveillance study of the safety and efficacy of nalfurafine hydrochloride (Remitch® capsules 2.5 μg) in 3,762 hemodialysis patients with intractable pruritus. International Journal of Nephrology and Renovascular Disease, 9-24.

[31] Lazenka, M. L., Moerke, M. J., & Townsend, E. A. et al. (2018) Dissociable effects of the kappa opioid receptor agonist nalfurafine on pain/itch-stimulated and pain/itch-depressed behaviors in male rats. Psychopharmacology, 235(1): 203-213.

[32] Brust, T. F., Morgenweck, J., & Kim, S. A. et al. (2016) Biased agonists of the kappa opioid receptor suppress pain and itch without causing sedation or dysphoria. Science signaling, 9(456): ra117-ra117.

[33] Ranjan, R., Pandey, S., & Shukla, A. K. (2017) Biased opioid receptor ligands: gain without pain. Trends in Endocrinology & Metabolism, 28(4): 247-249.

[34] Zamarripa, C. A., Pareek, T., & Schrock, H. M. et al. (2021) The kappa-opioid receptor agonist, triazole 1.1, reduces oxycodone self-administration and enhances oxycodone-induced thermal antinociception in male rats. Psychopharmacology, 238(12): 3463-3476.

[35] Huskinson, S. L., Platt, D. M., & Zamarripa, C. A. et al. (2022) The G-protein biased kappa opioid agonists, triazole 1.1 and nalfurafine, produce non-uniform behavioral effects in male rhesus monkeys. Pharmacology Biochemistry and Behavior, 217: 173394.

[36] Liu-Chen, L. Y., & Huang, P. (2022) Signaling underlying kappa opioid receptor-mediated behaviors in rodents. Frontiers in Neuroscience, 16: 964724.

[37] Dalefield, M. L., Scouller, B., & Bibi, R. et al. (2022) The kappa opioid receptor: a promising therapeutic target for multiple pathologies. Frontiers in pharmacology, 13: 837671.

[38] Peppin, J. F., & Raffa, R. B. (2015) Delta opioid agonists: a concise update on potential therapeutic applications. Journal of clinical pharmacy and therapeutics, 40(2): 155-166.

[39] Conibear, A. E., Asghar, J., & Hill, R. et al. (2020) A novel G protein–biased agonist at the δ opioid receptor with analgesic efficacy in models of chronic pain. The Journal of Pharmacology and Experimental Therapeutics, 372(2): 224-236.

[40] Cheng, L., Miao, Z., & Liu, S. et al. (2024) Cryo-EM structure of small-molecule agonist bound delta opioid receptor-Gi complex enables discovery of biased compound. Nature Communications, 15(1): 8284.